



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 34

Alan R. Katritzky

Advances in

**Heterocyclic
Chemistry**

Volume 34

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Preface

Pyrans, thiopyrans, and selenopyrans are comprehensively reviewed by Kuthan in the first unified treatment of this subject. The triazolopyridines were last reviewed in 1961: the chemistry of these five heterocyclic systems is covered by Jones and Sliskovic.

Meisenheimer complexes from heteroaromatic compounds have been intensively investigated in the last 20 years, and the field has now been summarized by Illuminati and Stegel of the Rome group, who have contributed much in this area.

Volume 33 of this series contains a survey of *2H*- and *3H*-pyrroles, nonaromatic isomers of the common *1H*-pyrroles. The present volume includes two chapters on *3H*- and *4H*-pyrazoles, the nonaromatic isomers of "normal" *1H*-pyrazoles, by Sammes and the series editor.

The chapters in this volume cover the literature up to and beyond 1981.

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The 3*H*-Pyrazoles

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ALAN R. KATRITZKY

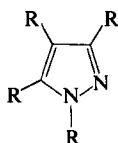
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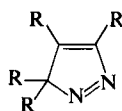
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I. Introduction

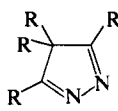
Isomeric with 1*H*-pyrazoles (1) two nonaromatic structures (2,3) may be drawn, each possessing a tetrahedral carbon atom in the ring. These ring systems, the 3*H*-pyrazoles (2) and the 4*H*-pyrazoles (3), also known as "pyrazolenines" and "isopyrazoles", have chemical properties quite different both from their 1*H*-isomers 1 and from each other. Structures 2 may be considered as cyclic unsaturated azo compounds, whereas structures 3 are cyclic azines. The 3*H*-pyrazoles are the subject of this review, but in the following chapter the 4*H* compounds are discussed.



(1)



(2)



(3)

A comprehensive Russian language review on the 3*H*-pyrazoles and 3*H*-indazoles was published in 1976,¹ but at the time of this writing it was not available in English. Reviews on 1*H*-pyrazoles^{2,3} and major treatises of heterocyclic chemistry⁴⁻⁶ also include discussions of the preparation and properties of some of these compounds.

The present review is comprehensive; *Chemical Abstracts* has been searched by indexes up to mid 1981 and by a computer "on-line" substructure search up to Issue 26 of Volume 96. A few more recent references are included directly from the commoner international journals. This review covers 3*H*-pyrazoles that have been isolated or characterized spectroscopically, although some examples that are only transient intermediates in rearrangement reactions are also mentioned. Compounds having exocyclic double bonds and the benz-fused derivatives, the 3*H*-indazoles, are considered to be outside its scope.

II. Synthesis of 3*H*-Pyrazoles

The most important method for the synthesis of 3*H*-pyrazoles is by 1,3-dipolar cycloaddition between a diazo compound and an alkyne, although alkenes bearing suitable leaving groups have also been used. Other methods include the cyclization of vinyl diazo compounds, and the oxidation of pyrazolines.

A. FROM DIAZO COMPOUNDS AND ALKYNES

The reaction between alkynes and diazomethane, or monosubstituted diazomethanes, has been known for almost a century to yield 1*H*-pyrazoles⁷ and is an important method for preparing these compounds.^{2,3,6} It proceeds via a 1,3-dipolar cycloaddition (Scheme 1) giving initially a 3*H*-pyrazole (4),

¹ R. R. Bekmukhametov, *Sovrem. Probl. Org. Khim.* **5**, 105 (1976) [*C A* **86**, 155533a (1977)].

² A. N. Kost and I. I. Grandberg, *Adv. Heterocycl. Chem.* **6**, 347 (1966).

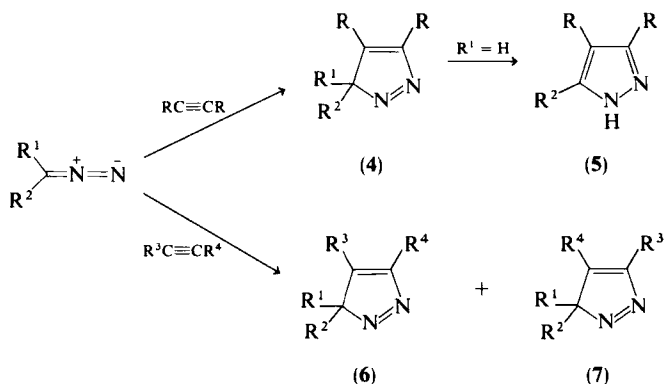
³ I. K. Korobitsyna, V. V. Bulusheva, and L. L. Rodina, *Khim. Geterotsikl. Soedin.*, 579 (1978) [*C A* **89**, 59843t (1978)].

⁴ T. L. Jacobs, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, Chapter 2. Wiley, New York, 1957.

⁵ R. H. Wiley (ed.), "Chemistry of Heterocyclic Compounds. Vol. XXII: Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings." Wiley (Interscience), New York, 1967.

⁶ J. Elguero, in "Comprehensive Heterocyclic Chemistry" (A. R. Katritzky and C. W. Rees, eds.), Vol. 4, Chapter 4.4. Pergamon, Oxford, 1983.

⁷ E. Buchner, *Ber. Dtsch. Chem. Ges.* **22**, 842 (1889).



SCHEME 1

which undergoes a subsequent prototropic shift to yield the 1*H*-pyrazole (5). When a disubstituted diazomethane is used ($R^1, R^2 \neq H$), 4 may be isolated, although it too may rearrange under the conditions of the reaction. For example, the first reported preparation of a 3*H*-pyrazole by this method⁸ was later shown to be in error,⁹ the product having rearranged to a 1*H* isomer. The use of an unsymmetrically disubstituted alkyne introduces a further complexity in that it can, and often does, result in the isolation of two regioisomers 6 and 7. Nevertheless, the method has been used successfully with a wide range of substituents R^1 – R^4 , and yields have generally been very high.

Reactions are normally carried out in anhydrous ether at room temperature or below and take from minutes to days to go to completion. Some have been conducted in more polar solvents such as MeCN or DMF, and sometimes an excess of the alkyne has been used as the solvent. Exceptionally, higher temperatures have been employed, but this usually results in isolation of the 1*H*-pyrazole from rearrangement.

1. Diazoalkane Substituents

The most commonly used diazoalkanes have been diphenyldiazomethane (DPD) and 2-diazopropane (DAP), on account of their ready accessibility. The numerous other examples include 1-phenyldiazoethane^{10,11};

⁸ O. Diels and H. König, *Ber. Dtsch. Chem. Ges.* **71**, 1179 (1938).

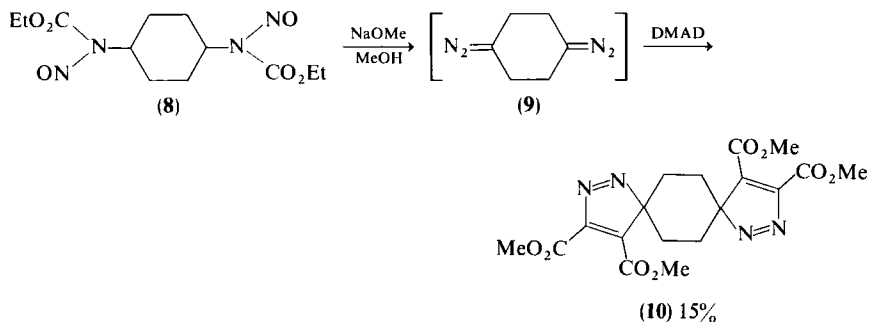
⁹ M. Franck-Neumann and C. Buchecker, *Tetrahedron Lett.*, 937 (1972).

¹⁰ R. Hüttel, J. Riedl, H. Martin, and K. Franke, *Chem. Ber.* **93**, 1425 (1960).

¹¹ H. Heydt and M. Regitz, *Justus Liebigs Ann. Chem.*, 1766 (1977).

methyl 4-diazo-4-phenylbutanoate¹²; hexafluoro-2-diazopropane^{13,14}; diaryl-diazomethanes¹⁰; diazocyclopentadienes and -indenes¹⁵⁻¹⁷; diazofluorenes^{11,15,16,18-20}; heterocyclic analogs²¹⁻²³ and six-^{24,25} and seven-membered ring²⁶ analogs of diazofluorene (cyclic diazo compounds give spiro-3H-pyrazoles); α -diazo ketones (acyclic^{9,27-29} and cyclic^{27,30-32}); α -diazo esters,^{9,12,28,33,34} including a sugar derivative³⁵; an α -diazonitrile⁹ and -sulfone³⁴; and a number of organometallic derivatives having the following substituents attached to the diazo carbon atom: Me₃Si,³⁶⁻³⁷ Me₃Sn,³⁷⁻³⁹ Me₃Pb,^{39,40} Me₂As, Me₂Sb, Me₂Bi, and MeHg.³⁹ The ionic (Me₂Tl)₂CN₂ failed to react, the authors suggesting that the cycloaddition does not proceed with the CN₂²⁻ ion.⁴¹ The bispiro-3H-pyrazole (10) (Scheme 2) has been prepared from dimethyl acetylenedicarboxylate (DMAD) and 1,4-bisdiazocyclohexane (9), formed *in situ* from the *N*-nitroso ester (8).⁴² In a number of

- ¹² I. Moritani, T. Hosokawa, and N. Obata, *J. Org. Chem.* **34**, 670 (1969).
- ¹³ D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Am. Chem. Soc.* **88**, 3617 (1966).
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- ¹⁵ H. Dürr and R. Sergio, *Tetrahedron Lett.*, 3479 (1972); *Chem. Ber.* **107**, 2027 (1974).
- ¹⁶ H. Dürr and W. Schmidt, *Justus Liebigs Ann. Chem.*, 1140 (1974).
- ¹⁷ H. Dürr, B. Ruge, and B. Weiss, *Justus Liebigs Ann. Chem.*, 1150 (1974).
- ¹⁸ J. van Alphen, *Recl. Trav. Chim. Pays-Bas* **62**, 491 (1943).
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- ²⁹ R. Huisgen, M. P. B. Verderol, A. Gieren, and V. Lamm, *Angew. Chem., Int. Ed. Engl.* **20**, 694 (1981).
- ³⁰ O. Tsuge, I. Shinkai, and M. Koga, *J. Org. Chem.* **36**, 745 (1971).
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- ³² M. Franck-Neumann and C. Buchecker, *Angew. Chem., Int. Ed. Engl.* **12**, 240 (1973).
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- ³⁷ M. F. Lappert and J. S. Poland, *J. Chem. Soc. C*, 3910 (1971).
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- ⁴¹ P. Krommes and J. Lorberth, *J. Organomet. Chem.* **120**, 131 (1976).
- ⁴² K. Heyns and A. Heins, *Angew. Chem.* **73**, 64 (1961).



SCHEME 2

cycloadditions the product isolated has been a *1H*-pyrazole, resulting from rearrangement of the initially formed *3H* compound (see Section IV,A,1).

2. Alkyne Substituents

The high reactivity of DMAD as a dipolarophile has made it the alkyne of choice in a large number of preparations. Many other alkynes have been used successfully, including ethyne^{19,43}; mono-⁴⁴⁻⁴⁶ and dialkylethyne¹³; cyclooctyne^{25,26,47}; trifluoromethylethyne^{14,15}; phenylethyne^{10,12,15,30,31,35,48,49}; diphenylethyne^{12,49a}; 3-propynols^{46,49-51} and an *O*-acetyl derivative⁵²; 1-diethylaminopropyne^{16,29,34}; ethoxyethyne⁵³; ethynyl thioethers,⁵⁴ sulfoxides,^{55,56} and sulfones^{55,57}; propynal^{10,58} and its di-*n*-propyl acetal⁴⁸; phenyl-

⁴³ G. Snatzke and H. Langen, *Chem. Ber.* **102**, 1865 (1969).

⁴⁴ M. E. Hendrick, W. J. Baron, and M. Jones, Jr., *J. Am. Chem. Soc.* **93**, 1554 (1971).

⁴⁵ W. J. Baron, M. E. Hendrick, and M. Jones, Jr., *J. Am. Chem. Soc.* **95**, 6286 (1973).

⁴⁶ G. F. Bettinetti, G. Desimoni, and P. Grünanger, *Gazz. Chim. Ital.* **94**, 91 (1964).

⁴⁷ G. Wittig and J. J. Hutchison, *Justus Liebigs Ann. Chem.* **741**, 89 (1970).

⁴⁸ R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, *Angew. Chem.* **73**, 170 (1961).

⁴⁹ C. Dumont, J. Naire, M. Vidal, and P. Arnaud, *C. R. Acad. Sci., Ser. C*, **268**, 348 (1969).

^{49a} J. A. Pincock, R. Morchat, and D. R. Arnold, *J. Am. Chem. Soc.* **95**, 7536 (1973).

⁵⁰ G. F. Bettinetti and G. Desimoni, *Gazz. Chim. Ital.* **93**, 658 (1963).

⁵¹ A. C. Day and M. C. Whiting, *J.C.S. Chem. Commun.*, 292 (1965); *J. Chem. Soc. C*, 1719 (1966).

⁵² A. C. Day and M. C. Whiting, *J. Chem. Soc. B*, 991 (1967).

⁵³ P. Grünanger and P. V. Finzi, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [8] **31**, 128 (1961) [*CA* **58**, 516c (1963)].

⁵⁴ M. Franck-Neumann and J.-J. Lohmann, *Tetrahedron Lett.*, 3729 (1978).

⁵⁵ M. Franck-Neumann and J.-J. Lohmann, *Angew. Chem., Int. Ed. Engl.* **16**, 323 (1977).

⁵⁶ M. Franck-Neumann and J.-J. Lohmann, *Tetrahedron Lett.*, 2397 (1979).

⁵⁷ G. Guillermin, A. L'Honoré, L. Veniard, G. Pourcelot, and J. Benaim, *Bull. Soc. Chim. Fr.*, 2739 (1973).

⁵⁸ R. Hüttel and A. Gebhardt, *Justus Liebigs Ann. Chem.* **558**, 34 (1947).

propynal^{10,59}; mono-^{28,49,50,60-62} and diacyl alkynes^{16,28,62,63}; propynoic esters^{10,15,17-19,21,23,28,48,62,64-66} and 3-alkyl-^{62,66-68} and 3-phenylpropynoic esters^{18,25,48,62,64,65,67,69-71}; propynonitrile^{28,62,72} and its 3-methyl⁶² and 3-phenyl derivatives^{62,70}; dicyanoethyne^{15,62,63,72}; diphenylphosphinyl-,¹¹ trimethylsilyl- and triethylstannyl-,⁵⁷ and trimethylgermylalkynes¹⁴; and benzyne, which gives 3H-indazoles.^{20,31} 1,3-Enynes may undergo addition at either or both multiple bonds, depending upon the substituents (see Section II,A,4).^{46,73-75}

3. Mechanism of the Reaction

The mechanism of the reaction has generally been discussed in terms of a thermally allowed concerted 1,3-dipolar cycloaddition process, in which control is realized by interaction between the highest occupied molecular orbital (HOMO) of the dipole (diazoalkane) and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile (alkyne).⁷⁶ In some cases unequal bond formation has been indicated in the transition state, giving a degree of charge separation. Compelling evidence has also been presented for a two-step diradical mechanism for the cycloaddition⁷⁷; but this issue has yet to be resolved.

A considerable body of data exists on the regioselectivity of the reaction. Table I shows the ratio of isomers **6** and **7** (Scheme 1) and the total yield of

- ⁵⁹ I. N. Domin, E. F. Zhuravleva, V. L. Serebrov, and R. R. Bekmukhametov, *Khim. Geterotsikl. Soedin.*, 1091 (1978) [CA **90**, 6300c (1979)].
- ⁶⁰ G. F. Bettinetti, G. Desimoni, and P. Grünanger, *Gazz. Chim. Ital.* **93**, 150 (1963).
- ⁶¹ C. Dumont and M. Vidal, *Bull. Soc. Chim. Fr.*, 2301 (1973).
- ⁶² C. Dietrich-Buchecker and M. Franck-Neumann, *Tetrahedron* **33**, 745 (1977).
- ⁶³ M. Franck-Neumann and D. Martina, *Tetrahedron Lett.*, 1767 (1975).
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TABLE I
REGIOSELECTIVITY IN THE ADDITION OF DIAZOALKANES TO UNSYMMETRICAL ALKYNES
(SCHEME 1)

Example	R ¹ , R ²	R ³	R ⁴	Ratio 6:7	Yield (%)	Reference
1	Me	H	Ph	1:0	12	49
2	Me	H	<i>p</i> -MeC ₆ H ₄ S	41:1	90	54
3	Me	H	<i>p</i> -MeC ₆ H ₄ S(O)	9:1	90	56
4	Me	H	CO ₂ Me	1:0	82	62
5	Me	Ph	CO ₂ Me	1:2.4	92	62
6	Me	<i>n</i> -C ₅ H ₁₁	CO ₂ Me	1:3	68	62
7	Me	Me	CO ₂ Me	1:6	82	66
8	Me	Me ₃ Si	CO ₂ Me	0:1	90	57
9	Me	<i>t</i> -Bu	COMe	0:1	80	62
10	Me	Me	CN	1:3	99	62
11	Me	Ph	CN	1:9	91	62
12	Ph	H	EtO	1.4:1	71	53
13	Ph	Me	SO ₂ Ph	1:1.9	100	57
14	Ph	Me	CO ₂ Me	1.5:1	86	68
15	Ph	Ph	CO ₂ Me	1:1.5	—	67
16	Ph	Ph	CHO	1:1.25	45	59

products formed from the reaction between selected unsymmetrical alkynes and DAP or DPD. Comparisons among the examples (e.g., 5 and 7 with 4, and with 14 and 15) show that both electronic and steric factors are important, as has been discussed by several authors.^{57,59,62,66,78,79} Although it has been suggested that when R³ = H, only isomer 6 is formed,⁶² there are exceptions (examples 2, 3, and 12, Table I; see also references 73 and 74). Some early workers isolated only one isomer^{10,64} where later two were found.^{67,71,80}

Successful qualitative predictions of isomer ratios have been made by calculating the difference in energy between the two senses of addition for simple alkynes, using a second order perturbation method.⁸¹ Predictions for disubstituted alkynes were made⁵⁹ via an additivity scheme.⁸¹ Results for alkynes having R³ = H show that when $\Delta E [=E_6 - E_7]$ is positive, isomer 6 is favored, being the only product for $\Delta E > 8.5$ kJ/mol. Likewise, negative values favor isomer 7. For smaller values of $|\Delta E|$, both isomers are predicted, the relative amounts depending upon the sign and magnitude of ΔE . A negative value in the case of methoxyethyne⁸¹ accounts for example 12 in

⁷⁸ R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **2**, 633 (1963).

⁷⁹ J. Bastide and J. Lematre, *Bull. Soc. Chim. Fr.*, 3543 (1970).

⁸⁰ P. J. Abbott, R. M. Acheson, R. F. Flowerday, and G. W. Brown, *J.C.S. Perkin I*, 1177 (1974).

⁸¹ J. Bastide and O. Henri-Rousseau, *Bull. Soc. Chim. Fr.*, 1037 (1974).

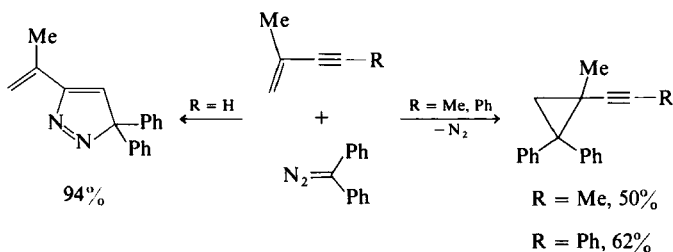
Table I (see also reference 74). For disubstituted alkynes, steric factors become increasingly important with smaller values of $|\Delta E|$.⁵⁹

The difference in energy between the HOMO of the dipole and the LUMO of the dipolarophile affects the rate of the reaction⁷⁶ and hence the conditions necessary for a successful cycloaddition. The HOMO and LUMO energies are modified, respectively, by substituents R^1 , R^2 and R^3 , R^4 . Thus for cycloadditions to DPD in DMF at 40°C, relative rates for phenylethyne, methyl propynoate, and DMAD are, respectively, 1:900:8200,⁴⁸ increasingly electron-withdrawing substituents R^3 and R^4 decreasing the alkyne LUMO energy to more favorable values. Likewise, electron-withdrawing substituents R^1 and R^2 lower the diazoalkane HOMO energy; conversely, electron-releasing groups R^1 , R^2 and R^3 , R^4 will raise, respectively, the energies of the diazoalkane HOMO and alkyne LUMO. In extreme cases of strong electron-withdrawing R^1 and R^2 , and -releasing R^3 and R^4 , the cycloaddition occurs via overlap of the diazoalkane LUMO with the alkyne HOMO.^{29,34} Intermediate examples are the reaction between 3,3-dimethyl-1-butyne and DAP, which is immeasurably slow at 25°C,⁴⁹ although addition occurs with DPD⁴⁵, and reactions of hexafluoro-2-diazopropane, which occur only at 150°C.^{13,14} Unfortunately, elevated temperatures often result in the rearrangement of the initially formed 3H-pyrazole.^{12,33}

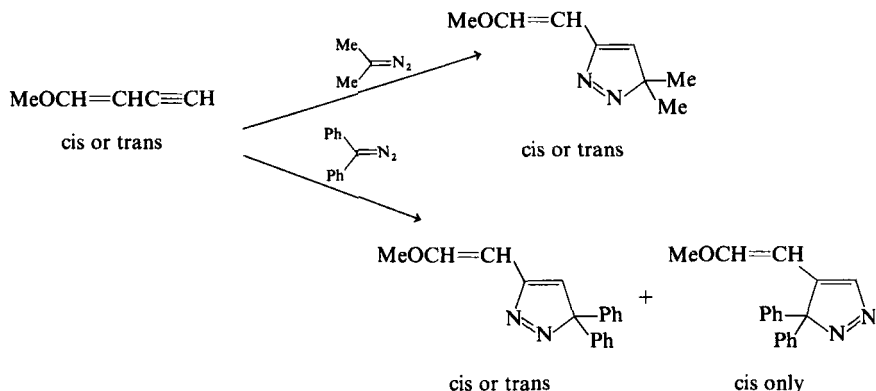
4. Additions to Conjugated Enynes

Electronic and steric factors seem to determine both the site and the orientation of addition of diazoalkanes to conjugated enynes. Although rates of addition of DPD to ethene and ethyne bearing identical single substituents are approximately the same,⁴⁸ addition to butenyne occurs almost exclusively at the double bond.⁴⁶

Substituents on the double bond direct the addition to the triple bond,^{46,73-74a} although when the latter is also substituted, the double bond is again preferred. Frequently only one sense of addition to a given bond is observed (Scheme 3),^{46,74,74a} although with 1-methoxybutenyne this depends



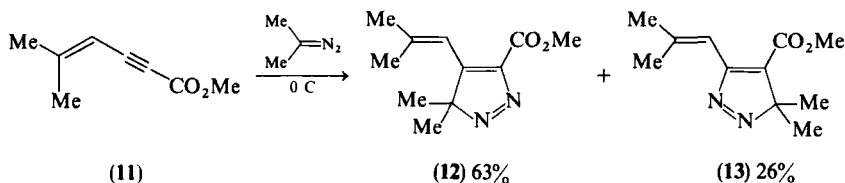
SCHEME 3



SCHEME 4

both on the geometry of the double bond (which is preserved) and on the nature of the diazoalkane (Scheme 4).^{73,74}

The enynic ester **11** is exceptional in that both senses of addition are observed with DAP, exclusively at the substituted triple bond (Scheme 5).⁷⁵

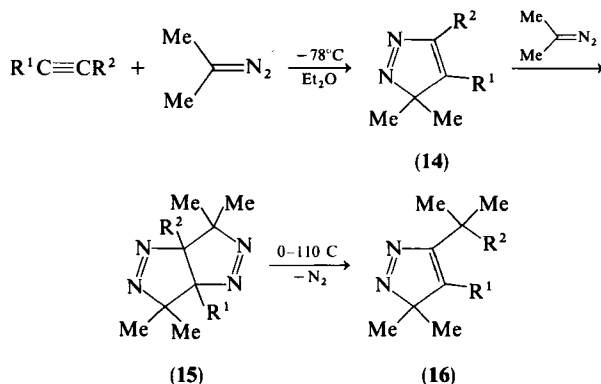


SCHEME 5

5. Byproducts from the Cycloaddition

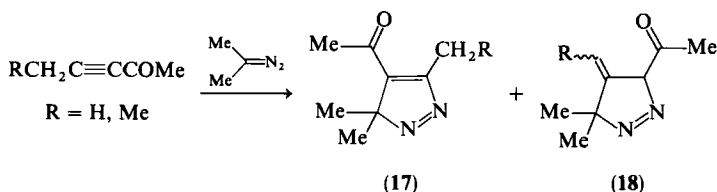
In the reaction between electron-deficient alkynes and DAP, a second mole of the latter may add to the product **14** to give a bis(pyrazoline) **15** (Scheme 6).^{62,63,65,82} For $R^1 = \text{COR}$, CO_2R , or CN , the formation of **14** occurs at -78°C in Et_2O . The byproduct **15** also forms at this temperature when $R^2 = R^1$, but at 0°C when $R^2 = \text{H}$, and not at all when R^2 is an alkyl or aryl group.⁶² Rearrangement of **15** to the *3H*-pyrazole **16** with loss of nitrogen may also occur at 0°C (e.g., when $R^1 = R^2 = \text{COPh}$), but this usually requires heat.⁶³

⁸² M. Franck-Neumann, *Angew. Chem. Int., Ed. Engl.* **6**, 79 (1967).



SCHEME 6

The reaction between DAP and conjugated ynones is reported to give two products (17 and 18), one being a tautomer of the anticipated second product (Scheme 7).⁴⁹



SCHEME 7

Azines, derived from two moles of diazoalkane with loss of nitrogen, have been observed as byproducts by several authors.^{11,53,71}

The isolation of 1*H*- and 4*H*-pyrazoles from thermally induced sigma-tropic rearrangements of initially formed 3*H*-pyrazoles is discussed in Section IV,A,1.

B. FROM DIAZO COMPOUNDS AND ALKENES BEARING SUITABLE LEAVING GROUPS

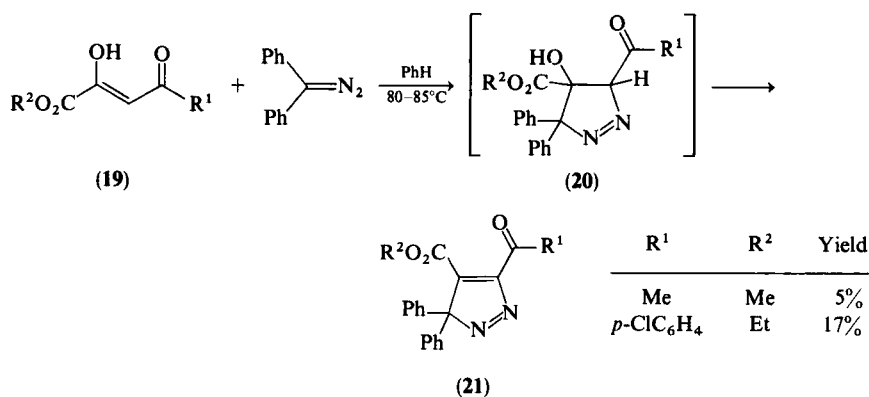
Alkenes substituted with potential leaving groups are masked alkynes and are thus useful alternative dipolarophiles. They react with diazo compounds, producing pyrazolines, which can undergo elimination to give 3*H*-pyrazoles.

Elimination may occur spontaneously during the reaction but generally has been carried out subsequently, sometimes accompanied by rearrangement to the 1*H*-pyrazole.

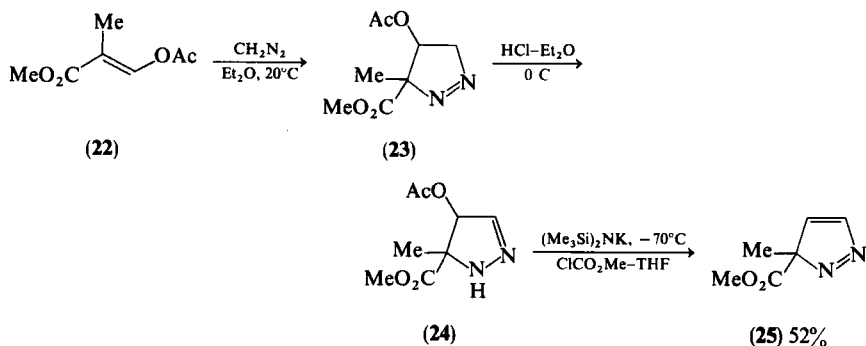
An advantage of the method is that in all reported examples only one sense of cycloaddition has been observed.

1. Alkenes with *O*-Linked Substituents

The enol forms **19** (Scheme 8) of α,γ -diketo esters add to DPD, giving low yields of 3*H*-pyrazoles **21** via the hydroxypyrazolines. **20**.⁸³ Noncyclic products are also formed.



SCHEME 8



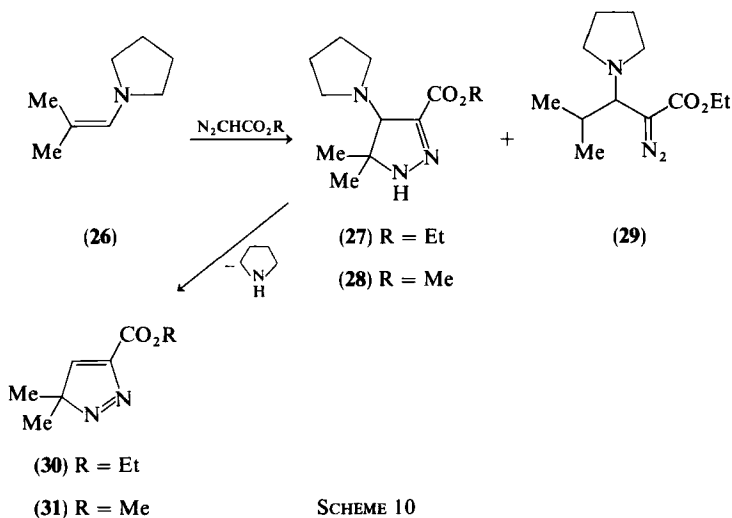
SCHEME 9

⁸³ A. L. Fridman, Y. S. Andreichikov, and V. L. Gein, *Zh. Org. Khim.* **13**, 1422 (1977) [*CA* **88**, 22831r (1978)].

The adduct **23** from the enol acetate **22** and diazomethane (Scheme 9) has been rearranged in acid to its tautomer **24**, which in turn has been converted at low temperature to the unstable 3*H*-pyrazole **25**.⁸⁴

2. Alkenes with *N*-Linked Substituents

Cycloaddition between the enamine **26** (Scheme 10) and ethyl diazoacetate in ethanol gave a mixture of the pyrazoline **27** and the diazo ester **29**. The former was converted to the 3*H*-pyrazole **30** by chromatography on alumina or by distillation.⁸⁵ Use of methyl diazoacetate in boiling chloroform gave, in contrast, a high yield of **28**, convertible almost quantitatively to **31** by chromatography on silica.⁸⁶ Other enamines gave 1*H*-pyrazoles.



SCHEME 10

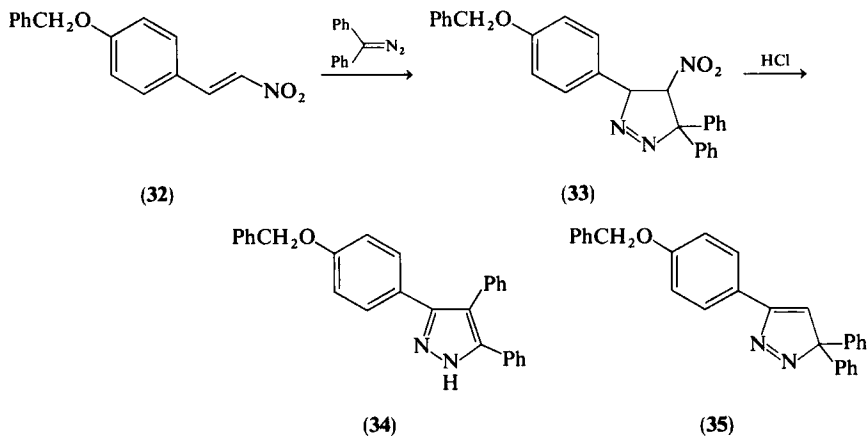
In the conversion of the pyrazoline **33**, formed from the β -nitrostyrene **32** and DPD, to the 1*H*-pyrazole **34** with HCl, migration of the phenyl group was believed to be concerted with loss of NO_2^- .⁸⁷ It is, however, possible that the reaction proceeds via rearrangement of an intermediate 3*H*-pyrazole **35** (Scheme 11).

⁸⁴ P. Schiess and H. Stalder, *Tetrahedron Lett.* **21**, 1413 (1980).

⁸⁵ E. Wenkert and C. A. McPherson, *J. Am. Chem. Soc.* **94**, 8084 (1972).

⁸⁶ R. Huisgen and H.-U. Reissig, *Angew. Chem., Int. Ed. Engl.* **18**, 330 (1979).

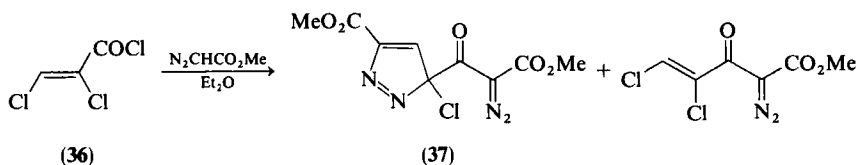
⁸⁷ W. E. Parham, C. Serres, Jr., and P. R. O'Connor, *J. Am. Chem. Soc.* **80**, 588 (1958).



SCHEME 11

3. Alkenes with Halogen Substituents

A number of 2-acyl-1-chloroethenes add to DPD in ether, losing HCl spontaneously from the intermediate pyrazolines, and giving 1*H*-pyrazoles from rearrangement of the transient 3*H* isomers.^{50,60} The acid chloride **36** gives a small amount of a 3*H*-pyrazole **37** from reaction with two moles of methyl diazoacetate (Scheme 12).⁸⁸



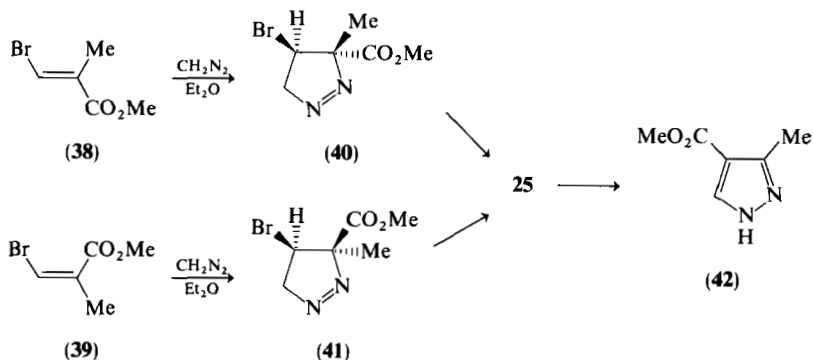
SCHEME 12

Diazomethane yields the isomeric pyrazolines **40** and **41**, respectively, from the bromo esters **38** and **39**. These undergo an autocatalytic exothermic conversion to the same 1*H*-pyrazole **42** on heating, or on standing in solution (Scheme 13). This is taken as evidence that **25** is an intermediate, because if group migration was concerted with loss of Br⁻, **40** and **41** should give different products.⁸⁹

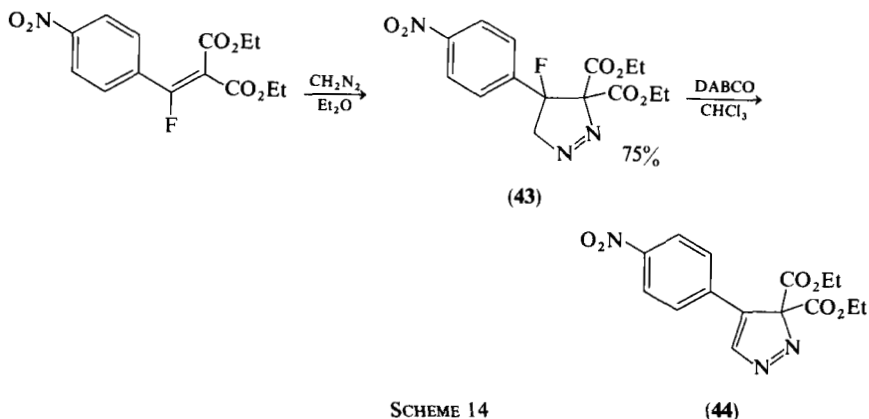
A number of halobenzyldienemalonate derivatives give unstable pyrazolines with diazomethane. One pyrazoline (**43**, Scheme 14) eliminated HF with

⁸⁸ A. Roedig, H. Aman, and E. Fahr, *Justus Liebigs Ann. Chem.* **675**, 47 (1964).

⁸⁹ D. E. McGreer and Y. Y. Wigfield, *Can. J. Chem.* **47**, 2095 (1969).



SCHEME 13



SCHEME 14

DABCO in chloroform, the transient 3H-pyrazole **44** being identified by ^1H -NMR spectroscopy before rearranging to isomeric 1H-pyrazoles.⁹⁰

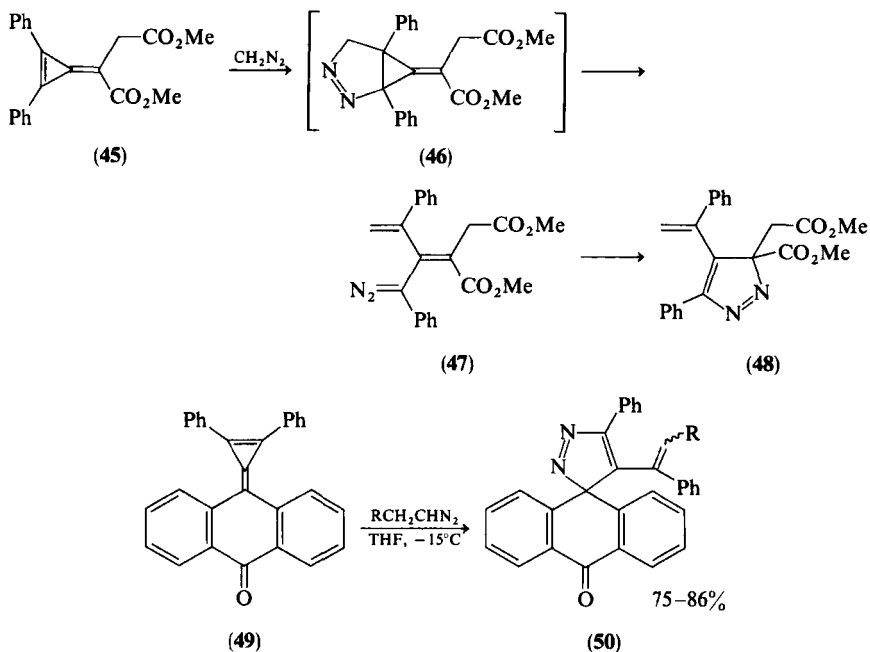
C. FROM DIAZO COMPOUNDS BY OTHER INTERMOLECULAR PROCESSES

1. Cycloadditions with Strained Cycloalkenes

a. *Methylene-Cyclopropenes*. The diester **45** gives with diazomethane the vinyl diazo compound **47** via the electrocyclic ring opening of the intermediate pyrazoline **46**.⁹¹ During 38 days at -15°C , **47** cyclizes to the

⁹⁰ Y.-M. Saunier, R. Danion-Bougot, D. Danion, and R. Carrié, *Nouv. J. Chim.* **3**, 47 (1979).

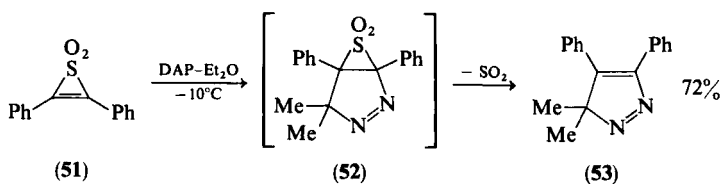
⁹¹ R. S. Pyron and W. M. Jones, *J. Org. Chem.* **32**, 4048 (1967).



SCHEME 15

3*H*-pyrazole **48** (Scheme 15). In a related reaction, the anthraquinone derivative **49** gave mixed geometric isomers of the spiro-3*H*-pyrazoles **50**.⁹²

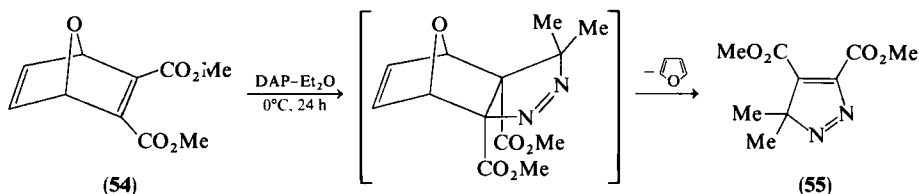
b. *Thiirene 1,1-Dioxides*. The adduct **52** from DAP and the thiirene dioxide **51** (Scheme 16) spontaneously extrudes sulfur dioxide with the formation of **53**.⁹³



SCHEME 16

⁹² T. Eicher and E. von Angerer, *Chem. Ber.* **103**, 339 (1970).

⁹³ M. Regitz and B. Mathieu, *Chem. Ber.* **113**, 1632 (1980).

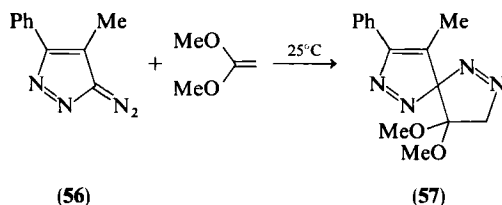


SCHEME 17

c. *Norbornadiene Analogs.* The adduct from furan and DMAD (54) forms a transient intermediate with DAP, which spontaneously extrudes furan, yielding quantitatively the 3H-pyrazole 55 (Scheme 17). Cycloaddition at the electron-deficient double bond in 54 was explained in terms of frontier orbital interactions.⁹⁴ 3H-Pyrazoles are transient intermediates in other related thermal cycloreversion reactions of pyrazolines.⁹⁵

2. From 3-Diazopyrazoles

1,1-Dimethoxyethene adds to the diazopyrazole 56, yielding the isolable spiro compound 57 (Scheme 18).⁹⁶



SCHEME 18

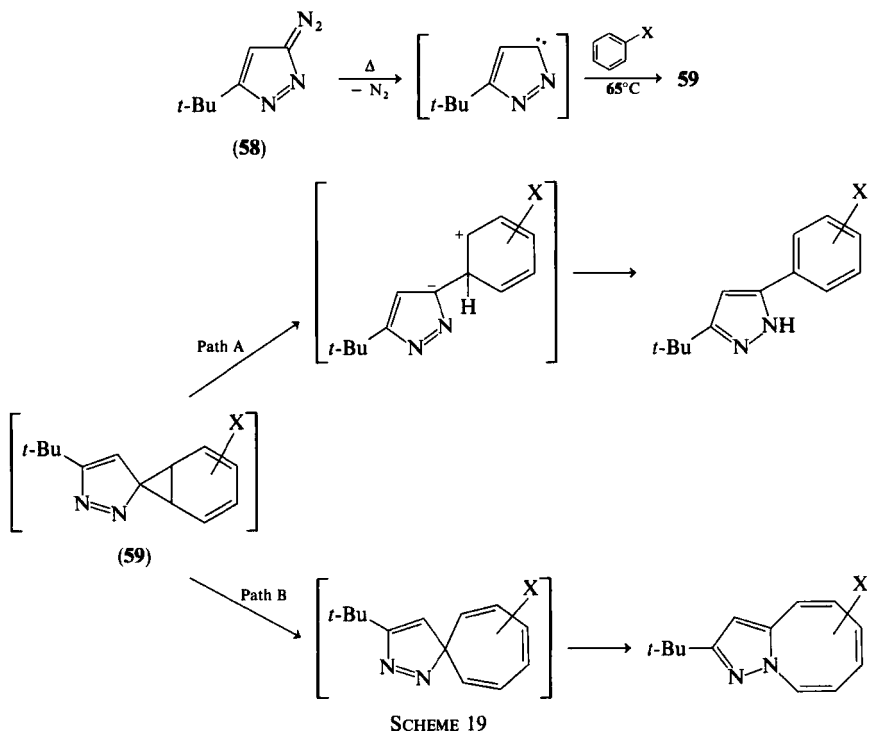
Thermolysis of 58 in the presence of substituted benzenes yields a transient 3H-pyrazole 59, which rearranges by two pathways, path A being favored by electron-donating X and path B by electron-withdrawing X (Scheme 19).⁹⁷

⁹⁴ D. Cristina, M. De Amici, and C. De Micheli, *Tetrahedron* **37**, 1349 (1981).

⁹⁵ J. C. Hinshaw and E. L. Allred, *J.C.S. Chem. Commun.*, 72 (1969); T. Toda, C. Tanigawa, A. Yamae, and T. Mukai, *Chem. Lett.*, 447 (1972).

⁹⁶ A. Padwa and T. Kumagai, *Tetrahedron Lett.* **22**, 1199 (1981).

⁹⁷ W. L. Magee and H. Shechter, *J. Am. Chem. Soc.* **99**, 633 (1977); *Tetrahedron Lett.* **20**, 4697 (1979).



D. BY CYCLIZATION OF VINYLDIAZO COMPOUNDS

1. Thermally

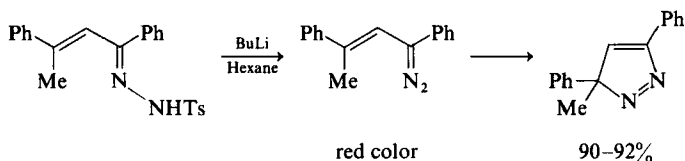
Ring closure of vinyldiazo compounds to 3*H*-pyrazoles is a thermally allowed process that competes with carbene formation via loss of N₂⁵¹ (see also Section IV,A,2). In a kinetic study it was shown that electron-withdrawing aryl substituents attached to the diazo carbon atom favor 3*H*-pyrazole formation.⁹⁸ The cyclization of **47** to **48** at -15°C (Scheme 15) is almost quantitative.⁹¹

Thermolysis of the tosylhydrazones of α,β -unsaturated ketones in the presence of alkoxide ion was found to give cyclopropenes⁹⁹ or 3*H*-

⁹⁸ J. A. Pincock and K. P. Murray, *Can. J. Chem.* **57**, 1403 (1979).

⁹⁹ G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.* **83**, 2015 (1961).

pyrazoles,¹⁰⁰ depending upon the solvent. Although an *N*-tosylpyrazoline was initially thought to be the intermediate,¹⁰⁰ the reaction was later shown to proceed via a vinyldiazo compound (Scheme 20).¹⁰¹



SCHEME 20

Vinyldiazo compounds are also formed by thermolysis of tosylhydrazone sodium salts in vacuo or in dry hydrocarbon solvents. Although these may cyclize to 3*H*-pyrazoles,¹⁰² the course of the reaction depends upon the nature of the substituents and, in the case of ring-fused systems, the size of the ring.^{103,104} Thus systems with a six-membered ring generally give 3*H*-pyrazoles (**60**, **61**), whereas those with five-membered rings may give alkenes, diazepines, or indenes (Scheme 21). The distance between the diazo group terminal nitrogen atom and the carbon atom bearing R¹ and R² (3.48 Å for six-membered and 3.82 Å for five-membered rings¹⁰³) is believed to be the determining factor. In the last example in Scheme 21, an intermediate distance (3.64 Å) results in intermediate behavior, 3*H*-pyrazole **62** being formed reversibly.¹⁰⁴

2. Photochemically

The sensitized photolysis of the tosylhydrazone **63** in the presence of sodium methoxide leads to **64** (Scheme 22), whereas unsensitized photolysis of both **63** and **64** gives a mixture of products (see Section IV, B, 2, b).¹⁰⁵

¹⁰⁰ G. L. Closs, L. E. Closs, and W. A. Böll, *J. Am. Chem. Soc.* **85**, 3796 (1963).

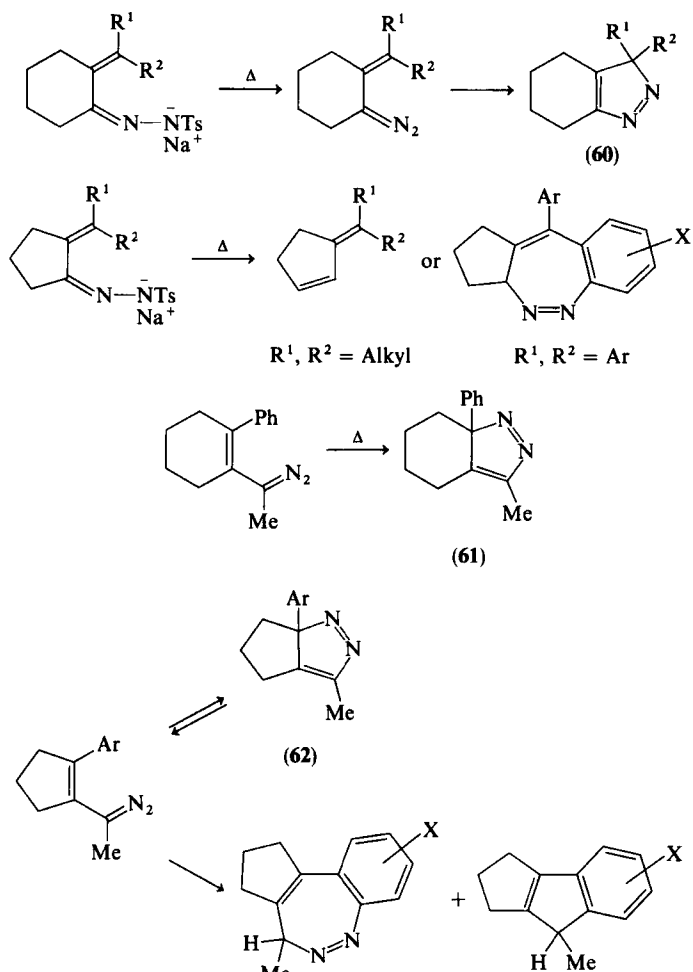
¹⁰¹ T. Sato and S. Watanabe, *Bull. Chem. Soc. Jpn.* **41**, 3017 (1968).

¹⁰² G. L. Closs and W. A. Böll, *Angew. Chem., Int. Ed. Engl.* **2**, 399 (1963).

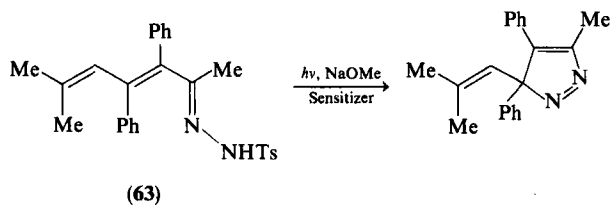
¹⁰³ R. H. Findlay, J. T. Sharp, and P. B. Thorogood, *J.C.S. Chem. Commun.*, 909 (1970); J. T. Sharp, R. H. Findlay, and P. B. Thorogood, *J.C.S. Perkin I*, 102 (1975).

¹⁰⁴ J. Dingwall and J. T. Sharp, *J.C.S. Chem. Commun.*, 128 (1975); K. L. M. Stanley, J. Dingwall, J. T. Sharp, and T. W. Naisby, *J.C.S. Perkin I*, 1433 (1979).

¹⁰⁵ H. E. Zimmerman and M. C. Hovey, *J. Org. Chem.* **44**, 2331 (1979).



SCHEME 21



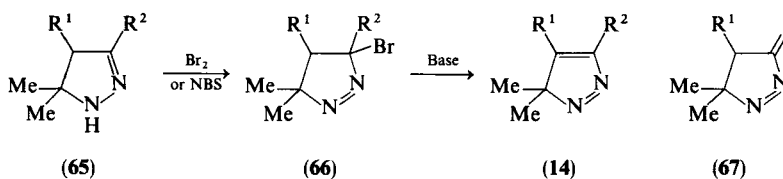
SCHEME 22

E. FROM PYRAZOLINES

1. By Oxidation

Δ^2 -Pyrazolines **65**, prepared from α,β -unsaturated ketones and hydrazine, give 3-bromo derivatives **66** (not *N*-bromo derivatives as reported earlier¹⁰⁶) with bromine or *N*-bromosuccinimide, which in turn eliminate HBr with base with the formation of 3*H*-pyrazoles **14** (Scheme 23).^{98,107-110} When $R^2 = \text{Me}$, methylenepyrazolines **67** are also formed. A new method uses manganese dioxide as the oxidizing agent, giving a yield >90%.^{110a}

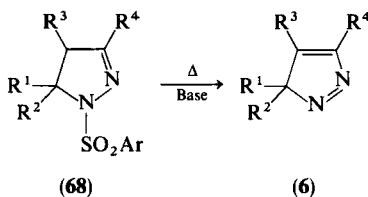
Direct bromination of a Δ^1 -pyrazoline in dichloromethane has been claimed to give a 3*H*-pyrazole in high yield, but no spectroscopic proof of structure was given.¹¹⁰



SCHEME 23

2. By Base Elimination of an *N*-Arylsulfonyl Group

N-Arylsulfonyl- Δ^2 -pyrazolines **68** on heating with base eliminate arylsulfonic acid to yield 3*H*-pyrazoles **6** (Scheme 24).¹¹¹ In some examples the



SCHEME 24

¹⁰⁶ J. Elguero and R. Jacquier, *C. R. Acad. Sci., Ser. C* **256**, 720 (1963).

¹⁰⁷ G. L. Closs and H. Heyn, *Tetrahedron* **22**, 463 (1966).

¹⁰⁸ W. M. Williams and W. R. Dolbier, Jr., *J. Am. Chem. Soc.* **94**, 3955 (1972).

¹⁰⁹ D. R. Arnold, R. W. Humphreys, W. J. Leigh, and G. E. Palmer, *J. Am. Chem. Soc.* **98**, 6225 (1976).

¹¹⁰ P. Schiess and H. Stalder, *Tetrahedron Lett.* **21**, 1417 (1980).

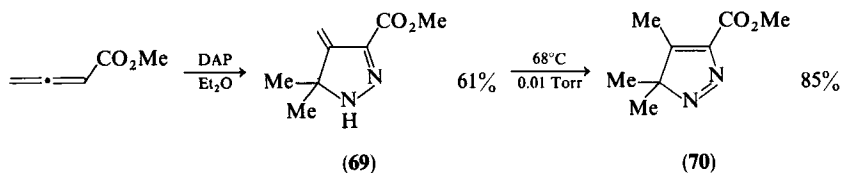
^{110a} M. Franck-Neumann and M. Miesch, *Tetrahedron Lett.* **23**, 1409 (1982).

¹¹¹ F. A. Gabitov, A. L. Fridman, and A. D. Nikolaeva, *Khim. Geterotsikl. Soedin.*, 234 (1972) [*CA* **76**, 140641d (1972)].

product is the rearranged 1*H*-pyrazole.¹¹²⁻¹¹⁴ When R⁴ = Me, products **67** are also formed.¹⁰⁷

3. By Thermal Rearrangement

The methylenepyrazoline **69**, formed from cycloaddition between an allenic ester and DAP, rearranges to **70** on slow distillation over glass wool (Scheme 25).¹¹⁵

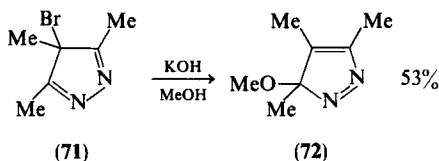


SCHEME 25

F. MISCELLANEOUS METHODS

1. From 4-Bromo-4*H*-pyrazoles

The bromo compound **71** (Scheme 26) on treatment with methanol and base is converted to the methoxy compound **72**.¹⁰⁷ A mechanism has been proposed.¹¹⁶



SCHEME 26

2. From a Tetrazolopyrimidine

Thermolysis of **73** leads via a nitrene and subsequent rearrangement to the 3-cyano compound **74** (Scheme 27) in low yield.¹¹⁷

¹¹² D. P. G. Hamon and L. J. Holding, *J.C.S. Chem. Commun.*, 1330 (1970).

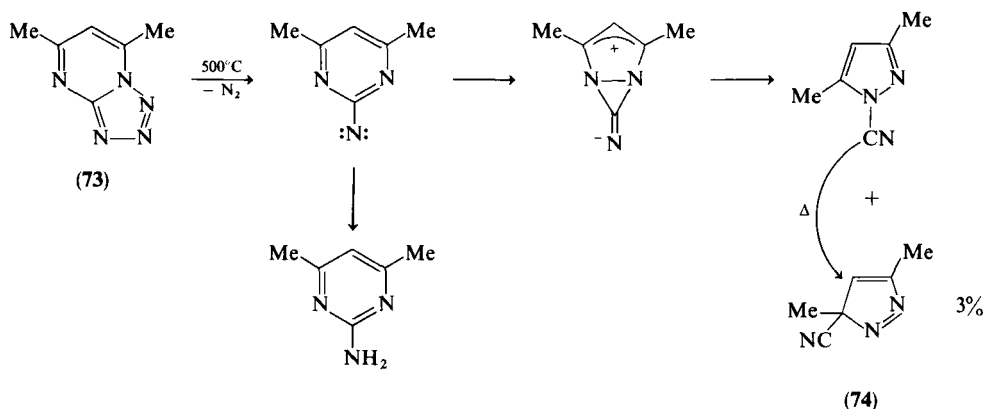
¹¹³ G. Ege, *Tetrahedron Lett.*, 1665 (1963).

¹¹⁴ M. Lempert-Sréter and K. Lempert, *Tetrahedron* **31**, 1677 (1975).

¹¹⁵ S. D. Andrews, A. C. Day, and R. N. Inwood, *J. Chem. Soc. C*, 2443 (1969).

¹¹⁶ P. Bouchet, J. Elguero, R. Jacquier, and F. Forissier, *C. R. Acad. Sci., Ser. C* **269**, 570 (1969).

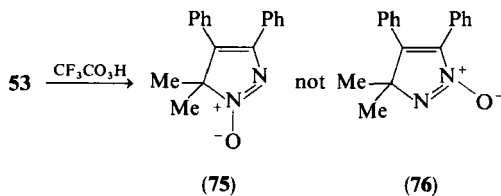
¹¹⁷ C. Wentrup and W. D. Crow, *Tetrahedron* **27**, 361 (1971).



SCHEME 27

G. METHODS FOR *N*-OXIDES1. *N*-Oxides

a. *By Oxidation of 3H-Pyrazoles.* Treatment of **53** with peracid gives only **75** with no **76** (Scheme 28).¹⁰⁸



SCHEME 28

b. *From Δ^1 -Pyrazoline *N*-Oxides.* The dichloro compound **77** on treatment with base gives **78** or **79** depending upon the conditions.^{118,119} Dehalogenation yields **80**,¹¹⁹ which is also formed on base treatment of **81**¹²⁰ (Scheme 29).

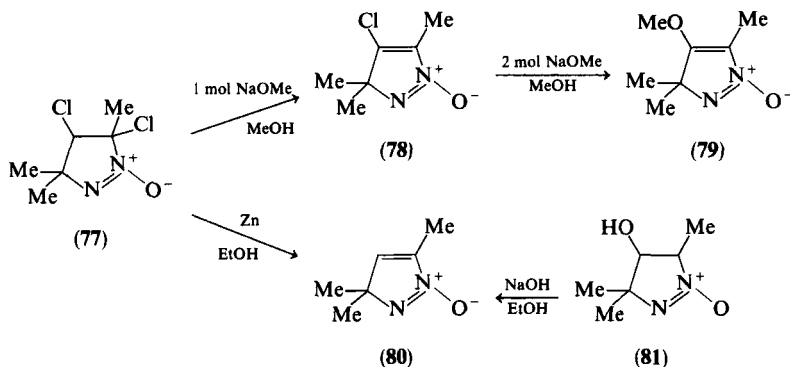
The isomer (**83**) of **80** results from base elimination of benzoic acid at 20°C from **82**.^{119,121} Fragmentation occurs at 50°C (Scheme 30).

¹¹⁸ R. Fusco and G. Trisoglio, *Atti Accad. Naz. Ital., Cl. Sci. Fis., Mat. Nat., Rend.* [7] **2**, 751 (1941) [*CA* **38**, 2927⁹ (1944)].

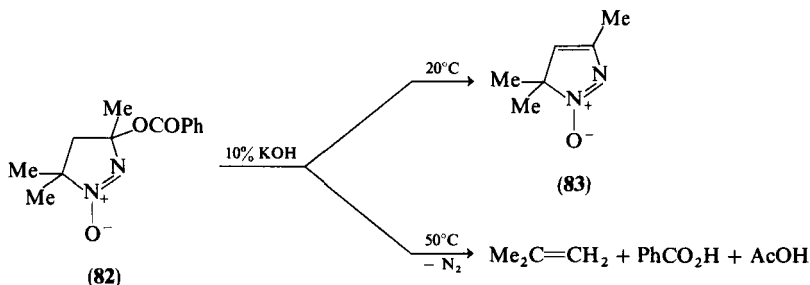
¹¹⁹ J. P. Freeman, *J. Org. Chem.* **27**, 1309 (1962).

¹²⁰ J. P. Freeman, *J. Org. Chem.* **27**, 2881 (1962).

¹²¹ J. P. Freeman, *Tetrahedron Lett.*, 749 (1961).



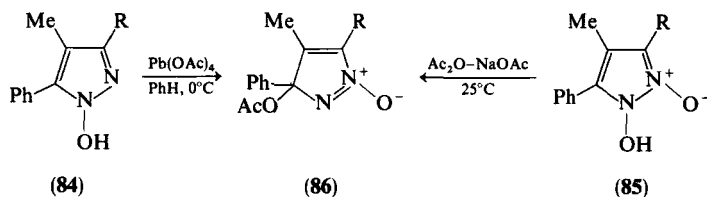
SCHEME 29



SCHEME 30

c. *From N-Hydroxypyrazole Derivatives.* Lead tetraacetate oxidation of **84** or acylation of **85** gives the *N*-oxides **86**.¹²² 3-*p*-Nitrobenzoyloxy derivatives were also prepared (Scheme 31).

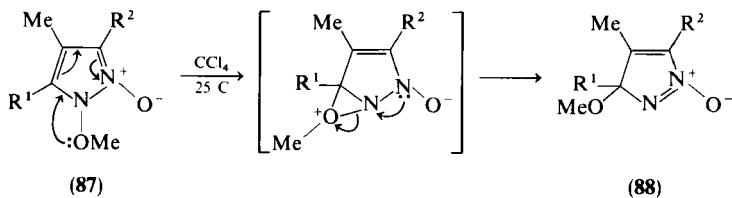
The *N*-methoxy compounds **87** (Scheme 32) rearrange thermally to the 3-methoxy isomers **88**.¹²³



SCHEME 31

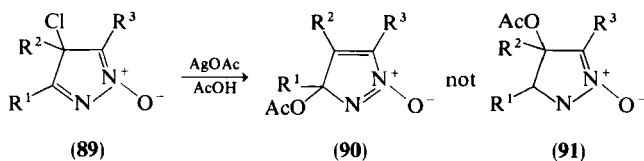
¹²² J. P. Freeman and J. J. Gannon, *J. Heterocycl. Chem.* **3**, 544 (1966); *J. Org. Chem.* **34**, 194 (1969).

¹²³ F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin I*, 167 (1973).



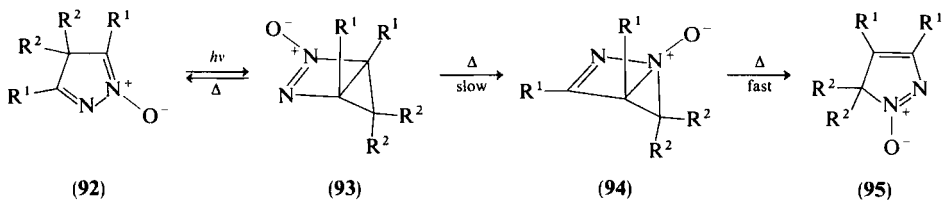
SCHEME 32

d. *From 4H-Pyrazole N-Oxides.* The chloro *N*-oxides **89** with silver acetate yield the 3*H*-acetoxy compounds **90**,¹²⁴ thought earlier¹²⁵ to be the 4*H*-isomers **91** (Scheme 33). The reaction is believed to proceed via a cyclic cation, although an $\text{S}_{\text{N}}2$ mechanism is possible.



SCHEME 33

Photolysis of the *N*-oxides **92** in dichloromethane results in rearrangement to the isomers **95** via the bicycles **93** (detectable by ^1H -NMR at -78°C) and **94** (Scheme 34).^{108,126} In refluxing methanol, **95** is still the main product, but at -55°C the intermediate **93** is attacked by the solvent to give an open-chain oxime.¹²⁷



SCHEME 34

¹²⁴ J. P. Freeman, E. R. Janiga, and J. F. Lorenc, *J. Org. Chem.* **42**, 3721 (1977).

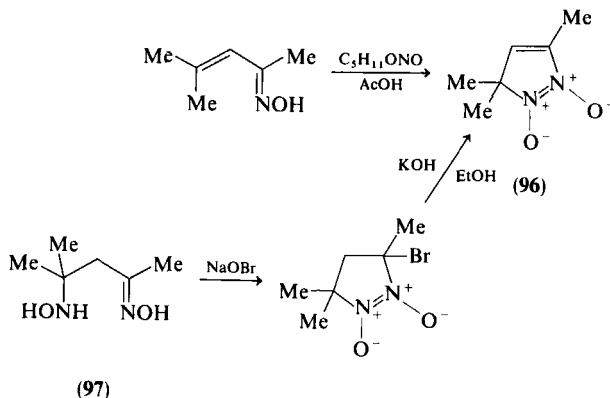
¹²⁵ J. P. Freeman and E. R. Janiga, *J. Org. Chem.* **39**, 2663 (1974).

¹²⁶ W. R. Dolbier, Jr. and W. M. Williams, *J.C.S. Chem. Commun.*, 289 (1970).

¹²⁷ R. Paredes and W. R. Dolbier, Jr., *Rev. Latinoam. Quim.* **6**, 29 (1975) [*CA* **83**, 8773p (1975)].

2. *N,N'*-Dioxides

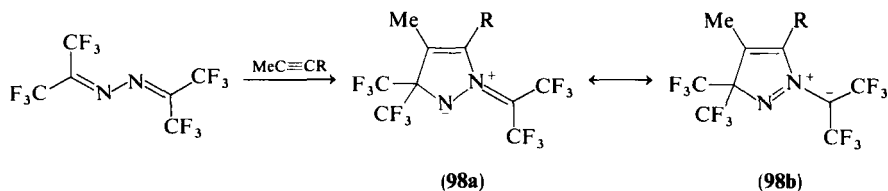
Nitrosation of mesityl oxide oxime leads to the dioxide **96**, correctly formulated by Freeman.¹¹⁹ Earlier workers had formulated the product as a nitrimine¹²⁸ and as a nitrosonitrone.¹¹⁸ Hypobromite oxidation of **97** leads to the same compound¹²⁹ (Scheme 35), whereas the 4-bromo analog of **96** has been prepared by base elimination of HBr from a dibromopyrazoline *N,N'*-dioxide precursor.¹¹⁹



SCHEME 35

H. *N*-YLIDES

Cycloaddition between hexafluoropropanone azine and electron-rich alkynes leads to the *N*-ylides **98** (Scheme 36), stable only in hexane at low temperature.^{130,131}



SCHEME 36

¹²⁸ C. D. Harries and R. Gley, *Ber. Dtsch. Chem. Ges.* **32**, 1330 (1899).

¹²⁹ L. B. Voldarskii and L. A. Tikhonova, *Khim. Geterotsikl. Soedin.*, 248 (1977) [CA **87**, 23135h (1977)].

¹³⁰ K. Burger, H. Schickaneder, F. Hein, and J. Elguero, *Tetrahedron* **35**, 389 (1979).

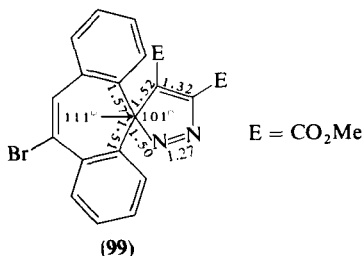
¹³¹ K. Burger and F. Hein, *Liebigs Ann. Chem.*, 133 (1979).

III. Structure and Physical Properties

A. STRUCTURE

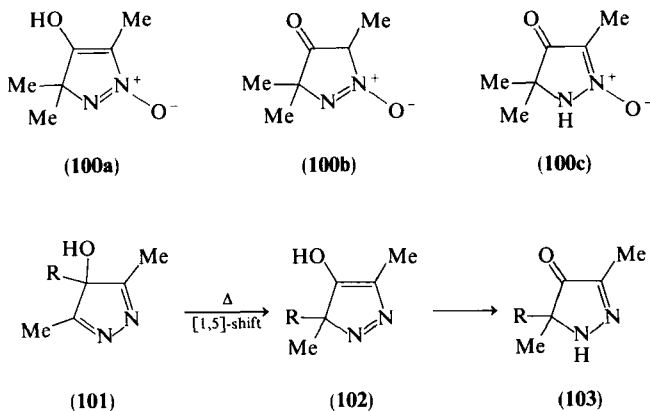
1. X-Ray Crystallography

Only one structure (**99**) based on X-ray crystallography has been reported, with incomplete data. Angles are in degrees, and bond lengths in Å.¹³²



2. Tautomerism

Where keto-enol tautomerism is possible, not surprisingly the keto form is preferred. Thus of three possible tautomeric structures **100**,¹¹⁸ IR and UV data favor **100c**.¹²⁰ Likewise, rearrangement of the 4-hydroxy-4*H*-pyrazoles **101** gives the pyrazolones **103** via the enols **102** (Scheme 37).¹³³



SCHEME 37

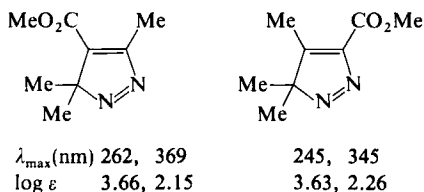
¹³² Unpublished results, quoted in H. Dürr and R. Gleiter, *Angew. Chem., Int. Ed. Engl.* **17**, 559 (1978).

¹³³ J. E. Baldwin, O. W. Lever, Jr., and N. R. Tzodikov, *J. Org. Chem.* **41**, 2874 (1976).

B. SPECTROSCOPIC PROPERTIES

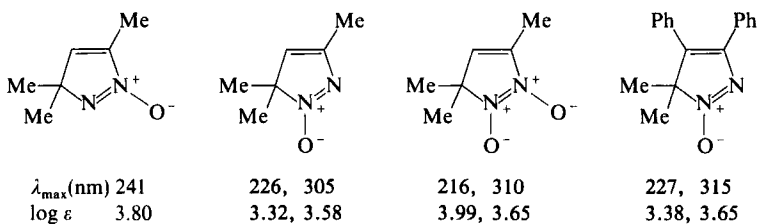
1. Ultraviolet Spectra

3*H*-Pyrazoles bearing simple nonconjugating substituents show two regions of absorption (hexane): near 245 nm ($\log \epsilon = \sim 3.3$) attributed to the C=C bond $\pi \rightarrow \pi^*$ transition, and near 355 nm ($\log \epsilon = \sim 2.4$) attributed to the N=N bond $n \rightarrow \pi^*$ transition.^{43,51,52,62,102} On changing the solvent to ethanol, the $\pi \rightarrow \pi^*$ band moves to longer wavelength, and the $n \rightarrow \pi^*$ band to shorter wavelength, each by ~ 10 nm; $\log \epsilon$ shows little change.^{51,52,66,107} For isomeric compounds bearing a conjugating substituent, the more conjugated isomer shows a bathochromic shift for both bands relative to the less conjugated form (Scheme 38).^{57,62,66,68} The effect of phenyl conjugation is not clear.



SCHEME 38

For *N*-oxides the absorption pattern depends on the position and number of oxygen atoms (Scheme 39).¹¹⁹ Substitution of two phenyl groups at the C=C bond has little effect on either $\lambda_{\max}$ or $\log \epsilon$.^{108,126}



SCHEME 39

2. Infrared Spectra

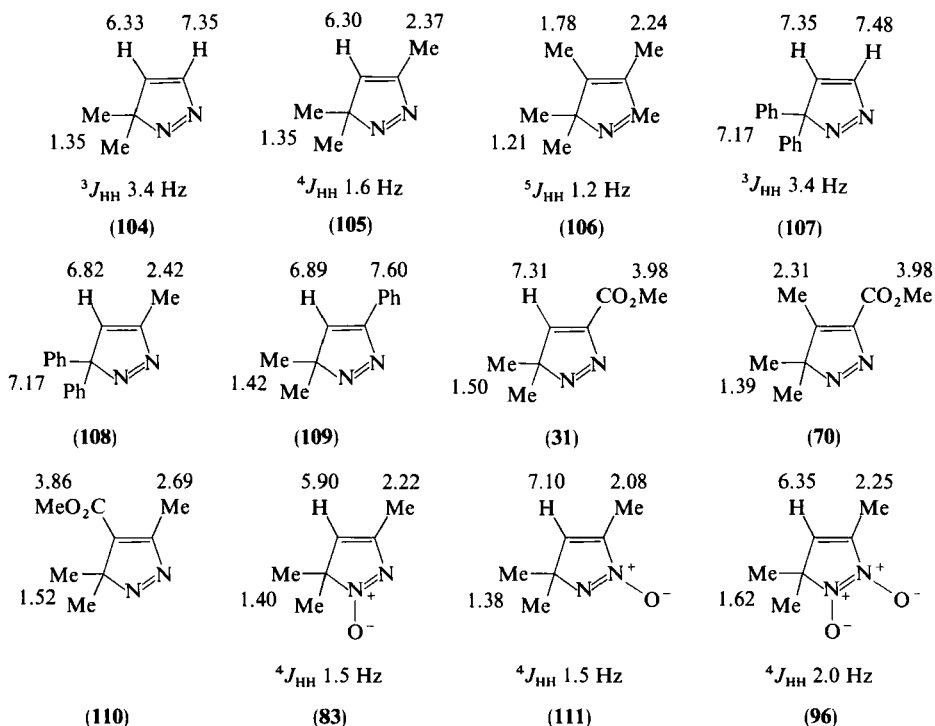
When unsubstituted at the C=C bond, 3*H*-pyrazoles absorb at 3080 and 1565 cm^{-1} .⁴³ With one conjugating acyl^{49,62} or ester^{62,65,66} group, the ring absorption (variously assigned to $\nu_{\text{N=N}}$ ^{66,93} and $\nu_{\text{C=C-N=N}}$ ⁶²) moves, respectively, to near 1600 cm^{-1} and 1625 cm^{-1} . It is found between 1620 and

1650 cm^{-1} in compounds disubstituted at the $\text{C}=\text{C}$ bond^{47,62,63,65,66,68,82,122} but does not seem to be useful for identifying the more conjugated of a pair of isomers. Such isomers may be distinguished by $\nu_{\text{C}=\text{O}}$, the band appearing at lower frequency in the more conjugated form,^{59,65,66} although there appears to be an exception to this.⁶⁸

In *N*-oxides, a common peak near 1500 cm^{-1} has been assigned to the fragment $\text{N}=\text{N}^+-\text{O}^-$ ^{119,122,126} while in *N,N'*-dioxides the $\text{O}-\text{N}^+=\text{N}^+-\text{O}$ moiety gives rise to a peak near 1480 cm^{-1} ^{119,129,134} and apparently also near 1380 cm^{-1} .¹²⁹ Absorption near 1630 cm^{-1} has been assigned to $\nu_{\text{C}=\text{C}}$.¹¹⁹

3. ¹H-NMR Spectra

The relationship between structure and ¹H-NMR spectra (CDCl_3 or CCl_4 , δ relative to Me_4Si) are illustrated for 3*H*-pyrazoles **104**,⁴³ **105**,¹⁰² **106**,¹⁰⁷ **107**,⁴³ **108**,⁴⁵ **109**,¹⁰⁷ **31**, **70**, and **110**⁶⁶; and for *N*-oxides **83**, **111**, and **96**.¹¹⁹ A *gem*-



¹³⁴ E. G. Bozzi and L. B. Clapp, *J. Heterocycl. Chem.* **15**, 1525 (1978).

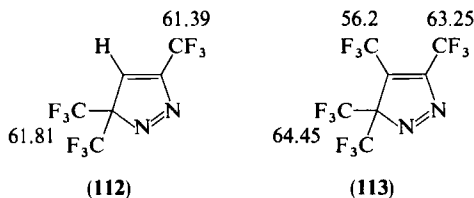
dimethyl signal appears to be shifted ~ 0.1 ppm upfield by a methyl group on the adjacent carbon atom; a number of data have been published for isomeric 3*H*-pyrazoles.^{11,62,68} The large difference in the ring proton chemical shift between the *N*-oxides **83** and **111** suggests a method for distinguishing isomers.

4. ¹³C-NMR Spectra

A selection from the few published ¹³C chemical shifts for 3*H*-pyrazoles are given in Table II. No data appear to have been recorded for *N*-oxides. The signal due to the tetrahedral C-3 lies between δ 93 and δ 110, the lower field values being observed when it is aryl-substituted, or when it forms part of a five-membered ring. Signals for C-4 and C-5 appear over ranges of 30 and 40 ppm, respectively, δ values being very sensitive to the nature of the ring substituents.

5. ¹⁹F-NMR Spectra

Few examples of ¹⁹F chemical shifts have been reported.^{13,14} Chemical shifts (ppm upfield from CFCl₃) for **112** and **113** are shown.¹⁴ The ring proton in **112** shows coupling with the fluorine atoms of the *gem*-(CF₃)₂ group (2.4 Hz) and with the CF₃ group at C-5 (5.7 Hz).



6. Mass Spectra

The parent ion is observable in most of the spectra that have been recorded, and in some instances it is the base peak. An $M^+ - 28$ ion also appears in most examples,^{11,16,30,43,103,104,135} accurate mass measurements having shown this to arise from loss of N₂.¹⁰³ Breakdown patterns for three substituted aryl derivatives (**62**, Scheme 21) are essentially the same as for their benzodiazepine isomers.¹⁰³ Some examples have been reported in which extrusion of a disubstituted alkyne by a reverse 1,3-dipolar cycloaddition reaction is an important process.¹³⁵

¹³⁵ H. Dürr, H. Kober, R. Sergio, and V. Formacek, *Chem. Ber.* **107**, 2037 (1974).

TABLE II
¹³C CHEMICAL SHIFTS FOR RING CARBON ATOMS AND SUBSTITUENTS IN SELECTED 3*H*-PYRAZOLES

Substituents				Chemical shift ^a						Reference
R ²	R ³	R ⁴	R ⁵	C-3	C-4	C-5	R ²	R ⁴	R ⁵	
	(CH ₂) ₅		(CH ₂) ₅	93.1	151.6	153.2	—	—	—	103
Me	Ph		(CH ₂) ₅	96.7	152.4	152.9	19.1	—	—	103
Ph	Ph	H	Me	105.5	137.5	153.3	—	—	13.0	103
Ph		(CH ₂) ₄	Me	110.2	148.5	168.8	—	—	11.6	104
Ph		(CH ₂) ₅	Me	99.8	147.5	150.7	—	—	11.1	104
Me	Me	H	CO ₂ Me	95.3	154.5	147.0	19.8	—	161.5	135
Me	Me	CN	Me	97.7	125.2	160.6	20.5	112.8	13.2	135
Me	Me	CN	CN	101.0	141.2	132.5	20.0	109.9 ^b	109.3 ^b	135
Ph	Ph	CO ₂ Me	CO ₂ Me	110.4	152.7	146.7	—	163.3 ^b	160.5 ^b	135
2,2'-Biphenylene		CO ₂ Me	CO ₂ Me	109.8	149.0	148.4	—	161.8 ^b	160.3 ^b	135
2,2'-Biphenylene		CN	CN	108.4	144.2	129.6	—	111.9 ^b	109.5 ^b	135

^a In CDCl₃, downfield from Me₄Si.

^b Assignments may be interchanged.

7. Photoelectron Spectra

The dihedral angle between the lone pairs on the two nitrogen atoms in the tetramethylpyrazole **106** has been shown by PE spectroscopy to be 0° .¹³⁶

IV. Reactions of 3H-Pyrazoles

A. THERMAL REACTIONS FORMALLY INVOLVING NO OTHER SPECIES

The most widely studied thermal reaction has been the van Alphen-Hüttel rearrangement, which gives 1H-pyrazoles, and is named from separate reports by van Alphen^{18,64} in 1943 and Hüttel^{10,137} in 1960; in an earlier paper the latter⁵⁸ had failed to recognize that a rearrangement had occurred. A second important reaction is thermal ring opening, followed by loss of nitrogen to give a cyclopropene or other products.

1. The van Alphen-Hüttel Rearrangement

The van Alphen-Hüttel rearrangement involves the migration of a substituent from the tetrahedral carbon atom (C-3) to another ring carbon or nitrogen atom, either thermally (with or without solvent), or under acid- or base-catalyzed conditions. In a number of cycloadditions between diazo compounds and alkynes (Section II,A), the migration occurred under the conditions of the reaction, either to carbon^{19,23,46,50,138-140} or to nitrogen^{8,9,27,29,31-33,36-39,47} or to both,²⁸ giving a rearranged 1H-pyrazole directly, rather than the cycloadduct 3H-pyrazole.

From a study of his and van Alphen's results, Hüttel identified three classes of rearrangement (Scheme 40).¹³⁷ Type A involved migration of a group from C-3 to unsubstituted C-4 (e.g., **114** → **115**⁶⁴), Type B an acyl migration from C-4 or C-5 to N (e.g., **116** → **117**⁶⁴ or **118** → **117**¹³⁷), and Type C an aryl migration from C-3 to N (e.g., **118** → **119**¹³⁷); the latter two modes were observed when all carbon atoms were fully substituted.

The observation that spontaneous rearrangement of some spiro-3H-pyrazoles led to isolable 4H-pyrazole derivatives (e.g., **120** → **121**, Scheme 41),^{15,16} was followed by the discovery¹⁴¹ that **122** rearranges in boiling acetic

¹³⁶ P. Rademacher, *Angew. Chem., Int. Ed. Engl.* **12**, 408 (1973).

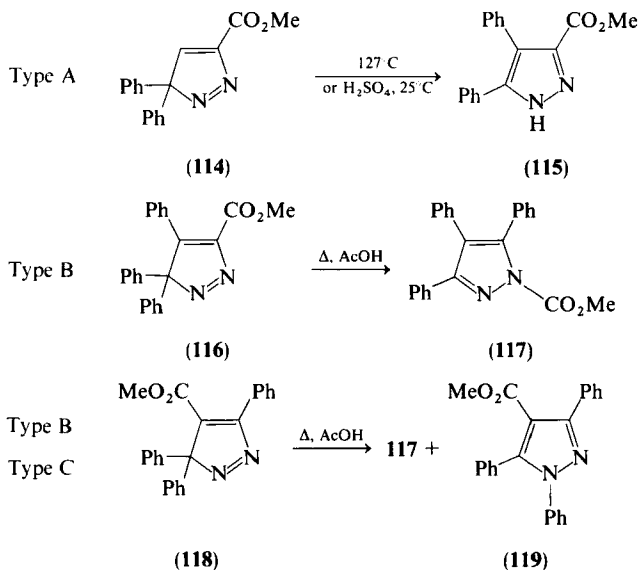
¹³⁷ R. Hüttel, K. Franke, H. Martin, and J. Riedl, *Chem. Ber.* **93**, 1433 (1960).

¹³⁸ W. Kirmse and L. Horner, *Justus Liebigs Ann. Chem.* **614**, 1 (1958).

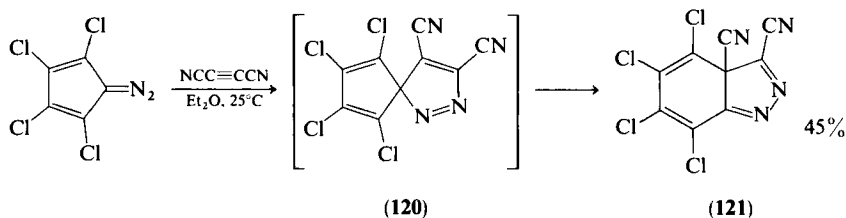
¹³⁹ D. J. Cram and R. D. Partos, *J. Am. Chem. Soc.* **85**, 1273 (1963).

¹⁴⁰ S. Mataka, T. Ohshima, and M. Tashiro, *J. Heterocycl. Chem.* **19**, 65 (1982).

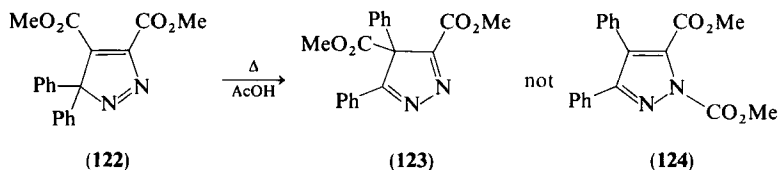
¹⁴¹ R. Baumes, J. Elguero, R. Jacquier, and G. Tarrago, *Tetrahedron Lett.*, 3781 (1973).



SCHEME 40

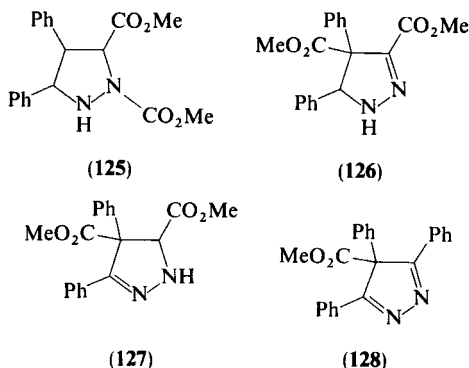


SCHEME 41



SCHEME 42

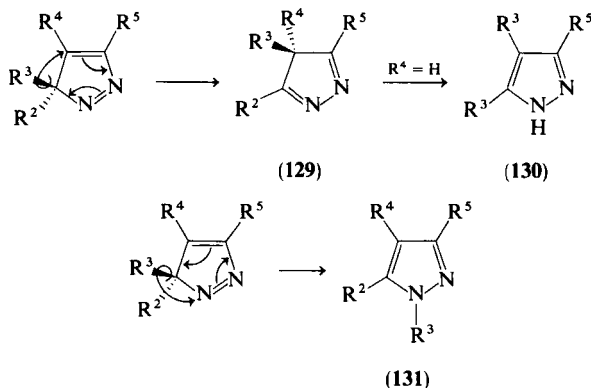
acid to the 4*H*-pyrazole **123** (Scheme 42), and not to the 1*H*-pyrazole **124**, as formulated by other workers.^{33,64} The structural proof of **124** had been established from its zinc-acetic acid reduction product, claimed to be **125**, on account of its forming only a mononitroso derivative,⁶⁴ but later shown to be a mixture of **126** and **127**.¹⁴¹



Subsequently, the rearrangement product of **118**, formulated earlier as **117**, was also shown by two independent groups to be **128**, proving *4H*-pyrazoles to be major products from the van Alphen-Hüttel rearrangement.^{70,80,142,143}

a. *The Mechanism of the Reaction.* Formation of the three types of products has been accommodated in terms of competitive suprafacial [1,5]-shifts by a substituent at C-3 (Scheme 43).¹⁴¹ Migration to C-4 gives a *4H*-pyrazole **129** (Hüttel Type B) or a *1H*-pyrazole **130** by subsequent prototropic shift when $R^4 = H$ (Hüttel Type A). Migration to N gives a *1H*-pyrazole **131** (Hüttel Type C).

It has been suggested that the thermal rearrangement proceeds via a radical pair, whereas the acid-catalyzed process is via a radical-radical cation



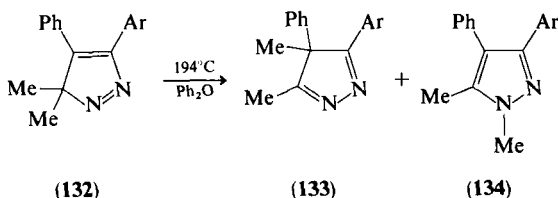
SCHEME 43

¹⁴² R. R. Bekmukhametov, *Sovrem. Probl. Khim.*, 61 (1973) [CA **81**, 136042v (1974)].

¹⁴³ M. I. Komendantov and R. R. Bekmukhametov, *Khim. Geterotsikl. Soedin.*, 79 (1975) [CA **82**, 111337c (1975)].

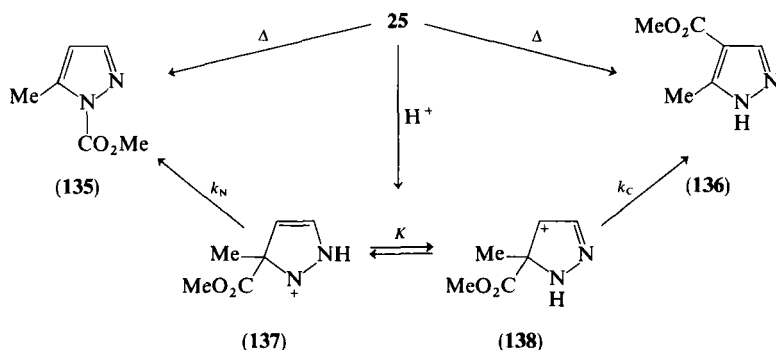
pair. Further, calculated coefficients for the HOMO and LUMO of the radicals and the radical cations predict that migration of phenyl to N should be preferred in the thermal process and to C-4 in the acid-catalyzed process.¹⁴³

In one kinetic study (Scheme 44), the ratio **133**:**134** (Ar = Ph) was 10:1, activation parameters being $E_a = 149 \pm 5$ kJ/mol and $\Delta S^\ddagger = -29 \pm 10$ J/mol/K for **133**, and $E_a = 143 \pm 3$ kJ/mol and $\Delta S^\ddagger = -23 \pm 7$ J/mol/K for **134**.¹⁴⁴ In addition, the rate was unaffected by added base and relatively insensitive to the substituent on Ar, indicating a concerted process. The 4*H*-isomer **133** was believed to be favored by decreasing steric interaction between Ph and Ar and increasing Ar conjugation in the transition state. The fact that **134** was a minor product suggested that its aromaticity must develop late in the rearrangement process.¹⁴⁴



SCHEME 44

In another study, **25** was found to rearrange to a mixture of **135** and **136** (Scheme 45).⁸⁴ In the thermal reaction, **136** increased at the expense of **135** with increasing solvent polarity, showing that migration to C involved a more polar transition state. With increasing acid concentration [trifluoroacetic acid (TFA) in dioxane] the rate of reaction increased rapidly, and the isomer ratio **135**:**136** changed from 78:22 in pure dioxane to 10:90 in 5 *M*

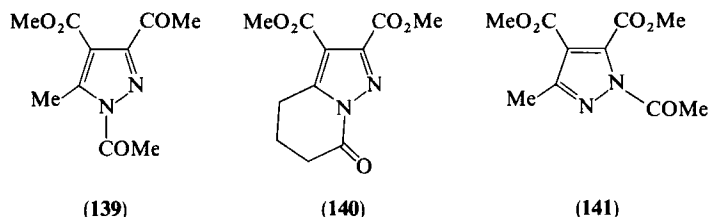


SCHEME 45

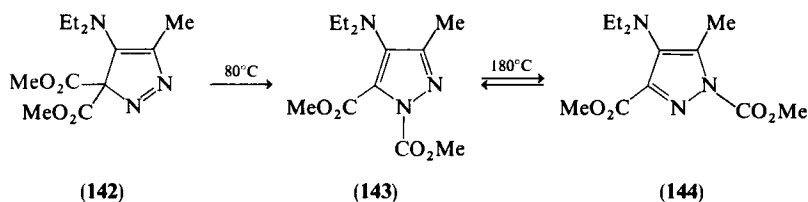
¹⁴⁴ W. J. Leigh and D. R. Arnold, *Can. J. Chem.* 57, 1186 (1979).

TFA. Rearrangement was believed to proceed via **137** and **138**, the ratio **135**:**136** depending upon K , and also on k_N and k_C .⁸⁴ The same authors in a related study concluded that there was substantial charge transfer in the transition state of acid catalyzed rearrangements, as compared with those in neutral media.¹¹⁰

b. Acyl or Organometallic Group at C-3. When the ring carbon atoms are fully substituted, migration of acyl, nitrile, sulfonyl, or organometallic groups has been exclusively to N.^{9,27-34,36-38,90,91} When the two C-3 substituents are different, acyl migrates more readily than alkyl,^{9,27,28,32} benzyl,^{31,119} or aryl,³¹ although nitrile⁹⁰ and sulfonyl³⁴ take precedence over carboxyalkyl. In refluxing ether, migratory aptitudes were reported as $\text{Me}_3\text{Sn} > \text{Me}_3\text{Si} > \text{H} > \text{CO}_2\text{Et}$ ³⁷; the apparent thermal stability of some trimethyllead derivatives conflicts with this.⁴⁰



That migration was by a single [1,5]-shift to the adjacent nitrogen atom was shown by the isolation of **139** (very similar spectroscopic properties to authentic **140**) rather than **141** from the reaction between DMAD and 3-diazo-2-butanone.²⁷ In one case a mixture of products from migration to both nitrogen atoms was observed⁹⁰ and in another the mixture was found to exist in equilibrium at 180°C (Scheme 46).³⁴ The same authors converted **142** directly to **144** by the catalytic action of $\text{Ph}_2\text{C}=\text{C}=\text{O}$, PhNCO , or PhNCS , the relative rates of the two steps for this process depending upon the catalyst.¹⁴⁵



SCHEME 46

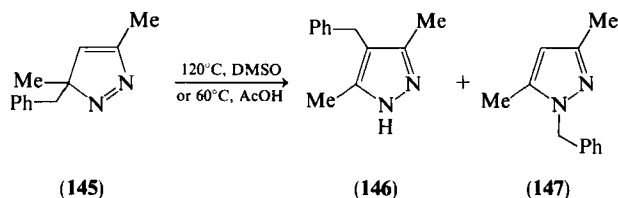
¹⁴⁵ H. U. Reussig and R. Huisgen, *J. Am. Chem. Soc.* **101**, 3648 (1979).

For rings unsubstituted at C-4, competitive migration occurs, giving a mixture of **130** and **131**. Under neutral conditions migration of carbo-methoxy and acetyl groups was predominantly to C-4,²⁸ although later workers observed the opposite.^{84,110} The difference may arise from the electronic nature of the substituent at C-5: acyl and nitrile in one case²⁸ and hydrogen⁸⁴ or methyl¹¹⁰ in the others. The rate of migration of the carbo-methoxy group decreases considerably in acidic media, and the ratio of products **130**:**131** changes dramatically^{84,110} (see also Section IV,A,1,a).

One rearrangement in the reverse sense is the formation of **74** from its *N*-cyano isomer (Scheme 27).¹¹⁷

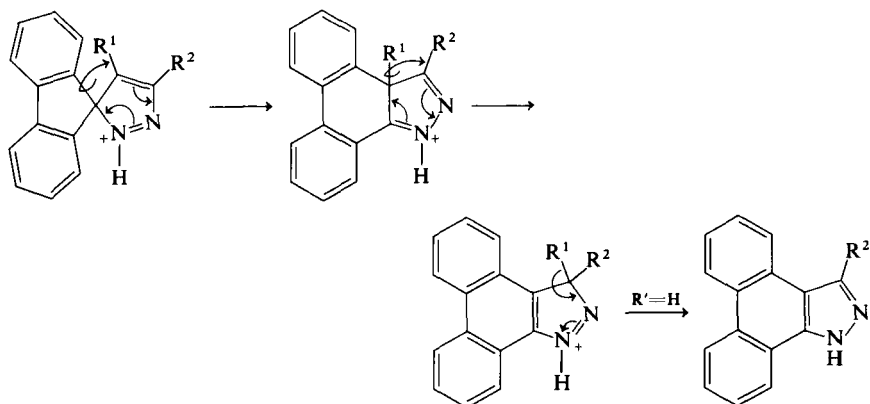
c. Aryl, Benzyl, or Alkyl Group at C-3. When C-4 is unsubstituted, alkyl and aryl groups have migrated exclusively to this atom, giving 1*H*-pyrazoles **130**.^{10-12,15,18,19,43,46,53,64,74,86,101,107,110,113,114,137,138} Ethyl migrates more rapidly than methyl, the difference being more pronounced in acid.¹¹⁰ Aryl groups migrate to the exclusion of alkyl groups,^{10-12,101,114,137} which themselves move only at high temperatures.^{28,86,103} For para substituents on aryl groups, the order of migratory aptitude was found to be $\text{Me}_2\text{N} \gg \text{H} > \text{Br}$.¹³⁷

The benzyl group is exceptional, **145** giving both **146** and **147** (Scheme 47) in a ratio of $\sim 2:1$ in neutral and acidic media, although in the latter medium the rate was greatly enhanced.¹¹⁰

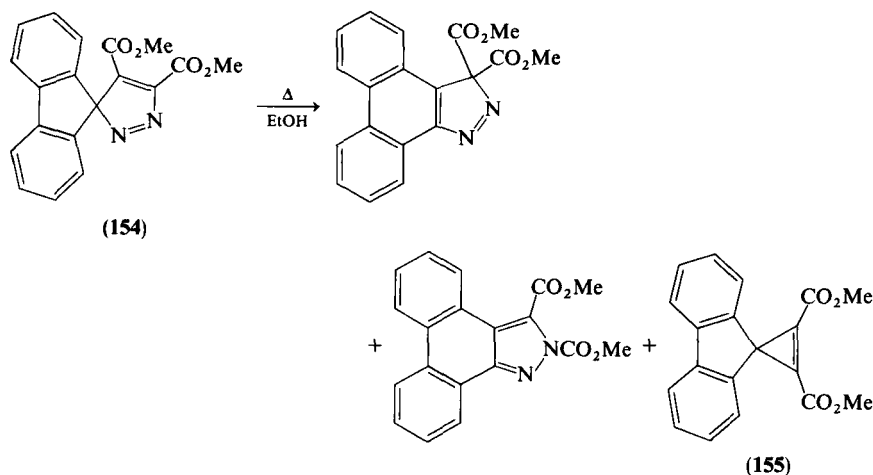


SCHEME 47

For the cases where all carbon atoms are fully substituted, competitive migration occurs to C and N, giving **129** (or its degradation products) and **131**. Normally, both products are observed, R^3 having been aryl,^{18,59,64,67,68,70,80,142,143} and in one example methyl.¹⁴⁴ In some instances only the product from migration to carbon was observed,^{11,15,16,104,141} whereas in others, only the N-substituted product.^{15,16,47,92} Some examples are shown (Scheme 48)^{47,59,104}; the unexpected isolation of **153** rather than **151** from rearrangement of **152** was explained in terms of steric inhibition of phenyl migration by the cyclohexane axial protons.¹⁰⁴



SCHEME 49



SCHEME 50

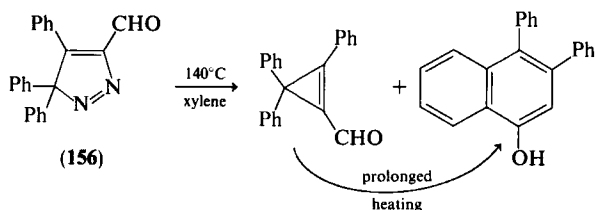
and ethyne, or three-piece fragmentation to triplet methylene, nitrogen, and ethyne.¹⁴⁷

In contrast, electrocyclic ring opening to give a vinylldiazo compound can be a favorable thermal process under certain circumstances and can compete with the van Alphen-Hüttel rearrangement when, e.g., ring substituents have low migratory aptitudes.^{13,14,98} It appears to occur most readily, however, when it results in release of steric constraint in the 3H-pyrazole as in **62** (Scheme 21),¹⁰⁴ and particularly when the resulting vinylldiazo compound is stabilized by extensive conjugation. This is true in the case of structures related to **154**; in extreme examples, cycloaddition between an alkyne and the

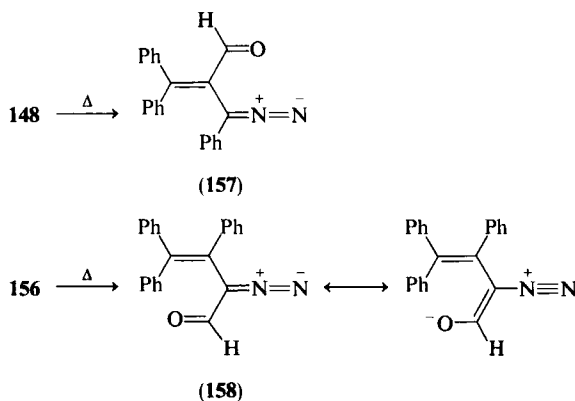
¹⁴⁷ A. J. Paine and J. Warkentin, *Can. J. Chem.* **59**, 491 (1981).

diazofluorene derivative yields only the vinyldiazo compound, unless steric constraints inhibit ring opening.^{21,23} The unstable red "spiro-3*H*-pyrazole" isolated by van Alphen from methyl propynoate and diazofluorene was thus probably the ring-opened diazo ester.¹⁸

Generally, a cyclopropene is the end result, often being the only product, and arising from loss of nitrogen followed by cyclization of the vinylcarbene. Its formation from the 3*H*-pyrazole can occur spontaneously at room temperature,^{19,20} although heating is normally required^{13,14,19,20,22,23,92,98,146,148} in line with the positive $\Delta S^\ddagger$ for the reaction.⁹⁸ At high temperatures, products from further rearrangement of the cyclopropene may be isolated.^{20,146,148} In some cases both cyclopropene and products from the van Alphen-Hüttel rearrangement have been observed (e.g., Scheme 50).^{22,23,143,146} Formation of the latter appears to be favored by polar solvents,^{22,23,146} cyclopropenes not being observed at all under acidic conditions^{143,144} but often being the major products in hydrocarbon solvents. The remarkable difference in behavior between **148** (Scheme 48) and its isomer **156** (Scheme 51) on thermolysis⁹⁹ probably arises from the stabilizing effect of the aldehyde group in **158**, absent in **157** (Scheme 52).



SCHEME 51



SCHEME 52

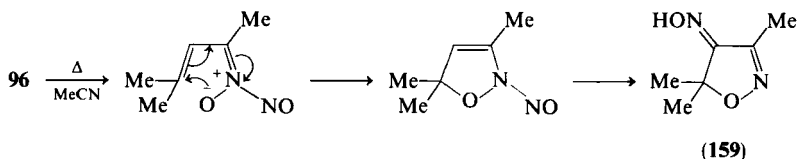
¹⁴⁸ H. Dürr, W. Schmidt, and R. Sergio, *Justus Liebigs Ann. Chem.* 1132 (1974).

Vinyldiazo compounds from ring opening can also be converted to diazepines and indenenes (Scheme 21)¹⁰⁴ and, by flash vacuum pyrolysis (450°C), to 1,3-dienes.¹⁰³

3. Other Thermal Processes

On standing at 25°C, the spiro-3*H*-pyrazole **57** is converted via an isolable 3-azopyrazole to a pyrazolotriazine.⁹⁶ Pyridazines have been prepared both from a 4-vinyl-3*H*-pyrazole by heating in acetic acid⁹² and from a 3-phenacyl-3*H*-pyrazole in strong base.¹¹⁴

The dioxide **96** rearranges to the isoxazolone oxime **159** (Scheme 53) in boiling acetonitrile.¹¹⁹



SCHEME 53

B. PHOTOCHEMICAL REACTIONS FORMALLY INVOLVING NO OTHER SPECIES

1. Processes Involving Loss of Nitrogen

Photolysis of dilute solutions (~0.5%) of 3*H*-pyrazoles in certain dry solvents (e.g., benzene, ether, or pentane), under nitrogen and at the wavelength of the ring $n \rightarrow \pi^*$ transition, results in loss of nitrogen and the formation of a cyclopropene. Irradiation is generally carried out in quartz or pyrex apparatus, using a high or medium pressure Hg lamp; radiation < 290 nm is filtered out. The cyclopropene is often the only product and may be isolated in high to quantitative yield (e.g., Scheme 54⁷⁵), making this a major preparative method.^{24,25,43,49a,52,65,66,98,102,110a,112,144,149-151}

When a 3-aryl substituent is present in the pyrazole, an indene is generally a coproduct,^{44,45,47,68,70,71,105,150-153} although it has not always been

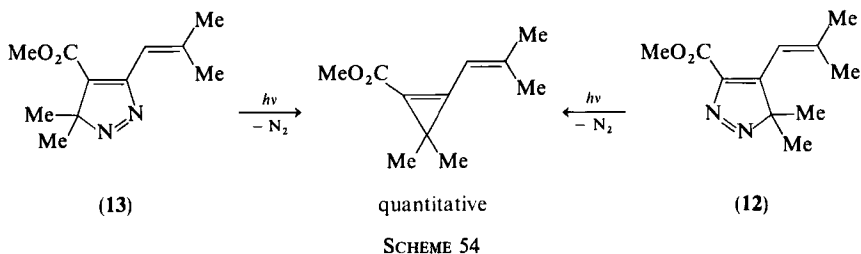
¹⁴⁹ G. Ege, *Tetrahedron Lett.*, 1667 (1963).

¹⁵⁰ H. Heydt and M. Regitz, *J. Chem. Res., Synop.*, 326 (1978); *J. Chem. Res., Miniprint*, 4248 (1978).

¹⁵¹ L. Schrader, *Chem. Ber.* **104**, 941 (1971).

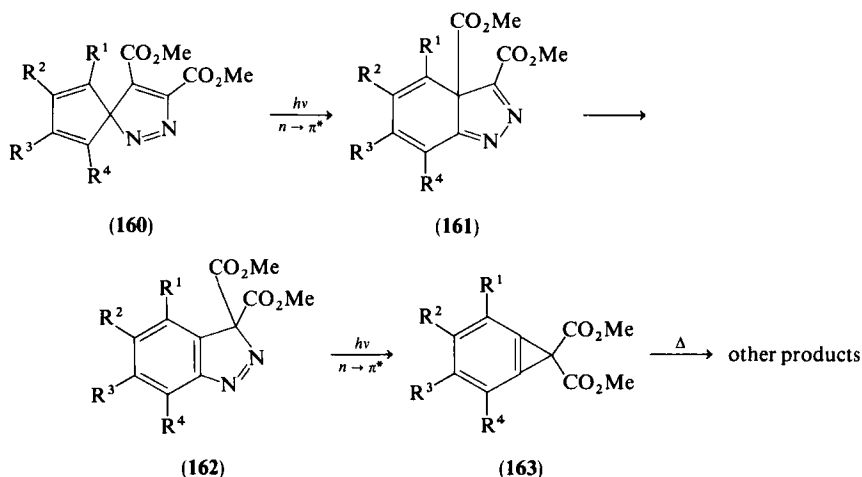
¹⁵² G. Ege and B. Hahn, *Justus Liebigs Ann. Chem.* **763**, 39 (1972).

¹⁵³ M. I. Komendantov, R. R. Bekmukhametov, and I. N. Domnin, *Zh. Org. Khim.* **14**, 759 (1978) [*CA* **89**, 23503t (1978)]; *Tetrahedron* **34**, 2743 (1978).



observed.^{43,44,142,143} In contrast, spirofluorene derivatives and their analogs seem only to give cyclopropenes, probably for steric reasons^{24-26,148,149,154} (e.g., **154** leads only to **155**^{148,149}), whereas spirocyclopentadienes **160** are converted to benzocyclopropenes **163** via a double photo van Alphen-Hüttel rearrangement, followed by loss of nitrogen (Scheme 55).¹⁵⁵⁻¹⁵⁸ These may rearrange further by thermal or photochemical processes. The mechanism has been investigated using Mauser diagrams, and the quantum yields of each step determined.¹⁵⁸ Spiroindene derivatives adopt an intermediate position, giving spirocyclopropenes¹⁵⁶ or naphthocyclopropenes,¹⁵⁵ depending upon substituents.

A mechanism accounting for all products observed is shown in Scheme 56.



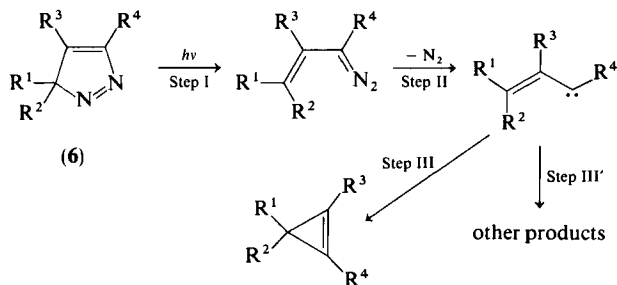
¹⁵⁴ H. Dürr, R. Sergio, and W. Gombler, *Angew. Chem., Int. Ed. Engl.* **11**, 224 (1972).

¹⁵⁵ H. Dürr and L. Schrader, *Angew. Chem., Int. Ed. Engl.* **8**, 446 (1969); *Chem. Ber.* **103**, 1334 (1970).

¹⁵⁶ H. Dürr, A. C. Ranade, and I. Halberstadt, *Tetrahedron Lett.*, 3041 (1974).

¹⁵⁷ H. Dürr and H. Schmitz, *Angew. Chem., Int. Ed. Engl.* **14**, 647 (1975).

¹⁵⁸ E. Lüddecke, H. Rau, H. Dürr, and H. Schmitz, *Tetrahedron* **33**, 2677 (1977).



SCHEME 56

a. *Step I: Ring Opening to a Vinyldiazo Compound.* The vinyl-diazo intermediate has been detected by its red color,^{12,52,66,159} UV absorption (490–510 nm, $\log \epsilon = 1.3$ –1.7),^{49a,51,66,109} and IR absorption (2010–2090 cm^{-1})^{12,49a,51,109,150,160}; in some cases it has been isolated.^{49a,69,161} It is formed on absorption of UV light at the wavelength of the pyrazole ring $n \rightarrow \pi^*$ transition.

That the diazo compound is a true intermediate was confirmed by a number of observations: a red color was formed during an induction period prior to nitrogen evolution¹⁵⁹; in one reaction only 10% cyclopropene had been formed when all of the 3H-pyrazole had disappeared^{49a}; the use of filters to give a narrow band of UV light (320–380 nm) results in formation of the diazo compound but suppression of the cyclopropene^{61,69,91,98,109,160}; and photolysis of the diazo compound, using a different set of filters (longer wavelength), yields the cyclopropene.^{69,98,109}

b. *Step II: Formation of Vinylcarbene.* Absorption of light at longer wavelength (>380 nm) results in loss of nitrogen and formation of a carbene. Examples of the latter have been isolated in a matrix at 5°K, and shown in most cases by ESR to exist as the triplet in the ground state,^{69,109} although one example was a singlet. It has subsequently been suggested that the relative stabilities of the singlet and the triplet depend largely on the nature and positions of substituents.^{71,98}

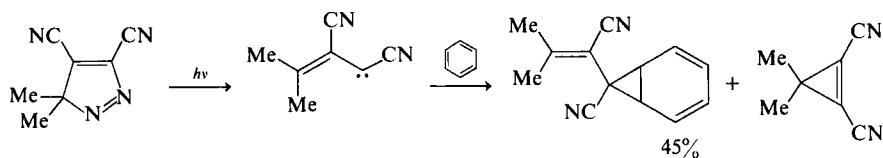
The existence of the carbene intermediate has also been demonstrated by formation of dimers^{12,54}, reaction with solvent (benzene) to form a norcaradiene [observed only with electron-deficient 3H-pyrazoles^{72,154,162} (Scheme 57)], by trapping with active alkenes^{55,56,162} and dienes^{55,72,162} (often

¹⁵⁹ G. L. Closs and W. A. Böll, *J. Am. Chem. Soc.* **85**, 3904 (1963).

¹⁶⁰ G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *J. Am. Chem. Soc.* **90**, 173 (1968).

¹⁶¹ C. Dietrich-Buchecker and M. Franck-Neumann, *Tetrahedron* **33**, 751 (1977).

¹⁶² M. Franck-Neumann and C. Dietrich-Buchecker, *Tetrahedron* **34**, 2797 (1978).

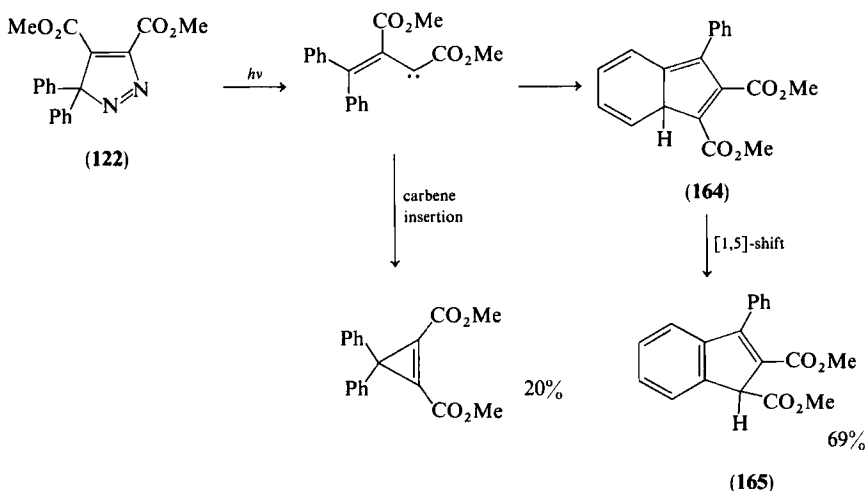


SCHEME 57

with high stereoselectivity) and with alkynes.¹⁶² Other inter- and intramolecular reactions of the carbenes are discussed in the next section.

c. *Steps III and III': the Fate of the Carbene.* When photolysis is conducted in an inert solvent, the major process is insertion of the carbene into the double bond to give a cyclopropene (Step III, Scheme 56), unless an alternative, energetically favorable, reaction pathway (Step III') exists. The most important of these is indene formation.

Attack by the carbene on a suitably placed aryl ring (Scheme 58¹⁵²) gives an intermediate **164**, which undergoes a thermally allowed suprafacial [1,5]-hydrogen shift to give the indene **165**.^{151,152} The intramolecular nature of the hydride shift was established by lack of exchange with deuterium in the solvent.¹⁵²



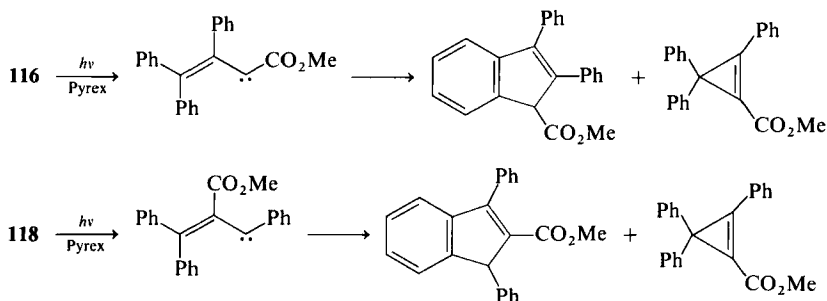
SCHEME 58

The ratio of cyclopropene to indene varies with different pyrazole ring substituents^{45,47,71,150,152,153} and thus may depend on the carbene singlet to triplet ratio.⁷¹ For R¹ = Ph and R² = alkenyl (Scheme 56), it has been suggested that the product distribution depends on the ratio of cisoid to transoid carbene.¹⁰⁵

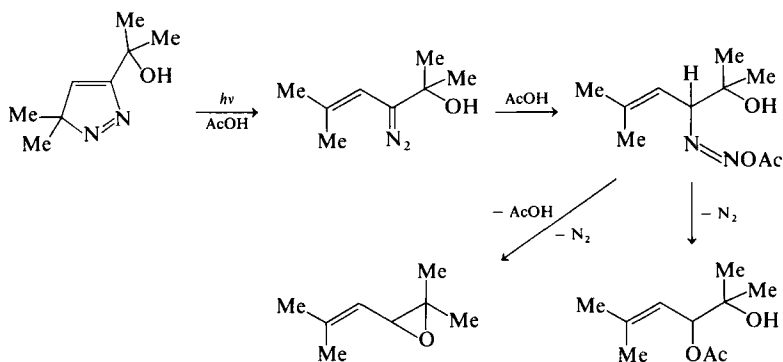
Although cyclopropene formation has been observed to be reversible,¹⁵⁰ and its conversion to indene has been achieved thermally,⁴³ the two products are not interconvertible under the photochemical reaction conditions, showing that they are formed by different pathways.^{45,153} An elegant proof of this is the isolation of different indenenes from **116** and **118** (Scheme 59).⁷¹

The vinylcarbene may also form a diene by a hydrogen shift^{49a,52,54,161}, undergo a Wolff rearrangement to a ketene (if derived from a diazo ketone^{61,161,162}), or take part in a more complex intramolecular reaction involving a nearby heteroatom-containing substituent^{51,52,56} (e.g., formation of a benzofuran from an ester^{9,23,158}), although a side-chain hydroxyl group does not always interfere.^{110a} Rearrangements to alkynes¹⁵⁰ and allenes^{51,52,150} have also been reported, and when the photolysis is conducted in the presence of oxygen, very complex mixtures have been obtained.⁶¹

Photolyses carried out in acetic acid give allylic acetates, apparently via a diazoacetate (Scheme 60)^{51,57}. Carbenes derived from spirofluorene derivatives have been trapped with pyridines and pyridazines to give useful photochromic spirodihydroindolizines.¹⁶³



SCHEME 59



SCHEME 60

¹⁶³ H. Gross and H. Dürr, *Angew. Chem., Int. Ed. Engl.* **21**, 216 (1982).

a. *Valence Isomerization.* At low temperatures (-55 to -70°C), photolysis of certain 3*H*-pyrazoles (**14**, Scheme 61), using a high or medium pressure Hg lamp with a pyrex filter, leads to 1,2-diazobicyclo[2.1.0]pent-2-enes (**166**) via a 4π disrotatory electrocyclic ring closure.^{144,159,160} The reaction has been observed only for fully alkyl-substituted pyrazoles; systems having R^1 and/or $\text{R}^2 \neq$ alkyl give only cyclopropenes **167**. It is remarkably solvent-dependent, giving exclusively **166** in methanol and dichloromethane, but increasing amounts of **167** also, as solvent polarity decreases.^{159,160} It appears to proceed via the same excited state as ring opening to give a diazoalkene, inasmuch as addition of a sensitizer has no effect on the product ratio.¹⁶⁰ The bicycle **166** is thermally unstable, reverting quantitatively to the 3*H*-pyrazole on warming to 0°C .^{144,160}

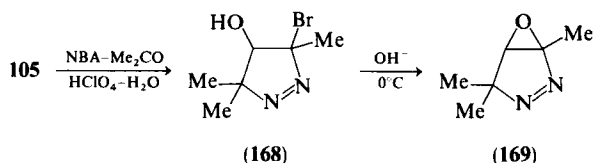
diazoalkene¹⁰⁵; the diazepine apparently arises from an 8π electrocyclic ring closure. The mechanism of the reverse process (diazepine $\rightarrow$ 3*H*-pyrazole) has been discussed.¹⁶⁴

A photo van Alphen-Hüttel rearrangement was referred to in Section IV,B,1.¹⁵⁵

C. REACTIONS OF RING ATOMS WITH ELECTROPHILES

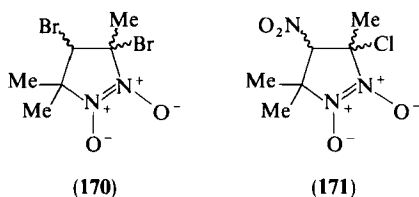
Protonation at ring nitrogen is a key step in the acid-catalyzed van Alphen-Hüttel rearrangement (Section IV,A,1,a; Scheme 45).

Few other electrophilic reactions are known. The trimethyl-3*H*-pyrazole **105** is oxidized by *N*-bromoacetamide (NBA) to the bromohydrin **168** and cyclized further to the epoxide **169** by base (Scheme 63).¹⁶⁵ Peracid oxidation of **53** gives the mono *N*-oxide **75** regioselectively (Scheme 28).¹⁰⁸



SCHEME 63

Bromine adds across the $\text{C}=\text{C}$ double bond of the *N,N'*-dioxide **96** to give a mixture of diastereomers of a dibromo derivative **170**,^{119,134} whereas nitrosyl chloride reacts with the 4-bromo analog of **96** forming mixed diastereomers of the nitrochloro derivative **171**.¹³⁴



D. REACTIONS OF RING ATOMS WITH NUCLEOPHILES

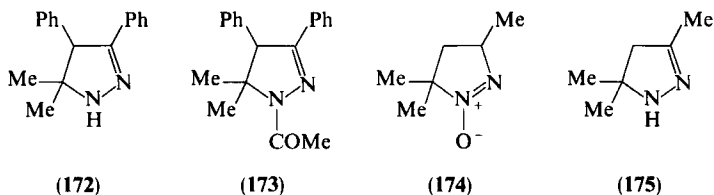
All examples of nucleophilic reactions have involved reducing agents; Δ^2 -pyrazolines are common products.

¹⁶⁴ C. D. Anderson, J. T. Sharp, E. Stefaniuk, and R. S. Strathdee, *Tetrahedron Lett.*, 305 (1976); C. D. Anderson, J. T. Sharp, and R. S. Strathdee, *J.C.S. Perkin I*, 2730 (1979).

¹⁶⁵ L. E. Friedrich, N. L. de Vera, W. P. Hoss, and J. T. Warren, *Tetrahedron Lett.*, 3139 (1974).

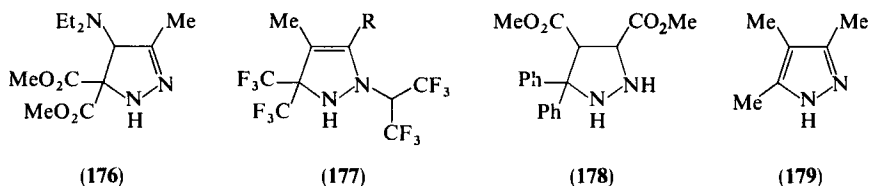
1. Catalytic Hydrogenation over Platinum

In acetic anhydride, the *N*-oxide **76** is reduced to the acetylpyrazoline **173** (93%), presumably via **172**.¹⁰⁸ The dioxide **96** is reduced in stages, each of which can be isolated; it gives first **83**, then **174**, and finally **175**.¹¹⁹



2. Metal Hydride Reductions

With NaBH_4 **142** yields the pyrazoline **176** in high yield,³⁴ whereas LiAlH_4 converts **76** to **172** quantitatively.^{108,126} The behavior of the oxo *N*-oxide **100** toward KBH_4 depends on the temperature, it being reduced to **81** at room temperature but to the product **80** from subsequent dehydration at 75°C .¹²⁰ The dipolar ions **98** give the pyrazolines **177** in low yield with LiAlH_4 at -30°C .¹³⁰



3. Dissolving-Metal and Related Reductions

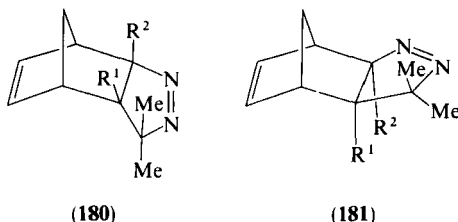
Zinc, in boiling acetic acid, is claimed to reduce the diester **122** to the pyrazolidine **178** (80%).⁶⁴ Treatment of the chloro *N*-oxide **78** with tin(II) chloride in hydrochloric acid yields mostly **175** with a little of the rearranged 1*H*-pyrazole **179**, whereas the methoxy *N*-oxide **79** and the oxo compound **100**, under the same conditions give mostly **179**.¹¹⁸

E. REACTIONS WITH CYCLIC TRANSITION STATES

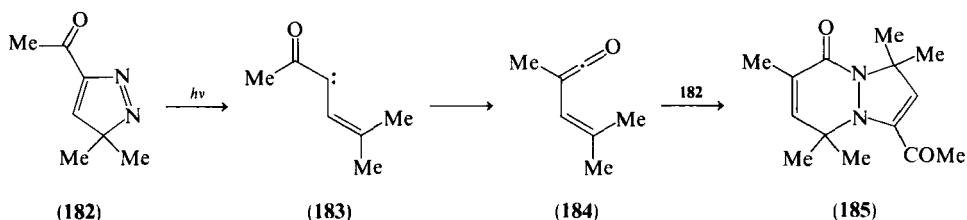
1. Six-Membered Rings: Diels-Alder Reactions

3*H*-Pyrazoles **14**, having R^2 , and sometimes also R^1 , as electron-withdrawing substituents, act as dienophiles at the $\text{C}=\text{C}$ double bond. Thus with cyclopentadiene high yields of mixed endo (**180**) and exo (**181**)

adducts result; although the former is strongly favored, the actual ratio depends upon the nature of R^1 and R^2 .¹⁶⁶ With isoprene, two regioisomers are formed together with cyclopropenes.¹⁶⁶



The vinylketene **184**, formed by Wolff rearrangement of the vinylcarbene **183**, in contrast adds across the $N=N$ bond of excess **182** to give the adduct **185** (Scheme 64).¹⁶²



SCHEME 64

2. Five-Membered Rings: 1,3-Dipolar Cycloadditions

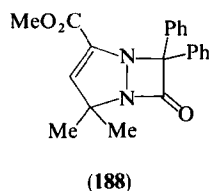
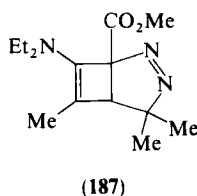
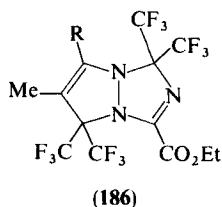
By analogy with the Diels–Alder reaction, 3H-pyrazoles with electron-withdrawing R^1 and/or R^2 may behave as dipolarophiles, adding a second mole of diazoalkane to yield structures **15** (Scheme 6),^{62,63,82} and in the opposite sense to give related systems.¹⁶⁷ Loss of nitrogen, with rearrangement, may yield a 3H-⁶³ or a 1H-pyrazole.¹⁶⁷

Compounds **98** behave as 1,3-dipoles in cycloaddition reactions with DMAD, ethyl cyanoformate, and alkenes: the structure of the adduct **186** from ethyl cyanoformate suggests that reaction is via form **98b**.¹³¹

Cycloaddition reactions of 3H-pyrazole *N*-oxides do not appear to have been studied.

¹⁶⁶ C. Dietrich-Buchecker, D. Martina, and M. Franck-Neumann, *J. Chem. Res., Synop.*, 78 (1978); *J. Chem. Res., Miniprint*, 1014 (1978).

¹⁶⁷ R. Huisgen and H. U. Reissig, *J.C.S. Chem. Commun.*, 568 (1979).



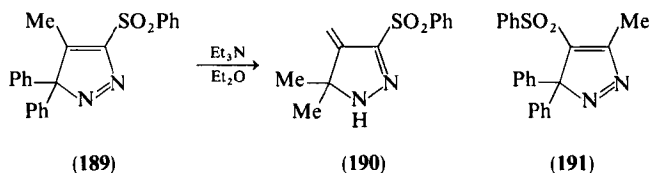
3. Four-Membered Rings

The nucleophilic *N,N*-diethyl-1-propynamine adds across the C=C bond of **31** at 20°C to yield the adduct **187**, whereas the electrophilic diphenylketene adds across the N=N bond at -8°C to give **188** (97%).¹⁶⁷ This difference in behavior finds a parallel in the Diels-Alder reactions (Section IV,E,1).

F. REACTIONS OF RING SUBSTITUENTS

1. C-Linked

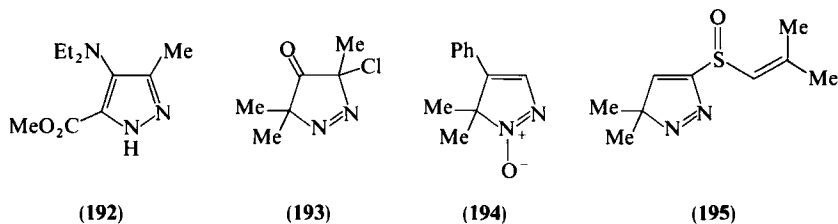
In the presence of base, the sulfone **189** rearranges to the methylene-pyrazoline **190**, whereas its regioisomer **191** shows no reaction (Scheme 65).⁵⁷ This is the reverse of the type of thermal rearrangement shown in Scheme 25.



SCHEME 65

Diazoalkanes add to 5-alkenyl-3*H*-pyrazoles at the side chain, and nitrogen is extruded, to give 5-cyclopropyl-3*H*-pyrazoles.^{46,74}

The diester **142** is decarboxymethylated quantitatively to **192** after four weeks in cold methanol.



2. Hetero-Linked

Acid hydrolysis of the methoxy *N*-oxide **79** gives **100**, which in turn is converted to the chloropyrazolinone **193** with hydrochloric acid via protonation at the *N*-oxygen and then loss of water.^{118,120} Treatment of **96** with hydrochloric acid leads to **77** by a similar sequence of reactions.¹¹⁹

Deoxygenation of the *N*-oxide **194** was achieved using hexachlorodisilane in chloroform.¹⁶⁸

The sulfoxide **195** was prepared by MCPBA oxidation of the corresponding sulfide.⁵⁶

Displacement of a ring halogen by methoxide is shown in Scheme 29.

V. Appendix

ADDITIONAL PAPERS

A few additional references have been found since this review was written. They are cross referenced here by relevant sections.

Section II,A,1: 3*H*-Pyrazoles have been prepared from 1,3,3,3-tetrafluoropropyne and DPD¹⁶⁹ and from 1-thioalkyl-2-trimethylsilylethynes with DAP.¹⁷⁰ One of the latter alkynes was formed via valence isomerism of a thioketene.¹⁷⁰

Section II,B: Addition of DAP to 3-(4-methylphenylsulfinyl)coumarin gives via facile elimination of 4-methylbenzensulfinic acid a 3*H*-pyrazolo[4,5-*c*]coumarin in high yield.¹⁷¹

Section II,D,1: The kinetics have been studied for competitive formation of 3*H*-pyrazoles and cyclopropenes thermally from the isomeric vinyl diazo compounds 2,3-dimethyl-1-phenyl-1-diazo-2-butene and 4-methyl-3-phenyl-2-diazo-3-pentene. The higher (12 kJ/mol) ground state energy of the latter accounts almost entirely for its larger ($\times 68$) rate of cyclization to a 3*H*-pyrazole, relative to its isomer.¹⁷²

Section III,B: Additional UV,^{172,173} IR,^{169,170,172,173} ¹H-NMR,^{169,170,172,173} ¹³C-NMR,¹⁷⁰ ¹⁹F-NMR,¹⁶⁹ and mass spectroscopic^{172,173} data for 3*H*-pyrazoles have been reported.

¹⁶⁸ A. G. Hortmann, J. Y. Koo, and C. C. Yu, *J. Org. Chem.* **43**, 2289 (1978).

¹⁶⁹ G. B. Blackwell, R. N. Haszeldine, and D. R. Taylor, *J.C.S. Perkin I*, 1 (1983).

¹⁷⁰ E. Schaumann, H. Behr, and J. Linstaedt, *Chem. Ber.* **116**, 66 (1983).

¹⁷¹ F. M. Dean and B. K. Park, *Tetrahedron Lett.*, 4275 (1974); *J.C.S. Perkin I*, 1260 (1976).

¹⁷² J. A. Pincock and N. C. Mathur, *J. Org. Chem.* **47**, 3699 (1982).

¹⁷³ H. Gstach and H. Kirsch, *Chem. Ber.* **115**, 2586 (1982).

Section IV,A,1: Attempts to prepare spiro-3*H*-pyrazoles from esters of 6-diazopenicillinic acid and 1-phenyl-2-propyn-1-one resulted in spontaneous rearrangement to the isomeric 1*H*-pyrazoles via a unique migration of the β -lactam 6-7 bond.¹⁷⁴ A similar spontaneous acyl migration was observed in the reaction between a 3-diazothiolan-4-one and DMAD.¹⁷⁵

Section IV,A,1,d: Reaction between 1,2,4-triazolo[4,3-*a*]pyridine and DMAD gives a 1*H*-pyrazole via double migration of an ester group in a 3*H*-pyrazole intermediate.¹⁷⁶

Section IV,A,2: Competition between van Alphen-Hüttel rearrangement and ring opening to a vinyl diazo compound is found to be substituent dependent for transient spiro-3*H*-pyrazoles formed from methyl propynoate and 4-diazopyrazolones.¹⁷⁷

Section IV,B,1: Selective irradiation of 1,2-diazaspiro[2,5]oct-1-ene in the presence of DMAD gives a spiro-3*H*-pyrazole through trapping of the intermediate diazocyclohexane. Several photodecomposition products were also formed and characterized.¹⁷³

¹⁷⁴ A. A. Jaxa-Chamiec, W. S. McDonald, P. G. Sammes, and R. R. Talekar, *Tetrahedron Lett.* **23**, 2813 (1982).

¹⁷⁵ J. M. Bolster and R. M. Kellogg, *J. Org. Chem.* **47**, 4429 (1982).

¹⁷⁶ D. G. Heath and C. W. Rees, *J.C.S. Chem. Commun.*, 1280 (1982).

¹⁷⁷ A. D. Woolhouse, T. C. Caruso, and A. Padwa, *Tetrahedron Lett.* **23**, 2167 (1982).

The 4*H*-Pyrazoles

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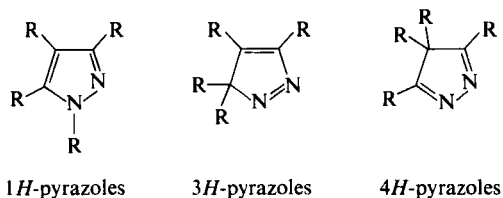
*Department of Chemistry, University of Florida,
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I. Introduction

As was pointed out in the preceding chapter,¹ pyrazoles are known in two nonaromatic forms (the *3H*- and *4H*-pyrazoles, Scheme 1) in addition to the more familiar aromatic *1H* form. The *3H*-pyrazoles, which may be considered as cyclic vinylazo compounds, have been discussed in reference 1; the *4H*-pyrazoles, which are cyclic azines, are the subject of this review.



SCHEME 1

Although the *4H*-pyrazoles have not previously been reviewed, some aspects of their synthesis and chemistry have been discussed in reviews and treatises²⁻⁵ dealing with the *1H* compounds. For the present review, the literature has been covered using *Chemical Abstracts*, by indexes up until mid 1981, and by computer "on-line" substructure search up to Issue 26 of Volume 96. Some more recent references have been taken directly from the commoner international journals.

¹ M. P. Sammes and A. R. Katritzky, *Adv. Heterocycl. Chem.* **34**, 1 (1983).

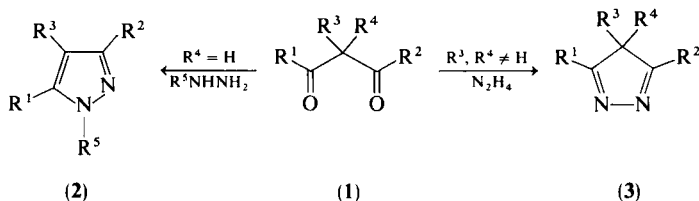
In scope the review attempts to cover all known 4*H*-pyrazoles, which as a class have received considerably less attention than their 3*H* counterparts. It includes some that are transient intermediates in chemical reactions; systems having an exocyclic double bond, however, are excluded.

II. Synthesis of 4*H*-Pyrazoles

The most widely used method for the synthesis of 4*H*-pyrazoles employs 2,2-disubstituted 1,3-diketones and hydrazine. Other useful methods include the reaction between 1*H*-pyrazoles and electrophiles, the transformation of pyrazolone derivatives, and thermal rearrangements of 3*H*-pyrazoles.

A. FROM 1,3-DIKETONES AND HYDRAZINE

The reaction between 1,3-dicarbonyl compounds **1** and hydrazines is the most general method for preparing 1*H*-pyrazoles **2** (Scheme 2).^{2,4,5} If a 2,2-disubstituted 1,3-diketone is employed (**1**: R³, R⁴ ≠ H), reaction with hydrazine hydrate gives instead a 4*H*-pyrazole **3**, as was first reported by Knorr.^{5a} Generally, the reactants are heated under reflux in a solvent such as methanol, ethanol, benzene, or carbon tetrachloride; yields range from 50% to quantitative.



SCHEME 2

² A. N. Kost and I. I. Grandberg, *Adv. Heterocycl. Chem.* **6**, 347 (1966).

³ T. L. Jacobs, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, Chapter 2. Wiley, New York, 1957.

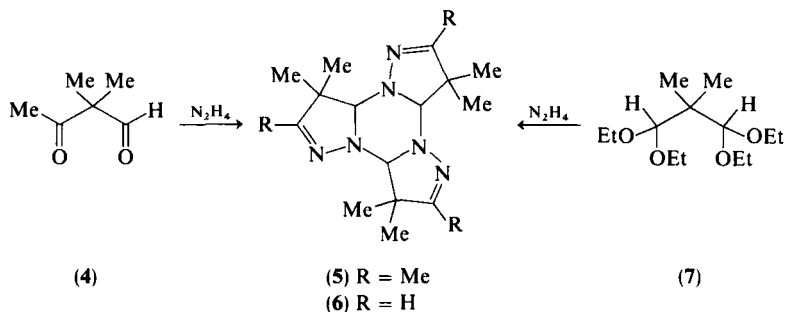
⁴ R. H. Wiley (ed.), "Chemistry of Heterocyclic Compounds," Vol. XXII. Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings. Wiley (Interscience), New York, 1967.

⁵ J. Elguero, in "Comprehensive Heterocyclic Chemistry" (A. R. Katritzky and C. W. Rees, eds.), Vol. 4, Chapter 4.4 Pergamon, Oxford, 1983.

^{5a} L. Knorr and B. Oettinger, *Justus Liebigs Ann. Chem.* **279**, 247 (1894).

1. Substituents at the 3- and 5-Positions

In most cases R^1 and R^2 have been the same, the commonest substituent being methyl,^{5a-15} although phenyl^{6,9,10,13,15} and, in one case, *p*-tolyl¹⁶ have also been reported. For those cases where $R^1 \neq R^2$, R^1 has been phenyl, and R^2 methyl^{10,15,17,18} or trideuteriomethyl.¹⁰ An attempt to prepare a 4*H*-pyrazole from 2,2-dimethylbutane-1,3-dione (4) led to the cyclic trimer 5 (Scheme 3).¹⁹ The bisacetal 7 likewise gave the analog 6.



SCHEME 3

2. Substituents at the 4-Position

a. Alkyl and Aryl Groups. The 1,3-diketones 1 have usually been prepared by dialkylation of the readily available precursors 2,4-pentanedione, 1-phenyl-1,3-butanedione, and 1,3-diphenyl-1,3-propanedione. For $R^1 = R^2 = Ph$, a Friedel-Crafts reaction between benzene and a disubstituted

⁶ K. von Auwers and F. Bergmann, *Justus Liebigs Ann. Chem.* **472**, 287 (1929).

⁷ I. I. Grandberg, A. P. Krasnoshchek, A. N. Kost, and G. K. Faizova, *Zh. Obshch. Khim.* **33**, 2586 (1963) [*CA* **60**, 515d (1964)].

⁸ J. Elguero, R. Jacquier, and D. Tizané, *Bull. Soc. Chim. Fr.*, 3866 (1968).

⁹ A. B. Evnin and D. R. Arnold, *J. Am. Chem. Soc.* **90**, 5330 (1968).

¹⁰ A. B. Evnin, D. R. Arnold, L. A. Karnischky, and E. Strom, *J. Am. Chem. Soc.* **92**, 6218 (1970).

¹¹ R. K. Bramley and R. Grigg, *J.C.S. Chem. Commun.*, 99 (1969).

¹² R. K. Bramley, J. Caldwell, and R. Grigg, *Tetrahedron Lett.*, 3207 (1973).

¹³ R. K. Bramley, R. Grigg, G. Guilford, and P. Milner, *Tetrahedron* **29**, 4159 (1973).

¹⁴ J. E. Baldwin, O. W. Lever, Jr., and N. R. Tzodikov, *J. Org. Chem.* **41**, 2874 (1976).

¹⁵ H. Gnichtel and U. Boehringer, *Chem. Ber.* **113**, 1507 (1980).

¹⁶ P. Yates and E. M. Levi, *Can. J. Chem.* **53**, 748 (1975).

¹⁷ L. A. Paquette and L. M. Leichter, *J. Am. Chem. Soc.* **93**, 5128 (1971).

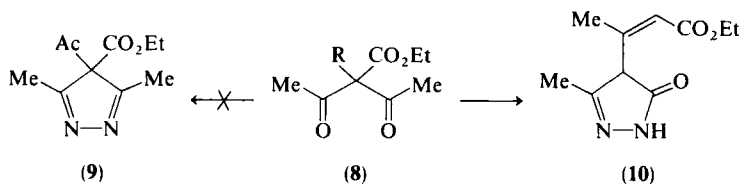
¹⁸ R. Gree, H. Park, and L. A. Paquette, *J. Am. Chem. Soc.* **102**, 4397 (1980).

¹⁹ G. Gubelt and J. Warkentin, *Chem. Ber.* **102**, 2481 (1969).

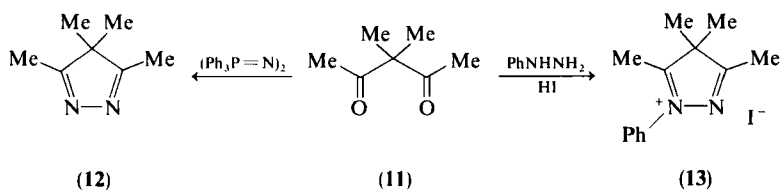
malonoyl dichloride has also been used.¹⁵ Dialkylation of the precursor 1,3-diketones may be accomplished in high overall yield in two steps, using sodium hydride in dimethyl sulfoxide. Yields are optimized and competing O-alkylation reduced by incorporating the larger of the two substituents first.¹⁸

In many compounds R^3 and R^4 have been the same, the commonest substituent being methyl,^{5a-10,13,15,17} although examples having ethyl,^{6,15} 2-cyanoethyl,⁷ 2-propenyl,^{7,11,13} 2-propynyl,¹³ benzyl,^{7,13} and phenyl¹⁵ are also known. Where R^3 and R^4 are different, R^3 has generally been methyl, and exceptionally trideuteriomethyl,¹⁸ or ethyl,^{12,13} whereas R^4 has been ethyl,¹⁸ 2-propenyl,^{7,13,18} 3-methyl-2-butenyl,^{12,13} 2-propynyl,^{13,18} or benzyl.^{7,10,13,18}

b. Other Substituents. 4H-Pyrazoles having a 4-hydroxy group have been prepared from the appropriate acetoxy¹⁶ or hydroxy diketones.¹⁴ An early claim to have isolated **9** from the triketo ester **8** ($R = \text{COMe}$, Scheme 4)²⁰ was later corrected, the product in fact being the isomer **10**, formed via the diacetyl compound (**8**: $R = \text{H}$).²¹



SCHEME 4



SCHEME 5

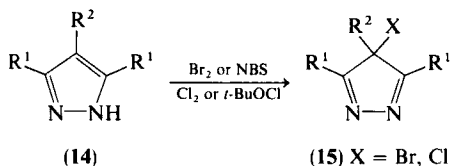
3. Preparations from Hydrazine Derivatives

With $(\text{Ph}_3\text{P}=\text{N})_2$ the 1,3-diketone **11** yields the tetramethylpyrazole **12** via a double Wittig reaction,²² whereas with phenylhydrazine the salt **13** is formed⁸ (Scheme 5).

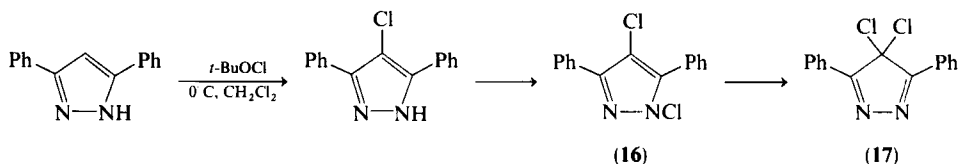
²⁰ F. Seidel, *Ber. Dtsch. Chem. Ges. B* **65**, 1205 (1932).

²¹ F. Seidel, W. Thier, A. Uber, and J. Dittmer, *Ber. Dtsch. Chem. Ges. B* **68**, 1913 (1935).

²² R. Appel and P. Volz, *Chem. Ber.* **108**, 623 (1975).



SCHEME 6



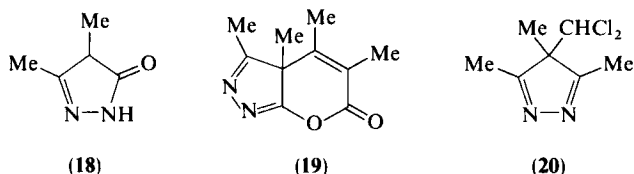
SCHEME 7

B. FROM 1H-PYRAZOLES AND ELECTROPHILES

1. Halogenating Agents

Treatment of 1*H*-pyrazoles (**14**: R^1 , R^2 = alkyl, Scheme 6) with *N*-bromosuccinimide (NBS)²³ or bromine^{23,24} in the cold leads to the 4-bromo compounds (**15**: X = Br). Similarly chlorine, or better, *t*-BuOCl, converts compound **14** (R^1 = Ph, R^2 = Me) to the corresponding chloro derivative (**15**: X = Cl),^{25,26} although when R^1 is alkyl, side-chain halogenation occurs. The dichloro derivative **17** has been prepared similarly, its precursor **16** (Scheme 7) having been detected by ¹H-NMR.²⁷

The pyrazolone **18** on treatment with bromine in chloroform, and then with sodium carbonate, is claimed to yield the 4*H*-pyrazolopyrone **19**



²³ G. L. Closs and H. Heyn, *Tetrahedron* **22**, 463 (1966).

²⁴ P. Bouchet, J. Elguero, R. Jacquier, and F. Forissier, *C. R. Acad. Sci., Ser. C* **269**, 570 (1969).

²⁵ J. P. Freeman and J. F. Lorenc, *J. Org. Chem.* **42**, 177 (1977).

²⁶ J. P. Freeman, E. R. Janiga, and J. F. Lorenc, *J. Org. Chem.* **42**, 3721 (1977).

²⁷ J. F. Hansen, Y. I. Kim, L. J. Griswold, G. W. Hoelle, D. L. Taylor, and D. E. Vietti, *J. Org. Chem.* **45**, 76 (1980).

(43%).²⁸ A 4-bromo-4*H*-pyrazolium cation is believed to be an intermediate in the oxidation of an *N*-arylpyrazole to a 4-bromopyrazolone.²⁹

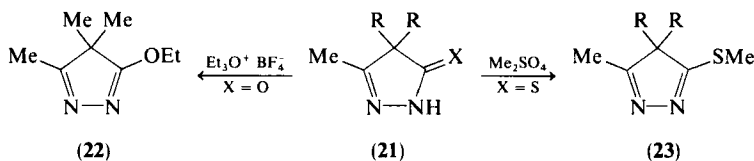
2. Dichlorocarbene

The dichloromethyl derivative **20** is isolated (10%) from 3,4,5-trimethylpyrazole and chloroform in the presence of sodium ethoxide; generation of dichlorocarbene by thermolysis of sodium trichloroacetate does not give any 4*H*-pyrazole.³⁰ The same product is formed, in lower yield, using chloroform and base with a phase-transfer catalyst.³¹

C. BY TRANSFORMATION OF PYRAZOLONE DERIVATIVES

Conversion of the HNC=O function of a 4-substituted pyrazolone to N=CX can generate the 4*H*-pyrazole ring system. This has been accomplished in several ways.

The pyrazolone **21** (R = Me, X = O, Scheme 8) gives **22** with Et₃O⁺BF₄⁻,³² while the thioxo analogs (**21**: X = S, R = Me or Et) are alkylated regio-specifically on sulfur with dimethyl sulfate to give products **23**.³³



SCHEME 8

Lead tetraacetate (LTA) converts **24** to a mixture of products, including the diacetoxy compound **25** (6%).³⁴ Although treatment of **24** with dimethyl sulfate, diazomethane,³⁵ or chlorotrimethylsilane and triethylamine³⁶ gave mainly N,N'- and N,O-dialkylation, a small amount of the dimethoxy analog of **25** was also formed in one reaction.³⁵

²⁸ R. Hüttel, E. Wagner, and B. Sickenberger, *Justus Liebigs Ann. Chem.* **607**, 109 (1957).

²⁹ J. Elguero, G. Guiraud, R. Jacquier, and H. C. N. Tien Duc, *Bull. Soc. Chim. Fr.*, 328 (1967).

³⁰ R. L. Jones and C. W. Rees, *J. Chem. Soc. C*, 2251 (1969).

³¹ F. De Angelis, A. Gambacorta, and R. Nicoletti, *Synthesis*, 798 (1976).

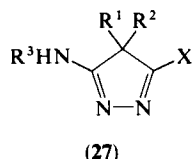
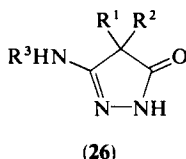
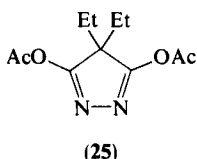
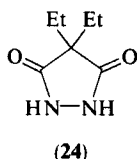
³² A. R. Katritzky, F. W. Maine, and S. Golding, *Tetrahedron* **21**, 1693 (1965).

³³ J. D. Kendall and G. F. Duffin, British Patent 730,489 (1955) [CA **49**, 15580a (1955)].

³⁴ B. T. Gillis and R. A. Izydore, *J. Org. Chem.* **34**, 3181 (1969).

³⁵ A. Steigel and R. Fey, *Chem. Ber.* **113**, 3910 (1980).

³⁶ A. Steigel, *Chem. Ber.* **113**, 3915 (1980).

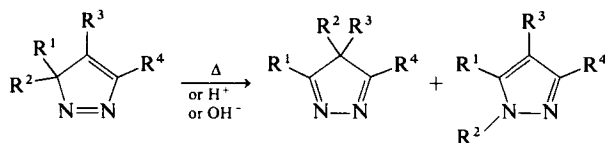


The aminopyrazolones **26** are converted to the corresponding bromides or chlorides (**27**: X = Br or Cl, R³ = H), respectively, by phosphorus tribromide or phosphorus oxychloride,^{37,38} whereas with acetic anhydride the acetoxyamide (**27**: X = OAc, R³ = Ac) is formed.³⁸ Some of these compounds have sedative action.

The fused-ring system **19** has also been prepared by heating **18** with ethyl 2-methyl-3-oxobutanoate.³⁹

D. BY THERMAL REARRANGEMENT OF 3*H*-PYRAZOLES

3*H*-Pyrazoles, when substituted at C-4, undergo thermal-, acid-, or base-catalyzed rearrangement to a mixture of 1*H*- and 4*H*-pyrazoles (Scheme 9).



SCHEME 9

This is known as the van Alphen-Hüttel rearrangement; its mechanism, scope, and limitations were discussed in the preceding chapter.¹ In cases where the 4*H*-pyrazole has been isolated, the migrating group R² has most frequently been phenyl.⁴⁰⁻⁴⁶ In one example it has been methyl,⁴⁷ and in an

³⁷ J. Druey, U.S. Patent 2,636,039 (1953) [CA **48**, 5227i (1954)].

³⁸ G. Mester and J. Vargha, *Chem. Ber.* **96**, 2334 (1963).

³⁹ L. Wolff and W. Schreiner, *Ber. Dtsch. Chem. Ges.* **41**, 550 (1908).

⁴⁰ R. R. Bektukhametov, *Sovrem. Probl. Khim.*, 61 (1973) [CA **81**, 136042v (1974)].

⁴¹ R. Baumes, J. Elguero, R. Jacquier, and G. Tarrago, *Tetrahedron Lett.*, 3781 (1973).

⁴² P. J. Abbott, R. M. Acheson, R. F. Flowerday, and G. W. Brown, *J.C.S. Perkin I*, 1177 (1974).

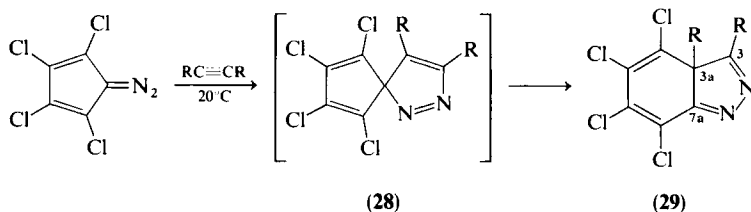
⁴³ M. I. Komendantov and R. R. Bektukhametov, *Khim. Geterotsikl. Soedin.*, 79 (1975) [CA **82**, 111337c (1975)].

⁴⁴ M. I. Komendantov and R. R. Bektukhametov, *Tezisy Dokl.-Vses. Konf. Khim. Atsetilena, 5th, 1975*, 374 (1975) [CA **88**, 190677p (1978)].

⁴⁵ V. V. Razin, *Zh. Org. Khim.* **11**, 1457 (1975) [CA **83**, 178913b (1975)].

⁴⁶ J. Dingwall and J. T. Sharp, *J.C.S. Chem. Commun.*, 128 (1975); K. L. M. Stanley, J. Dingwall, J. T. Sharp, and T. W. Naisby, *J.C.S. Perkin I*, 1433 (1979).

⁴⁷ W. J. Leigh and D. R. Arnold, *Can. J. Chem.* **57**, 1186 (1979).

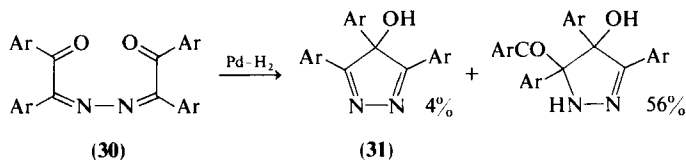


SCHEME 10

unusual case, alkyl rather than phenyl.⁴⁶ The spirocyclopentadiene derivatives **28** ($R = \text{CO}_2\text{Me}$, COPh , or CN , Scheme 10) also rearrange spontaneously to isolable products **29**,^{48,49} while analogous compounds appear to be transient intermediates in the rearrangements of related spirofluorenes.^{50,51}

E. MISCELLANEOUS METHODS

The pyrazole **12** and its 4,4-diethyl analog have been prepared by deoxygenation of the corresponding *N*-oxides with phosphorus trichloride in chloroform.⁵² Treatment of the azine **30** ($\text{Ar} = 4\text{-MeC}_6\text{H}_4$, Scheme 11) with hydrogen over palladium gives, as a minor byproduct (4%), the hydroxypyrazole **31**. A radical mechanism was proposed.¹⁶



SCHEME 11

Reaction between diphenylmethylsodium and benzonitrile is reported to yield the pyrazoline **32** (Scheme 12), which may be oxidized to **33**. The product was believed not to be the isomeric 4*H*-imidazole **34**⁵³; the melting points are very similar.

The diazonium salt **35** (Scheme 13) couples with the chloro ketones **36** to yield the pyrazoles **37** via a Japp-Klingemann type reaction followed by ring

⁴⁸ H. Dürr and R. Sergio, *Tetrahedron Lett.*, 3479 (1972).

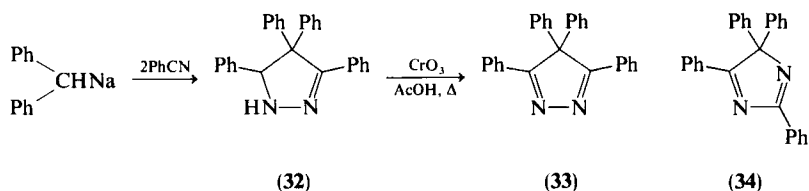
⁴⁹ H. Dürr and W. Schmidt, *Justus Liebigs Ann. Chem.*, 1140 (1974).

⁵⁰ S. Mataka, K. Takahashi, T. Ohshima, and M. Tashiro, *Chem. Lett.*, 915 (1980).

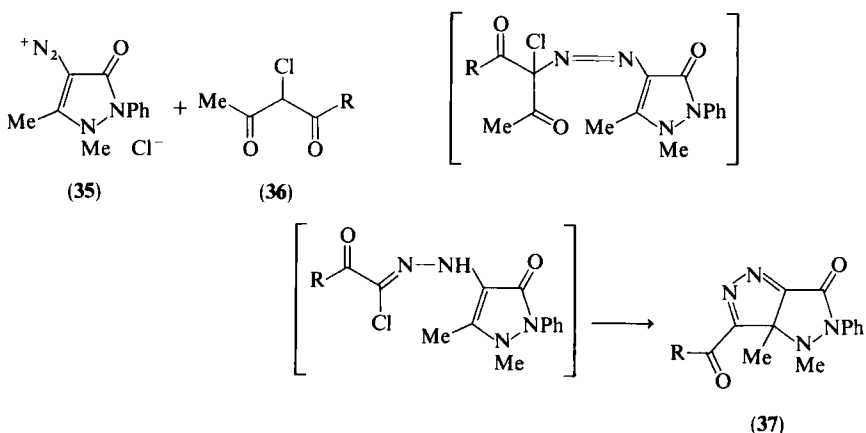
⁵¹ S. Mataka and M. Tashiro, *J. Org. Chem.*, **46**, 1929 (1981).

⁵² H. Gnichtel and H. J. Schönherr, *Chem. Ber.*, **99**, 618 (1966).

⁵³ R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 323 (1941).



SCHEME 12



SCHEME 13

closure. Strangely, the products are reported to show NH absorption in the IR.⁵⁴

Certain bicyclic azo compounds undergo thermal cycloreversion to give 4*H*-pyrazoles, either as transient intermediates⁵⁵ or as isolable products.¹⁰

F. METHODS FOR *N*-OXIDES

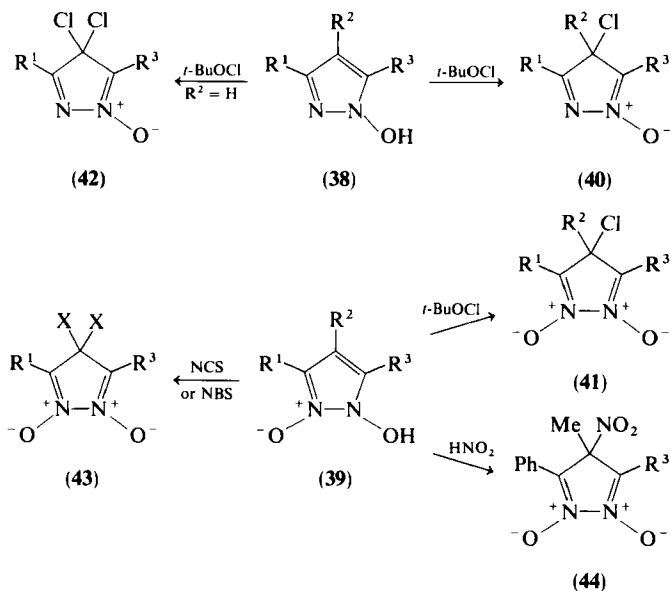
1. From Pyrazole Precursors

N-Hydroxypyrazoles **38** and their *N'*-oxides **39** are converted by *t*-BuOCl to the 4-chloro-4*H*-pyrazoles **40** and **41**, respectively^{25,26,56} (Scheme 14). Unlike Scheme 6, the reaction proceeds even when R¹ and R³ are alkyl. When

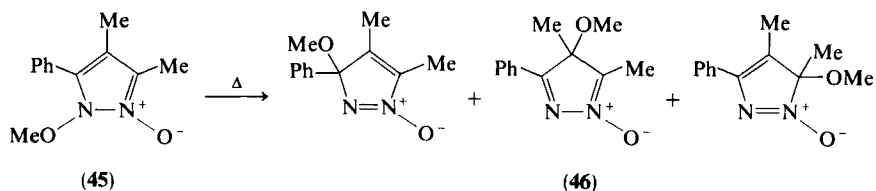
⁵⁴ M. H. Elnagdi, H. A. Elfahham, M. R. H. Elmoghayer, K. U. Sadek, and G. E. H. Elgemeie, *J.C.S. Perkin I*, 989 (1982).

⁵⁵ J. C. Hinshaw and E. L. Allred, *J.C.S. Chem. Commun.*, 72 (1969); L. A. Paquette, M. J. Wyvratt, H. C. Berk, and R. E. Moerck, *J. Am. Chem. Soc.* **100**, 5845 (1978).

⁵⁶ J. P. Freeman and E. R. Janiga, *J. Org. Chem.* **39**, 2663 (1974).



SCHEME 14



SCHEME 15

$R^2 = \text{H}$, $t\text{-BuOCl}$ transforms **38** to **42**, whereas N -chlorosuccinimide (NCS) and NBS convert **39** to **43** ($X = \text{Cl}$ and Br , respectively).²⁷ Treatment of **39** with nitrous acid gives the nitro derivatives **44**.⁵⁷

Thermolysis of the methoxy N -oxide **45** results in rearrangement to three isomeric products including the 4*H* compound **46** (Scheme 15). A mechanism was suggested.⁵⁸ The thermal rearrangement of a 3-acetoxy-3*H*-pyrazole 1-oxide to the 4-acetoxy 4*H* isomer is presumably a related reaction.⁵⁶

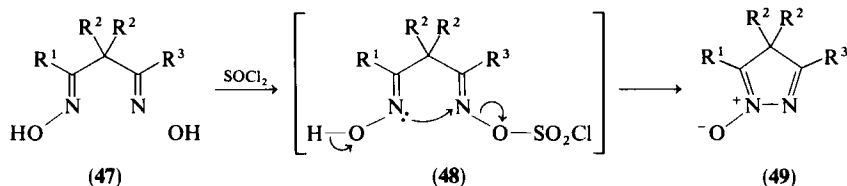
⁵⁷ J. P. Freeman and D. L. Surbey, *Tetrahedron Lett.*, 4917 (1967); J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.* **34**, 187 (1969).

⁵⁸ F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin I*, 167 (1973).

4,4-Dimethyl-3,5-diphenyl-4*H*-pyrazole has been oxidized directly to the *N*-oxide (4%) with $\text{CF}_3\text{CO}_3\text{H}$.⁵⁹

2. From Open-Chain Precursors

Dioximes **47** (Scheme 16), formed in the anti (*E,E*) configuration from diketones **1** and hydroxyammonium chloride,¹⁵ are converted via intermediates **48** to *N*-oxides **49** on heating with thionyl chloride.^{15,52}

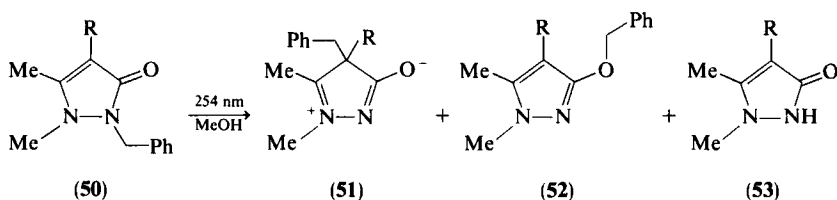


SCHEME 16

Treatment of the dioxime of pentane-2,4-dione with sodium hypobromite⁶⁰ or *N*-bromoacetamide²⁷ gave the dioxide **43** ($\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{X} = \text{Br}$; 39% and 82%, respectively).

G. BETAINES

Only one report on betaines has appeared. Photolysis of the pyrazolone **50** gave the betaine **51** ($\text{R} = \text{Me}$, 56%; $\text{R} = \text{PhCH}_2$, 27%) together with products **52** and **53** (Scheme 17).⁶¹ The mechanism is believed to involve homolysis to benzyl radicals.



SCHEME 17

⁵⁹ W. R. Dolbier, Jr. and W. M. Williams, *J.C.S. Chem. Commun.*, 289 (1970); W. M. Williams and W. R. Dolbier, Jr., *J. Am. Chem. Soc.* **94**, 3955 (1972).

⁶⁰ L. Volodarskii and L. A. Tikhonova, *Khim. Geterotsikl. Soedin.*, 248 (1977) [CA **87**, 23135h (1977)].

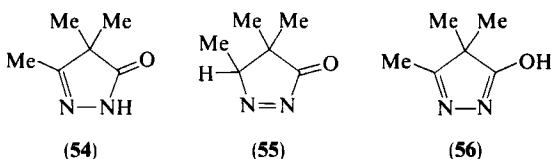
⁶¹ G. Singh, D. Singh, and R. N. Ram, *Tetrahedron Lett.* **22**, 2213 (1981).

III. Structure and Physical Properties

A. STRUCTURE

1. Tautomerism

The tautomerism of 4*H*-pyrazolones has been discussed.⁶² Of the three forms **54**–**56** that might exist in equilibrium, there is no spectroscopic evidence for **55** or **56**.³² Likewise **24** does not appear to be in equilibrium with its dihydroxy tautomer.³⁵



Structures **26** ($R^3 = H$) are found in the amino rather than the imino form.³⁸

2. Dipole Moments

The dipole moment of one *N*-oxide (**49**: $R^1 = R^3 = Me$, $R^2 = Et$) has been reported as 6.76 D (benzene, 20°C).⁵²

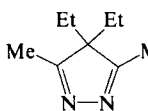
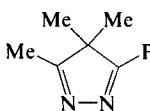
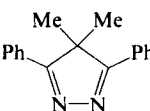
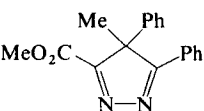
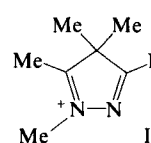
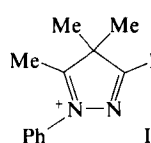
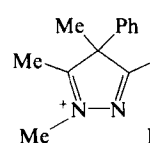
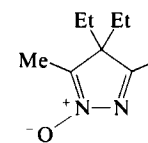
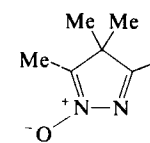
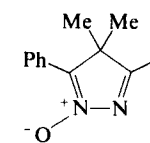
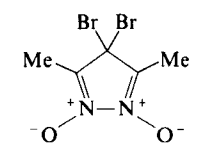
B. SPECTROSCOPIC PROPERTIES

1. Ultraviolet Spectra

4*H*-Pyrazoles with nonconjugating substituents show only one region of UV absorption (200–230 nm, $\log \epsilon = 3.1$ – 3.8).^{14,15,30} Salt formation results in a bathochromic shift in $\lambda_{\max}$, and a small increase in $\log \epsilon$.^{8,47} With aryl conjugation there is a large bathochromic shift, and a second band appears.^{10,15,42,43,45,47} The illustrated examples **57**–**59**,¹⁵ **60**,⁴⁵ **61**, **62**,⁴⁷ and **13**,⁸ show the effect of substituents and salt formation. A change of solvent from ethanol to hexane causes a small hypsochromic shift.^{45,47}

Data for some *N*-oxides **63**–**65**¹⁵ and **66**,⁶⁰ (ethanol) are also illustrated. In contrast to the parent compounds above, the spectra are markedly influenced

⁶² J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem., Suppl.* **1**, 346–348 (1976).

			
(57)	(58)	(59)	(60)
$\lambda_{\max}$ (nm) 203	208, 275	222, 313	222, 306
$\log \epsilon$ 3.8	3.9, 4.1	3.9, 4.3	4.06, 4.12
			
(61)	(13)	(62)	
$\lambda_{\max}$ (nm) 222	270	219, 299	
$\log \epsilon$ 4.15	3.97	4.36, 3.99	
			
(63)	(64)	(65)	(66)
$\lambda_{\max}$ (nm) 198, 269	232, 312	263, 344	272
$\log \epsilon$ 4.1, 3.4	3.9, 4.0	4.1, 4.0	3.58

by the dielectric constant of the solvent. The 4,4-dimethyl analog of **63** absorbs at 259.5 nm ($\log \epsilon = 2.88$) in water, and 291.5 nm ($\log \epsilon = 2.10$) in cyclohexane.⁵²

The mesoion (**51**: R = Me) shows one peak at 300 nm ($\log \epsilon = 3.68$).

2. Infrared Spectra

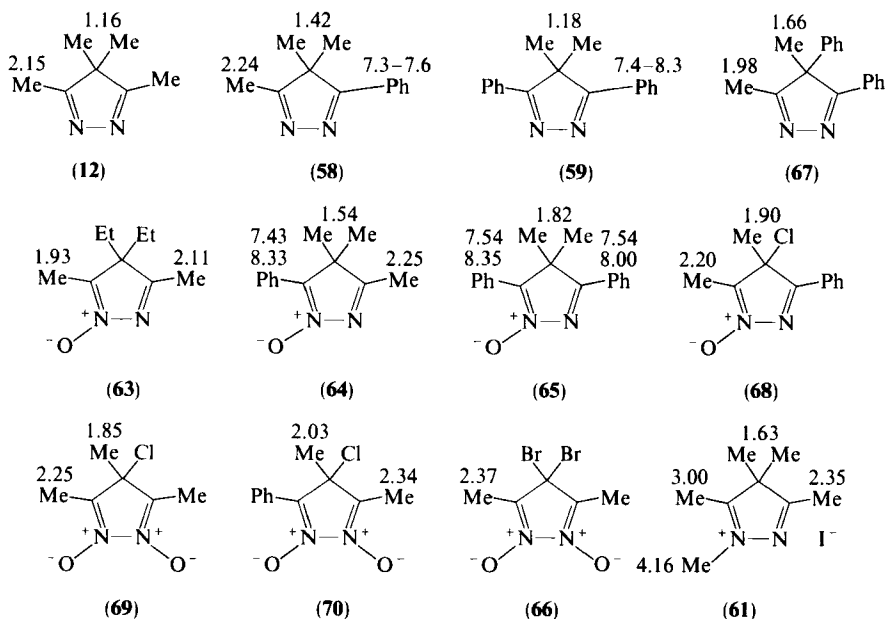
For simple alkyl substituted 4*H*-pyrazoles, $\nu_{C=N}$ is found near 1600 cm^{-1} in neat liquids¹⁴ and near 1580 cm^{-1} in KBr,¹⁵ but in solution in carbon tetrachloride two bands are found, respectively, near 1615 cm^{-1} (m) and 1580 cm^{-1} (s).⁵² Two such traces have been published.⁷ With aryl conjugation, the band is found in the range 1580–1570 cm^{-1} .^{18,47} Trends for salts are less clear.⁴⁷

In *N*-oxides a common band is found between 1590 and 1575 cm^{-1} , and another near 1145 cm^{-1} .^{15,59} with an electronegative 4-substituent, $\nu_{C=N}$ increases to 1610–1595 cm^{-1} .²⁶

All *N,N'*-dioxides reported have an electronegative 4-substituent; there is a common band between 1695 and 1635 cm^{-1} .^{26,60}

3. ¹H-NMR Spectra

No examples of 4H-pyrazoles are known having a proton directly attached to a ring carbon. ¹H-NMR spectra (CDCl₃, CCl₄, CH₂Cl₂) have been reported for a variety of 4H-pyrazoles,^{8,10,14,15,18,24,30,45,57,59} N-oxides,^{15,26,52,59} N,N'-dioxides,^{26,57,60} and salts,^{8,47,63,64} each bearing ring methyl groups. A selection of these are illustrated. In **65**, the ortho protons signal for the phenyl group closest to the N-oxide function appears at lower field than that for the more remote phenyl.^{15,59} In **61** and related salts,^{8,47} long-range coupling is observable between the N-methyl and 5-methyl groups; similar coupling (*J* = 1 Hz) is reported between the analogous methyl groups in **51**.⁶¹

4. ¹³C-NMR Spectra

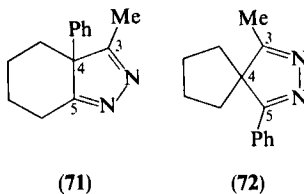
Very few ¹³C-NMR data have been reported. For structures **29**, signals for carbons C-3, C-3a, and C-7a are found in the ranges δ 148.8–155.2, δ 78.7–79.6, and δ 161.9–162.8, respectively.⁶⁵ Spectra of the two 4H-pyrazoles **71** and **72** show the C-4 signal at δ 63.3 and 67.9, respectively,

⁶³ D. S. Melament and J. M. McBride, *J. Am. Chem. Soc.* **92**, 4586 (1970).

⁶⁴ M. E. Landis, R. L. Lindsey, W. H. Watson, and V. Zabel, *J. Org. Chem.* **45**, 525 (1980).

⁶⁵ H. Dürr, H. Kober, R. Sergio, and V. Formacek, *Chem. Ber.* **107**, 2037 (1974).

whereas those for C-3 and C-5 lie in the range δ 177.9–181.9. Methyl groups at C-3 give signals at δ 12.5 and 13.1, respectively.⁴⁶



5. Mass Spectra

Simple 4*H*-pyrazoles break down in mass spectroscopy by loss of one 4-substituent to give an aromatic ion, followed by elimination of nitrogen and fragmentation of the remaining carbon skeleton.^{15,66,67} For the fused-ring systems **29**, nitrogen loss is not apparent,^{49,65} and in the case of structures **71** and **72**, accurate mass measurements have shown that initial loss of 28 units is due to C₂H₄ and not N₂.⁴⁶

The spectrum of **63** shows a small *M* – 16 peak due to loss of the *N*-oxygen.⁶⁸ This is not apparent in related *N*-oxides.¹⁵

6. Photoelectron Spectra

The energy of splitting, $\Delta\epsilon = 2.28$ eV, of the nonbonding orbitals of the two nitrogen atoms in **12** leads to a dihedral angle of 0°.⁶⁹

IV. Chemical Reactions

A. THERMAL REACTIONS FORMALLY INVOLVING NO OTHER SPECIES

1. Migration of 4-Substituent

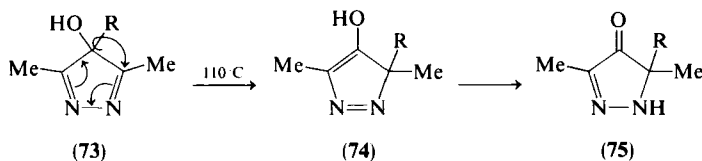
a. *To C-3.* The 4-hydroxy compounds **73** (Scheme 18) undergo a thermally allowed [1,5]-sigmatropic shift at 110°C, to give, via the enols **74**,

⁶⁶ R. A. Khmel'nitskii, A. P. Krasnoshchek, A. A. Polyakova, and I. I. Grandberg, *Zh. Org. Khim.* **3**, 1540 (1967) [*CA* **68**, 34199r (1968)].

⁶⁷ A. P. Krasnoshchek, R. A. Khmel'nitskii, A. A. Polyakova, I. I. Grandberg, and V. I. Minkin, *Zh. Org. Khim.* **4**, 1690 (1968) [*CA* **70**, 19432j (1969)].

⁶⁸ N. Bild and M. Hesse, *Helv. Chim. Acta* **50**, 1885 (1967).

⁶⁹ P. Rademacher, *Chem. Ber.* **108**, 1548 (1975).



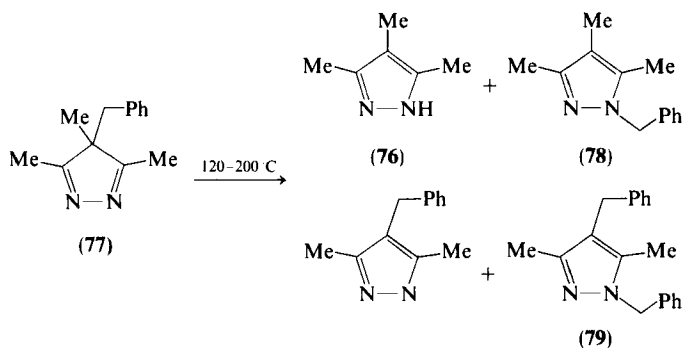
SCHEME 18

the pyrazolones **75**.¹⁴ The group R migrates with retention of configuration, and the rate is not affected by acid catalysis.

Analogous rearrangement of **31** on heating with methanolic HCl¹⁶ may thus be a thermal rather than an acid-catalyzed process.

b. *To Nitrogen.* On prolonged heating at 182°C, the tetramethyl compound **12** isomerizes to 1,3,4,5-tetramethylpyrazole.⁴⁷ At 400°C a small amount of 3,4,5-trimethylpyrazole (**76**) is also formed; a free radical mechanism was indicated by scrambling of CD₃ groups in the rearrangement of the 3,5-bistrideuteriomethyl analog of **12**.¹³

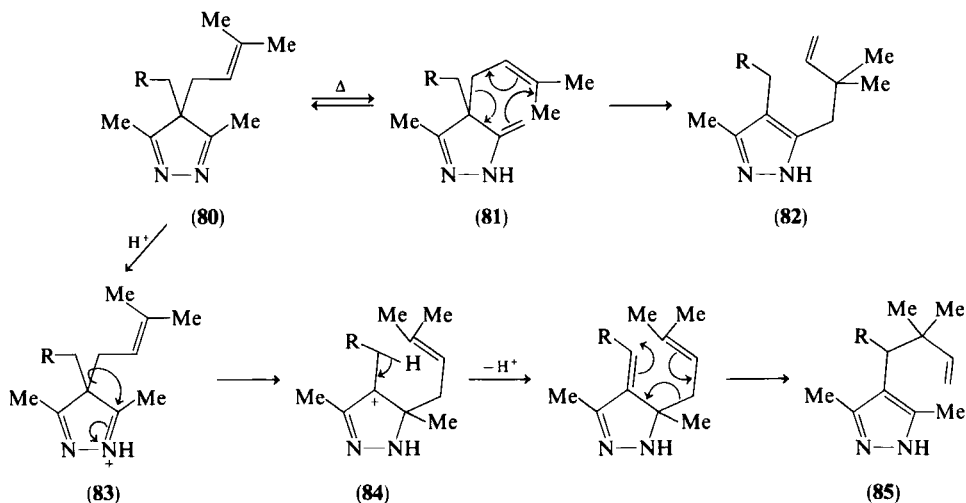
Vacuum distillation of the benzyl derivative **77** gave a mixture of equal amounts of four products (Scheme 19); stilbene was also formed, again suggesting a radical mechanism.⁷ A dilute solution in boiling tetralin, however, gave only **76** (60%) and **78** (18%).¹³ In the case of **59** both a methyl and a phenyl group were observed to migrate.¹³



SCHEME 19

2. Cope Rearrangements

3,5-Dimethyl-4H-pyrazoles, bearing a 2-propenyl or a 2-propynyl group in the 4-position, rearrange by [3,3]-sigmatropic processes.¹¹⁻¹³ If a 4-methyl or 4-ethyl substituent is also present (**80**: R = H or Me), two competing pathways are observed (Scheme 20).



SCHEME 20

The first apparently proceeds via the enamine **81** to give the “normal” products **82** (30% and 35%). The second is believed to be catalyzed by traces of Lewis acid, **83** being converted to **84** by a [1,2]-shift before rearranging further to the “anomalous” products **85** (40% and 44%).^{12,13}

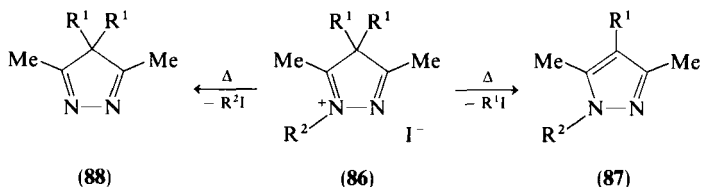
In contrast to **77**, thermal rearrangement (*o*-dichlorobenzene solvent) of 4,4-diallyl-3,5-diphenyl-4*H*-pyrazole gave only 1,4-diallyl-3,5-diphenylpyrazole (93%), suggesting a [3,3]-sigmatropic process rather than a free radical mechanism.¹³

3. Rearrangements of Salts

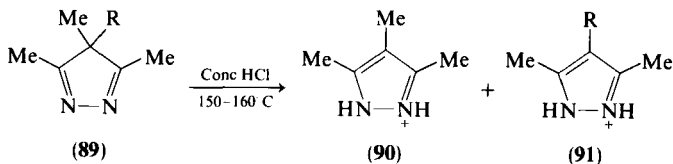
Oettinger⁷⁰ first reported the formation of 1,3,4,5-tetramethylpyrazole from dry thermolysis of the iodide salt **61**; subsequently, 1,2,3,4,5-pentamethylpyrazolium iodide was identified as a coproduct.⁴⁷ The latter authors also observed that thermolysis of **62** gave 1,5-dimethyl-3,4-diphenylpyrazole with none of the 1,3-dimethyl isomer, showing that no migration of the *N*-methyl substituent occurs.⁴⁷

A detailed study into the effects of substituents and temperature on salts **86** showed that both C—C and C—N bond cleavage occur, with the formation of **87** and **88**, respectively (Scheme 21).⁶ For $R^1 = \text{Me}$, **87** predominated over **88** when $R^2 = \text{Et}$, Pr , and *i*- Pr ; the reverse was true when $R^2 = \text{CH}_2=\text{CHCH}_2$ or PhCH_2 . For $R^1 = \text{Et}$, **87** predominated (> 75%) for

⁷⁰ B. Oettinger, *Diss. Jena* (1894) (see ref. 6).



SCHEME 21



SCHEME 22

all substituents R^2 . On raising the temperature, the minor product increased at the expense of the major.⁶ The mechanism presumably involves nucleophilic attack of the anion on the 4- or the *N*-substituent.

Thermolysis of **88** ($\text{R}^1 = \text{PhCH}_2$) with excess benzyl chloride to give **79** (87%) must be a related reaction, as must that between pyrazoles **89** (Scheme 22) and hydrochloric acid to yield **90** and **91**.⁷ Labeling with $^{14}\text{CH}_3$ at C-4 showed ease of loss of R to be $\text{PhCH}_2 > \text{CH}_2=\text{CHCH}_2 \gg \text{Me}$; for $\text{R} = \text{benzyl}$, benzyl chloride (91%) was also isolated.⁷

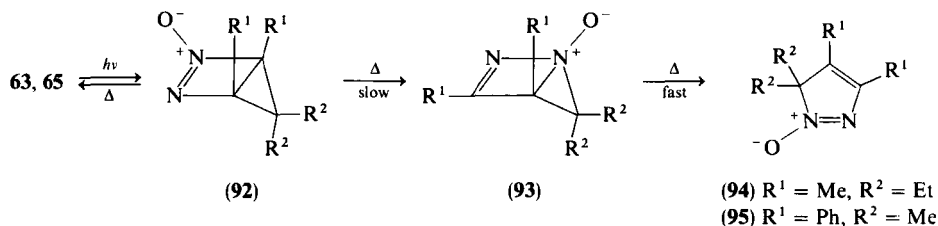
On heating to 200°C , the mesoion **51** ($\text{R} = \text{Me}$) is converted back to **50** (67%).⁶¹

B. PHOTOCHEMICAL REACTIONS FORMALLY INVOLVING NO OTHER SPECIES

Only one photochemical reaction involving no other species has been reported. Photolysis of the *N*-oxides **63** or **65** (medium pressure Hg lamp, pyrex filter) in dichloromethane leads to the 3*H*-isomers **94** (29%) and **95** (71%) (Scheme 23).⁵⁹ The bicycle **92**, derived from **63** and formed by an electrocyclic ring closure, was detected by $^1\text{H-NMR}$ at -78°C and was indefinitely stable below -20°C . On warming to room temperature, part reverted to **63**, and part to **94** via the rearranged bicycle **93**.⁵⁹

Photolysis of **63** in methanol led to a ring-opened methoxy oxime, from attack of the solvent on the corresponding **92**.⁷¹

⁷¹ R. Paredes and W. R. Dolbier, Jr., *Rev. Latinoam. Quim.* **6**, 29 (1975) [*CA* **83**, 8773p (1975)].



SCHEME 23

C. REACTIONS OF RING ATOMS WITH ELECTROPHILES

1. Salt Formation

Concentrated hydrochloric acid up to its boiling point converts **12** to its hydrochloride salt without rearrangement⁷ (compare Scheme 22).

Chlorination of **12** and **88** ($R^1 = \text{PhCH}_2$) at -70°C also gave the respective hydrochlorides rather than the anticipated 3,5-dichloro adducts. In the $^1\text{H-NMR}$ spectra of the salts, there was only one signal for the 3- and 5-methyl groups, showing rapid exchange of the acidic proton between the two nitrogen atoms.⁶³

Alkylation of **12**^{5,6,8,47} and **67**⁴⁷ gives the mono-*N*-alkyl cations in good to excellent yields. Generally the iodide has been used, but chlorides and bromides also apparently form salts at high temperatures prior to rearrangement.⁷ With methyl *p*-toluenesulfonate, compounds **23** form the corresponding 2-methyl cations.³³

2. Complex Formation

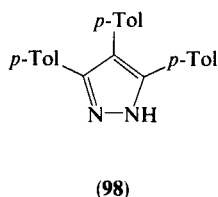
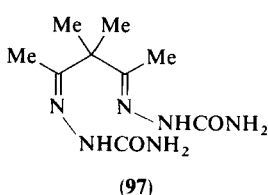
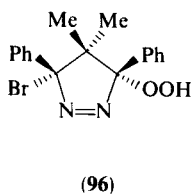
Compound **59** forms complexes of the type $\text{L}(\text{CuCl})_2$, L_2CuBr_2 , L_2PdCl_2 ; IR spectra show coordination to be via the nitrogen lone pairs. They show a bridging tendency toward iron and molybdenum in, e.g., $\text{LFe}_2(\text{CO})_7$ and $[\text{LMo}(\text{CO})_4]_2$.⁷²

3. Halogenating Agents

Although **12** does not take up chlorine in the manner of azines,⁶³ **59** reacts with 1,3-dibromo-5,5-dimethylhydantoin and hydrogen peroxide to give **96**

⁷² H. Tom Dieck, I. W. Renk, and H. P. Brehm, *Z. Anorg. Allg. Chem.* **379**, 169 (1970) [*CA* **74**, 27599s (1971)].

(75%), the molecule having a *cis* configuration.⁶⁴ Compound **96** oxidizes alkenes to oxiranes, in moderate yields,⁷³ and sulfides and tertiary amines, respectively, to sulfoxides and *N*-oxides almost quantitatively.⁷⁴



4. Oxygen

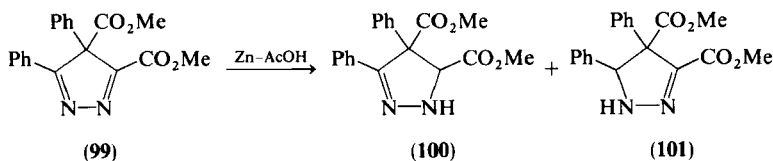
Compound **59** behaves differently from azines toward sensitized photo-oxidation, showing little reaction after 26 h, whereas azines give the parent ketone and nitrogen.⁷⁵

Ozonolysis of **12** consumes two moles of ozone, the product on treatment with semicarbazide yielding the bissemicarbazone **97**.⁷⁶

D. REACTIONS OF RING ATOMS WITH NUCLEOPHILES

1. Reducing Agents

Zinc in acetic acid reduced **31** to **98**.¹⁶ The same reagent converted **99** to a mixture of **100** and **101** (Scheme 24), thus establishing **99** as a product from the van Alphen-Hüttel rearrangement.⁴¹



SCHEME 24

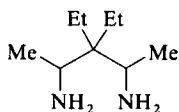
The *N*-oxide **63** gives **102** with zinc in hydrochloric acid and **103** with lithium aluminum hydride⁵²; the latter reducing agent transforms salts **86** (*R*¹ = Me) to *N*-substituted analogs of **103** in high yields.⁸

⁷³ A. L. Baumstark, D. R. Chrisope, and M. E. Landis, *J. Org. Chem.* **46**, 1964 (1981).

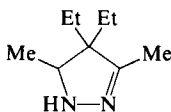
⁷⁴ A. L. Baumstark and D. R. Chrisope, *Tetrahedron Lett.* **22**, 4591 (1981).

⁷⁵ S. S. Talwar, *Indian J. Chem., Sect. B* **16**, 980 (1978).

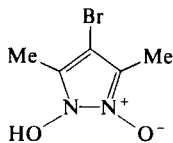
⁷⁶ J. P. Wibaut and J. W. P. Boon, *Helv. Chim. Acta* **44**, 1171 (1961).



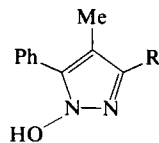
(102)



(103)



(104)



(105)

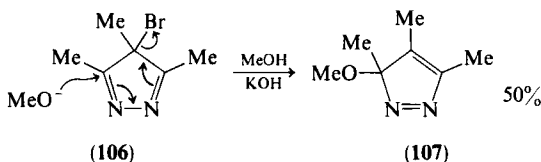
Sodium borohydride reduces the dioxide **66** to the hydroxy *N*-oxide **104**,²⁷ whereas compounds **44** give the related structures **105** with sodium dithionite.⁵

Hydrogenation of **51** ($R = \text{Me}$) over palladium leads to **53** (96%).⁶¹

2. Oxygen Nucleophiles

Most reactions with oxygen nucleophiles that have been reported have involved displacement of a 4-halogen substituent.

Methanol converts **106** to **107** under basic conditions (Scheme 25)²³; a mechanism has been suggested.²⁴



SCHEME 25

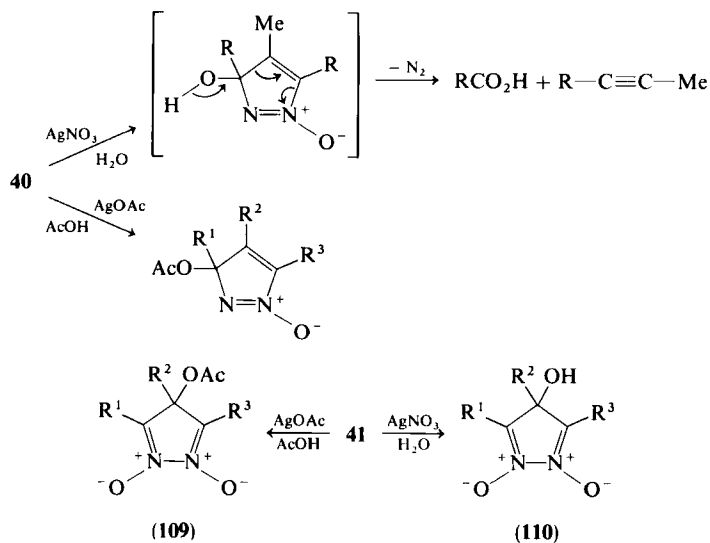
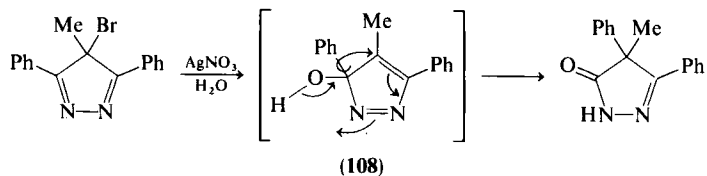
The course of Ag^+ -catalyzed reactions is strongly influenced by the nature of the substrate and of the nucleophile (Schemes 26^{26,56} and 27²⁷); the intermediate is thought to be cationic. Unlike the intermediate **108**, hydroxypyrazole **111** shows no tendency to rearrange to a pyrazolone.²⁷ The dihalide **43** is hydrolyzed to **112** both for $X = \text{Cl}$ ²⁷ and $X = \text{Br}$.^{27,60}

Nitro compound **44** gives **110** ($R^1 = R^3 = \text{Ph}$, $R^2 = \text{Me}$) when heated in chloroform; in ethanol **112** ($R^1 = R^3 = \text{Ph}$) is also formed.⁵⁷

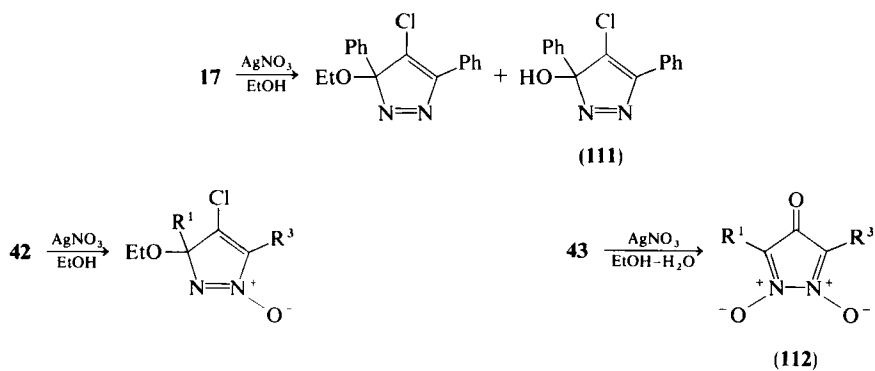
E. REACTIONS WITH CYCLIC TRANSITION STATES

On heating with cyclopropanone **113** (Scheme 28), **59** gives equal amounts of two products; **114** arises from a Diels–Alder reaction, and **115** from direct attack of the pyrazole nitrogen at the carbonyl group.⁷⁷

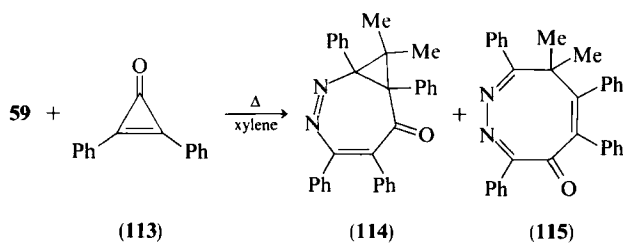
⁷⁷ T. Sasaki, K. Kanematsu, Y. Yukimoto, and E. Kato, *Synth. Commun.* **3**, 249 (1973).



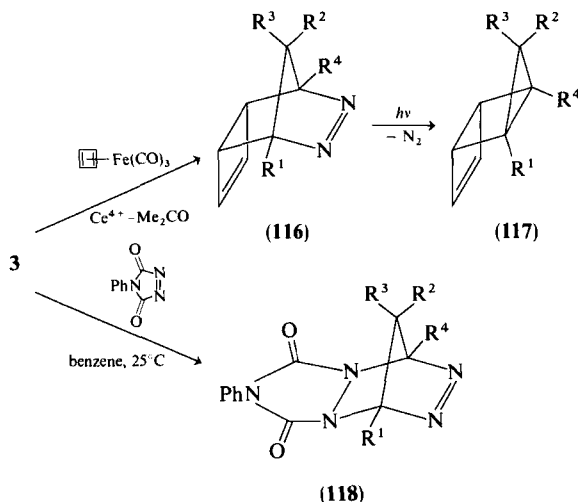
SCHEME 26



SCHEME 27



SCHEME 28



SCHEME 29

Pyrazoles **3** also undergo Diels–Alder addition with cyclobutadiene to give **116** (Scheme 29), which provides a ready entry into the *trans*-tricyclo[4.1.0.0^{2,5}]-3-heptene system **117**.^{17,18,78,79} Where R^2 and R^3 are different, R^3 is the more bulky.¹⁸

Adducts **118** are also readily formed (~100%), R^3 again being the more bulky substituent.^{9,10,80} The *N*-oxide **63** undergoes similar reactions.⁸¹

Attempts to cyclize **51** with dienophiles were unsuccessful.⁶¹

F. REACTIONS OF RING SUBSTITUENTS

1. *C-Linked*

The 3- and 5-methyl groups of 4*H*-pyrazoles are sufficiently acidic to exchange with D₂O in base^{10,11}; rearrangement of **20** to **119** (Scheme 30) also involves base attack at this position, the reaction being analogous to that for dichlorocarbene adducts of pyrroles.⁸²

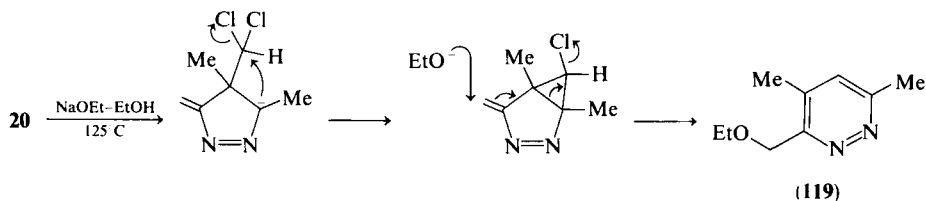
⁷⁸ L. A. Paquette and L. M. Leichter, *J. Am. Chem. Soc.* **92**, 1765 (1970).

⁷⁹ L. A. Paquette and L. M. Leichter, *Org. Photochem. Synth.* **2**, 52 (1976) [*CA* **86**, 189346g (1977)].

⁸⁰ D. R. Arnold, A. B. Evnin, and P. H. Kasai, *J. Am. Chem. Soc.* **91**, 784 (1969).

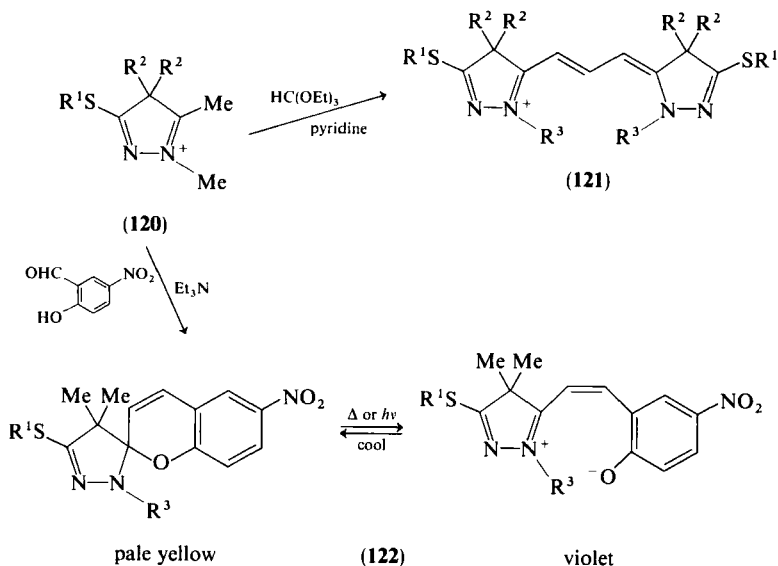
⁸¹ W. R. Dolbier, Jr., W. D. Loehle, and W. M. Williams, *J. C.S. Chem. Commun.*, 867 (1972).

⁸² R. L. Jones and C. W. Rees, *J. Chem. Soc. C*, 2255 (1969).



SCHEME 30

Cations **120** are even more reactive (Scheme 31), readily forming cyanine dyes **121**⁸³ and the photochromic compounds **122**.⁸³

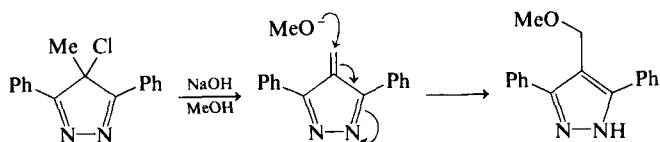


SCHEME 31

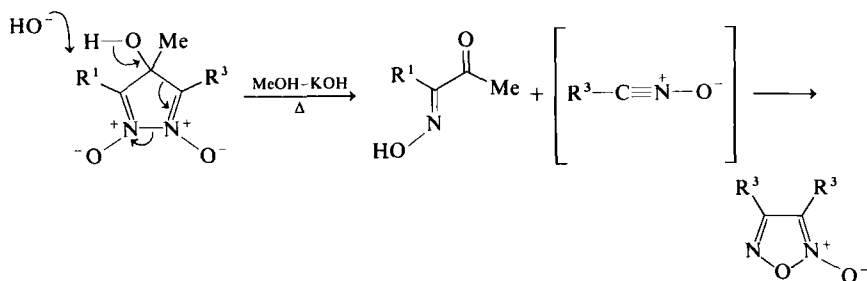
A 4-methyl group in 4-halogenopyrazoles is also susceptible to base attack, a methoxymethyl-1*H*-pyrazole being formed in high yield (Scheme 32). The corresponding *N*-oxide and *N,N'*-dioxide give analogous products.²⁵

The diester **99** is readily decarboxymethylated, yielding 3,4-diphenylpyrazole-5-carboxylic acid on heating with aqueous base and the corresponding methyl ester with acetic acid.⁴¹

⁸³ K. Reynolds, British Patent 1,315,825 (1973) [CA 79, 53316v (1973)].



SCHEME 32



SCHEME 33

2. O-Linked

The *N*-oxide **63** is protonated on oxygen to yield a hydrochloride ($\nu_{\max} = 2174\text{--}2000\text{ cm}^{-1}$); it has also been deoxygenated using phosphorus trichloride in chloroform.⁵²

Treatment of **110** (R² = Me) with strong base results in an interesting fragmentation (Scheme 33).²⁶

The Chemistry of the Triazolopyridines

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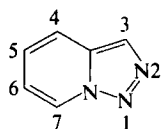
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I. Introduction

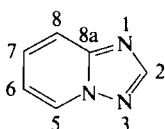
The general class of triazolopyridines includes five heterocyclic systems. Three have bridgehead nitrogen, compounds 1-3; and two do not, compounds 4 and 5. In general these two major divisions reflect differences in synthesis or in properties. Compounds 4 and 5 can exist in several tautomeric forms; there is little direct evidence on the major tautomer, and the compounds are therefore shown throughout in the 1*H* form.

This review covers the literature in primary journals to early 1981 and in Chemical Abstract Subject Indexes to Volume 94. The names used are those adopted by Chemical Abstracts, and the numbering system is [1,2,3] etc. for triazoles rather than the *v*- or *s*- symbols.



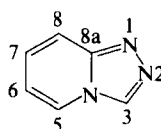
(1)

[1,2,3]Triazolo[1,5-*a*]
pyridine



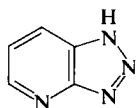
(2)

[1,2,4]Triazolo[1,5-*a*]
pyridine



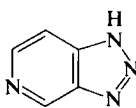
(3)

[1,2,4]Triazolo[4,3-*a*]
pyridine



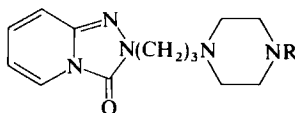
(4)

1*H*-[1,2,3]Triazolo
[4,5-*b*]pyridine



(5)

1*H*-[1,2,3]Triazolo
[4,5-*c*]pyridine



(6)

R = 3-ClC₆H₄
Trazadone

There has been one review on the triazolopyridines 1-3¹ up to 1961. The only other reviews deal with the chemistry and pharmacology of Trazodone (AF 1161) (6).²⁻⁶

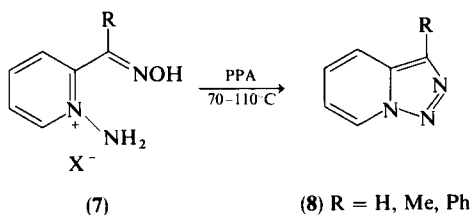
II. Syntheses of the Triazolopyridines

For each heterocycle 1-5 in turn, the syntheses are subdivided into those starting from pyridines and those starting from triazoles; the former predominate in all cases. Within the two major groupings those syntheses involving the formation of only one bond appear first, then those in which two bonds are formed, and finally syntheses by rearrangement of other heterocycles.

A. SYNTHESIS OF [1,2,3]TRIAZOLO[1,5-*a*]PYRIDINES

Syntheses from Pyridines

a. *Formation of One Bond.* There are no syntheses in which a bond is formed between positions 2 and 3. Cyclization of the *N*-aminopyridinium oxime mesylates 7 by polyphosphoric acid gives good yields of 3-substituted triazolopyridines (8).⁷ The related amidoxime 9 is cyclized by acetic anhydride to give 3-acetylaminotriazolopyridine.⁸



¹ W. L. Mosby, "Heterocyclic Compounds. Systems with Bridgehead Nitrogen," Part 2. Wiley (Interscience), New York, 1961.

² G. Palazzo, *Curr. Ther. Res. Clin. Exp.* **15**, 745 (1973) [*CA* **80**, 52299 (1974)].

³ N. Mattusek and W. Greil, *Psychopharmacology* **2**, 1251 (1977) [*CA* **87**, 95177 (1977)].

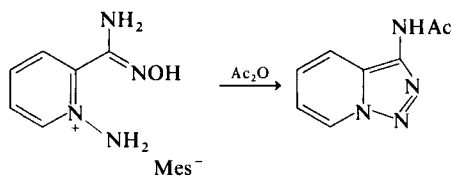
⁴ S. Garattini, *Mod. Probl. Pharmacopsychiatry* **9**, 29 (1974) [*CA* **82**, 25521 (1975)].

⁵ V. G. Longo and A. Scotti de Carolis, *Mod. Probl. Pharmacopsychiatry* **9**, 4 (1974) [*CA* **82**, 25520 (1975)].

⁶ S. Gershon, M. H. Lader, and A. D. S. Caldwell, "New Directions in Antidepressant Theory: An International Review of the Triazolopyridine Derivatives." Academic Press, New York, 1981.

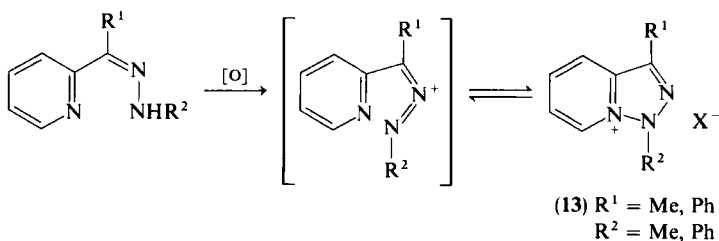
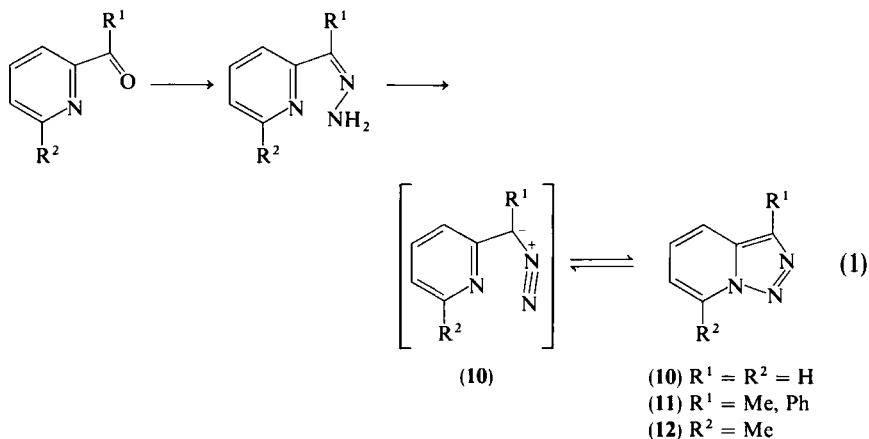
⁷ Y. Tamura, J.-H. Kim, Y. Miki, H. Hiyashi, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 681 (1975).

⁸ A. Tomazic, M. Tisler, and B. Stanovnik, *Tetrahedron* **37**, 1787 (1981).



(9) $\text{Mes}^- = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{SO}_2$

The majority of the [1,2,3]triazolo[1,5-*a*]pyridines have been prepared by formation of a bond between the pyridine nitrogen atom and a side-chain nitrogen (bond 7*a*-1), making use of the fact that the equilibrium $10 \rightleftharpoons 1$ in Eq. (1) lies almost entirely to the right. The most straightforward route involves an oxidation of the hydrazone of a pyridine-2-aldehyde or ketone as shown in Eq. (1); for the synthesis of the parent **1**, 2-pyridylcarboxaldehyde hydrazone is oxidized by silver oxide⁹ or potassium ferricyanide.¹⁰ Nickel peroxide^{11,12} or manganese dioxide¹³ have been used to obtain 3-substituted



⁹ J. H. Boyer, R. Borgers, and L. T. Wolford, *J. Am. Chem. Soc.* **79**, 678 (1957).

¹⁰ J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).

¹¹ S. Mineo, S. Kawamura, and K. Nakagawa, *Synth. Commun.* **6**, 69 (1976).

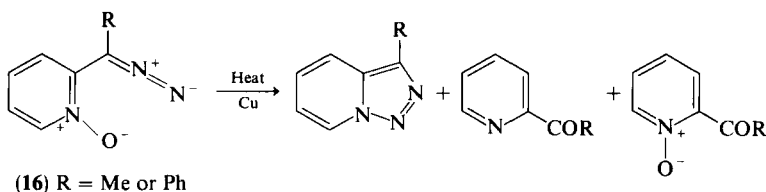
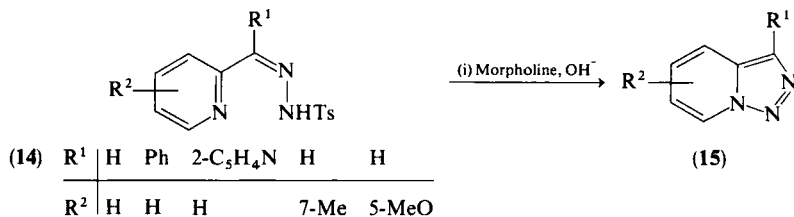
¹² H. Ogura, S. Mineo, K. Nakagawa, and S. Shiba, *Yakugaku Zasshi* **101**, 329 (1981) [*CA* **95**, 80801 (1981)].

¹³ B. Eistert and E. Endres, *Justus Liebigs Ann. Chem.* **734**, 56 (1970).

triazolopyridines (**11**), and from 6-methylpyridine-2-carboxaldehyde hydrazone, 7-methyltriazolopyridine (**12**) has been obtained.¹⁴

If an N-substituted hydrazone is used, a quaternary triazolopyridinium salt (**13**) is the product. Such oxidations have been performed with lead tetraacetate,¹⁵ with *N*-bromosuccinimide,¹⁶ or electrochemically.¹⁷

A variant on this synthesis uses the tosylhydrazones **14**, which on treatment with a base (aqueous alkali,¹⁸ morpholine¹⁹ or sodium ethoxide²⁰) give the triazolopyridines **15**, often in excellent yield. Heating or irradiating such tosylhydrazones in basic media can give triazolopyridines.²¹



Pyridyldiazoalkanes **16**, when pyrolyzed with or without copper as catalyst, give triazolopyridines among other products.²² Other reactions that probably involve pyridyldiazoalkanes as intermediates are noted in Sections I, A, 1, b and c.

b. *Formation of Two Bonds.* Regitz has shown^{23,24} that diazo groups can be directly transferred to active methylene groups under basic conditions, using tosyl azide as the source of the diazo group. Substituted

¹⁴ G. Jones and D. R. Sliskovic, *J.C.S. Perkin I*, 967 (1982).

¹⁵ R. Kuhn and W. Münzing, *Chem. Ber.* **85**, 29 (1952).

¹⁶ R. Kuhn and W. Münzing, *Chem. Ber.* **86**, 858 (1953).

¹⁷ M. Lacan, K. Jakopcic, V. Rogic, S. Damoni, and O. Rogic, *Synth. Commun.* **4**, 219 (1974).

¹⁸ J. H. Boyer and N. Goebel, *J. Org. Chem.* **25**, 304 (1960).

¹⁹ M. Paddon-Row, unpublished results.

²⁰ H. Reimlinger, F. Billiau, and M. Peiren, *Chem. Ber.* **97**, 3493 (1964).

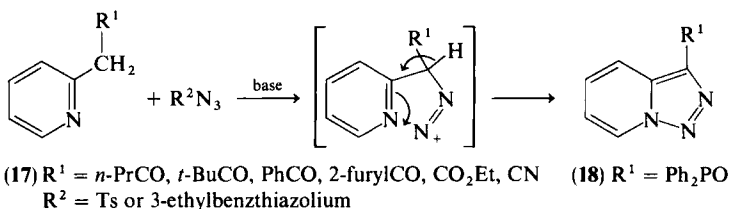
²¹ T. Miyaska, *Iyo Kizai Kenkyusho Hokoku (Tokyo Ika Shika Daigaku)* **2**, 67 (1968) [*CA* **70**, 106324 (1969)].

²² R. A. Abramovitch, C. S. Menon, M. Murata, and E. M. Smith, *J.C.S. Chem. Commun.*, 693 (1974).

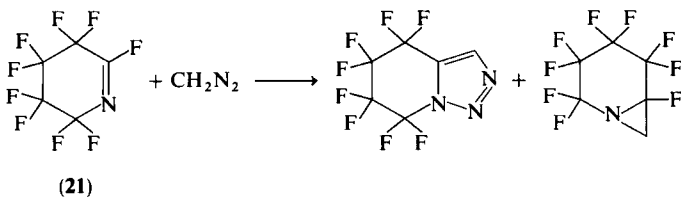
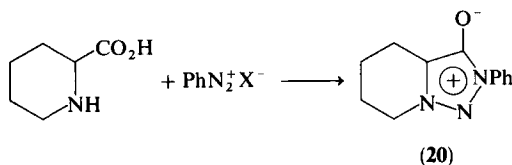
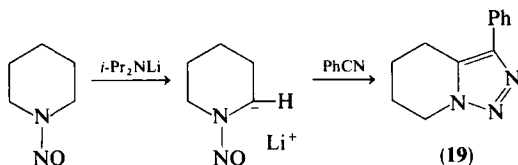
²³ M. Regitz and A. Liedhegener, *Chem. Ber.* **99**, 2918 (1966).

²⁴ M. Regitz, *Angew. Chem.* **77**, 428 (1965).

2-methylpyridines (17) are sufficiently activated to undergo such a reaction (2-picoline itself is not sufficiently reactive), and the products are triazolo[1,5-*a*]pyridines. Thus have been prepared 3-acyl- and 3-aryltriazo-
lopyridines,^{23,24} 3-ethoxycarbonyltriazolopyridines,²⁵ and the phosphine
oxide 18.²⁶ In most cases a sodium alkoxide was used as the base; in one case²⁶
phenyllithium was used. In the synthesis of 3-cyanotriazolopyridine the
diazio group was derived from 2-azido-3-ethylbenzthiazolium fluoroborate.²⁷



Three methods for making 4,5,6,7-tetrahydrotriazolopyridines use two
fragments to form the triazole ring. The lithium derivative of *N*-nitro-
sopiperidine reacts with benzonitrile to give the 3-phenyl derivative 19.²⁸
Diazonium salts react with α -amino acids to give mesoionic triazole oxides;
if pipecolic acid is used, the product is a tetrahydrotriazolopyridine 3-oxide



²⁵ G. Jones and D. R. Sliskovic, unpublished results.

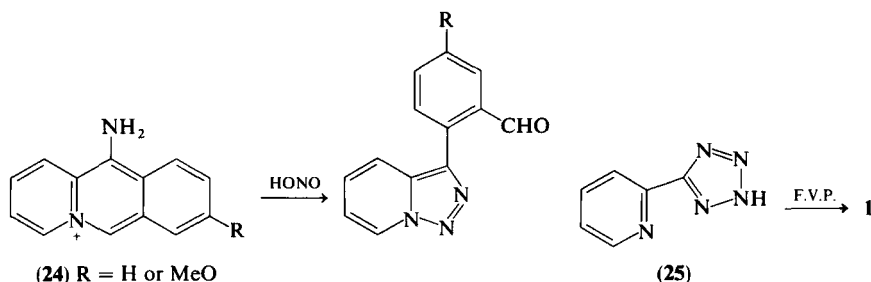
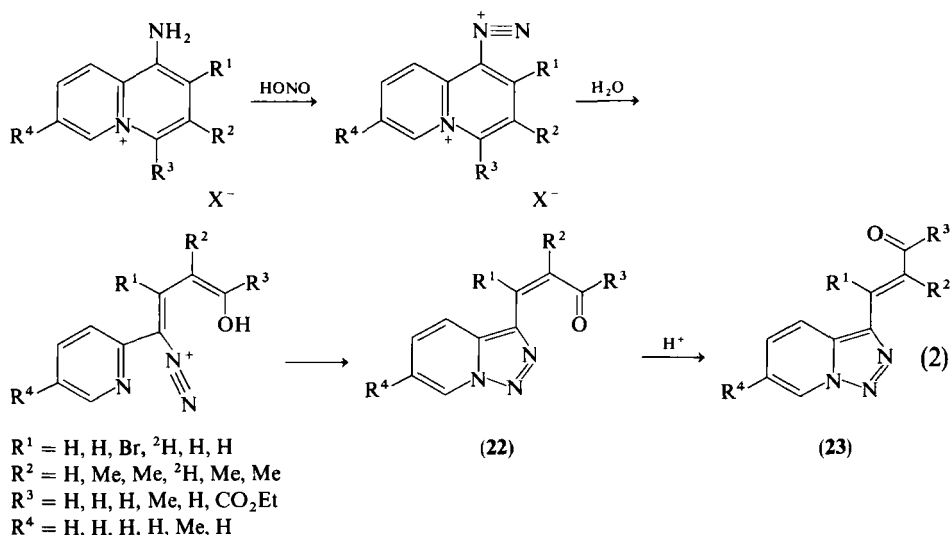
²⁶ M. Regitz and W. Anschutz, *Chem. Ber.* **102**, 2216 (1969).

²⁷ H. Balli, R. Löw, V. Muller, H. Rempfler, and A. Sezen-Gezgin, *Helv. Chim. Acta* **61**, 97 (1978).

²⁸ D. Seebach, D. Enders, R. Dach, and R. Pieter, *Chem. Ber.* **110**, 1879 (1977).

(20).^{29,30} The minor product in the reaction between perfluoropiperidine (21) and diazomethane is an octafluorotetrahydrotriazolopyridine.³¹

c. *By Rearrangement from Other Heterocycles.* When 1-aminoquinolizinium salts are treated with nitrous acid, triazolopyridines with unsaturated side chains are formed, as shown in Eq. (2).^{32,33} Under carefully controlled conditions the *Z* alkenes **22** are formed, but these isomerize under acid conditions rapidly and irreversibly to the *E* isomers **23**. In a reaction of similar mechanism, the aminobenzo[*b*]quinolizinium salts **24** give 3-(2-formylphenyl)triazolopyridines.³⁴



²⁹ Abu-el-Haj, J. Marwen, and J. W. McFarland, U.S. Patent 4,002,636 (1972).

³⁰ Abu-el-Haj, J. Marwen, and J. W. McFarland, Ger. Offen. 2,239,400 [CA 78, 136300 (1973)].

³¹ P. L. Coe and A. G. Holton, *J. Fluorine Chem.* **10**, 553 (1977).

³² L. S. Davies and G. Jones, *J. Chem. Soc.*, 688 (1970).

³³ L. S. Davies and G. Jones, *Tetrahedron Lett.*, 1549 (1969).

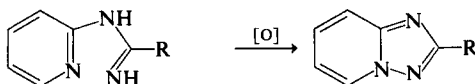
³⁴ C. K. Bradsher and L. S. Davies, *J. Org. Chem.* **38**, 4167 (1973).

Flash vacuum pyrolysis of 5-(2-pyridyl)tetrazole (**25**) gives triazolo-pyridine **1** in low yield, presumably via the diazoalkane.³⁵

B. SYNTHESIS OF [1,2,4]TRIAZOLO[1,5-*a*]PYRIDINES

1. Syntheses from Pyridines

a. *Formation of One Bond.* Major routes to [1,2,4]triazolo[1,5-*a*]-pyridines start from pyridylamidines or pyridylamidoximes. Amidines of general type **26** are oxidized to 2-substituted triazolopyridines; the oxidizing agent can be lead tetraacetate (**26a–26d**),^{10,36} or sodium hypochlorite in a basic medium (**26b**).³⁷



(**26a**) R = Me

(**26b**) R = Ph

(**26c**) R = 4-MeC₆H₄

(**26d**) R = CF₂Cl, 5-Me-8-Et

Cyclization of pyridylamidoximes or their derivatives can give a triazolo-pyridine with a free 2-position; *N*-(2-pyridyl)amidoxime (**27**) gives an O-acetyl derivative that yields the parent triazolopyridine **2** on heating.³⁸ More commonly the oximes are cyclized in an acid medium, as for example in PPA for the preparation of 7-nitrotriazolopyridine (**28**)^{39,40} or of 8-oxadiazolyltriazolopyridine (**29**).⁴¹ In the latter case heating the oxime at 195–205°C without acid gives 8-cyanotriazolopyridine (**30**).⁴¹ Tosyl chloride has been used in the synthesis of 2-benzyltriazolopyridine (**31**).⁴² When oxidized by lead tetraacetate, amidoximes can give *C*-nitrosoimines, which cyclize on heating to give a triazolopyridine 3-oxide (**32**)^{43,44}; bromine in

³⁵ C. Wentrup, *Helv. Chim. Acta* **61**, 1755 (1978).

³⁶ H. Reimlinger, F. Billiau, and W. R. F. Lingier, *Chem. Ber.* **109**, 118 (1976).

³⁷ V. J. Grenda, R. E. Jones, G. Gal, and M. Stetzing, *J. Org. Chem.* **30**, 259 (1965).

³⁸ B. Vercek, B. Stanovnik, M. Tisler, and Z. Zrimsek, *Org. Prep. Proced. Int.* **10**, 293 (1978).

³⁹ S. Polanc, B. Vercek, B. Stanovnik, and M. Tisler, *Tetrahedron Lett.*, 1677 (1973).

⁴⁰ S. Polanc, B. Vercek, B. Sak, B. Stanovnik, and M. Tisler, *J. Org. Chem.* **39**, 2143 (1974).

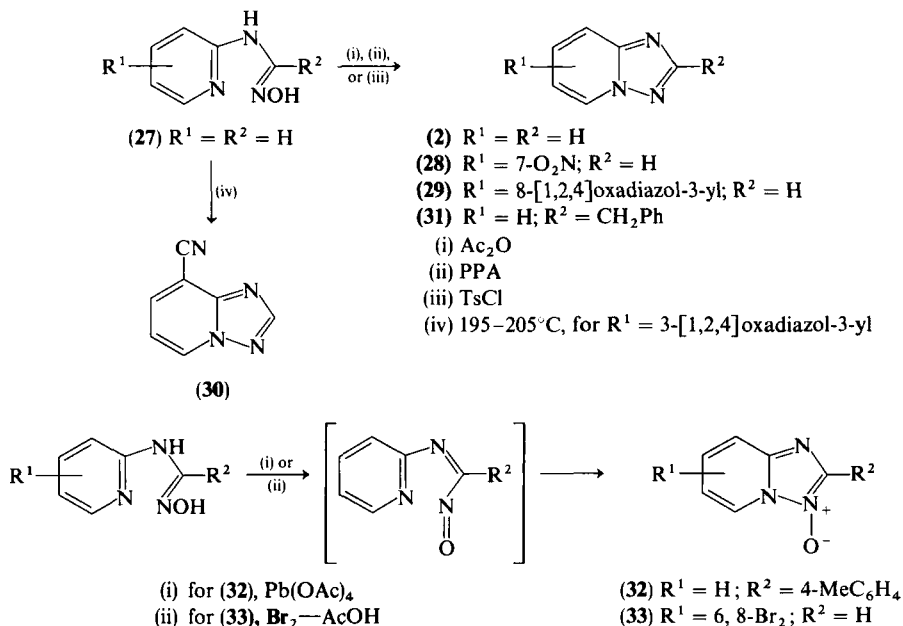
⁴¹ B. Vercek, B. Stanovnik, and M. Tisler, *J. Org. Chem.* **44**, 1695 (1979).

⁴² H. Berner and H. Reimshagan, *Monatsh. Chem.* **106**, 1059 (1975).

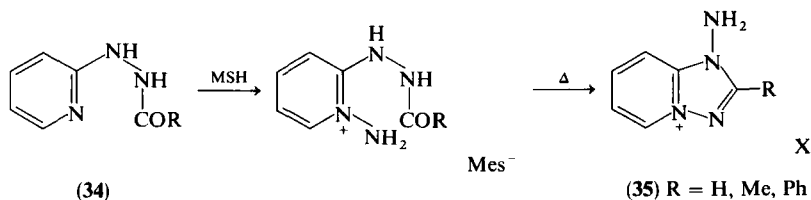
⁴³ T. L. Gilchrist, M. T. Peek, and C. W. Rees, *J.C.S. Chem. Commun.*, 913 (1975).

⁴⁴ T. L. Gilchrist, C. J. Harris, D. G. Hawkins, C. J. Moody, and C. W. Rees, *J.C.S. Perkin I*, 2166 (1976).

acetic acid causes direct oxidative cyclization to the *N*-oxide **33**.⁴⁵ The *N*-oxides can be deoxygenated by phosphorus trichloride.



There are two routes to [1,2,4]triazolo[1,5-*a*]pyridines from *N*-aminopyridinium salts. In one, *N*-(2-pyridyl)hydrazides (**34**) are converted by MSH (mesitylsulfonylhydroxylamine) to *N*-aminopyridinium salts, and these cyclize on heating, giving 1-aminotriazolopyridinium salts (**35**).⁴⁶ In the other, *N*-aminopyridinium salts are treated with *N*-ethoxycarbonylacetimidate to give pyridinium ylides (**36**), which cyclize on heating, giving mixtures of triazolopyridines and imidazopyridines.^{47,48}

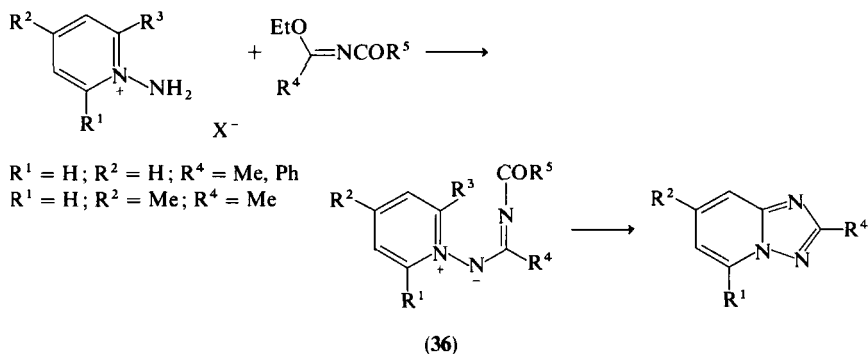


⁴⁵ K. Babic, S. Molan, S. Polanc, B. Stanovnik, J. Stres-Bratos, M. Tisler, and B. Vercek, *J. Heterocycl. Chem.* **13**, 487 (1976).

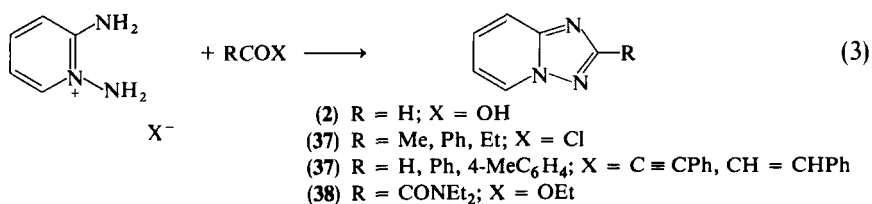
⁴⁶ E. E. Glover and K. T. Rowbottom, *J.C.S. Perkin I*, 367 (1976).

⁴⁷ A. Kakehi, K. Uchiyama, Y. Konno, and K. Kondo, *J. Org. Chem.* **42**, 443 (1977).

⁴⁸ A. Kakehi, S. Ito, K. Uchiyama, and Y. Konno, *Chem. Lett.* **5**, 413 (1976).

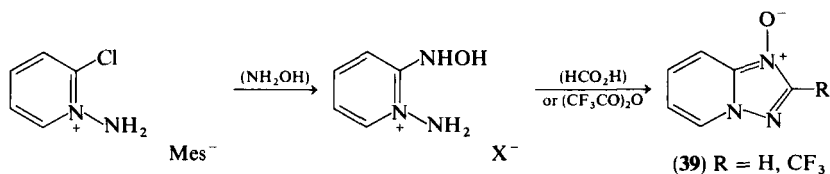


b. Formation of Two Bonds. Reaction between 1,2-diaminopyridinium salts and carboxylic acids (or their chlorides) gives [1,2,4]triazolo[1,5-*a*]pyridines (37); formic acid gives the parent 2.⁴⁹ The range of other acids that can be used is indicated in Eq. (3).



The 1,2-diaminopyridinium salts also react with α,β -unsaturated compounds with the loss of the alkene or alkyne fragment to give 2-substituted triazolopyridines (37),⁵⁰ and with ethyl *N,N*-diethyloxamate to give the amide 38.⁵¹

In a closely related reaction, 1-amino-2-chloropyridinium mesylate is treated with hydroxylamine, and the intermediate hydroxylamine is cyclized by formic acid or by trifluoroacetic anhydride to give the *N*-oxides 39.⁵²

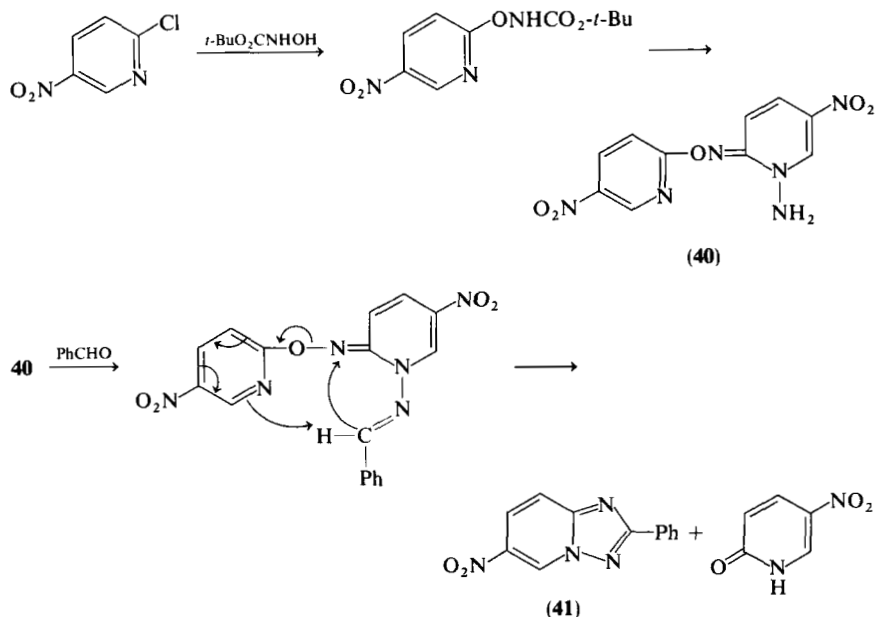


⁴⁹ K. T. Potts, H. R. Burton, and J. Bhattacharyya, *J. Org. Chem.* **31**, 260 (1966).

⁵⁰ Y. Tamura, J.-H. Kim, Y. Sumida, and I. Masazumi, *Yakugaku Zasshi* **95**, 1497 (1975) [*CA* **84**, 90091 (1976)].

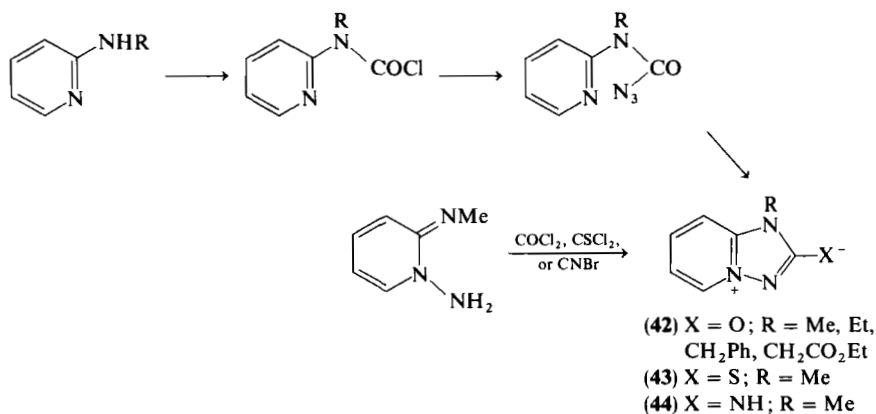
⁵¹ C. Casagrande and A. Invernizzi, *Farmaco, Ed. Sci.* **27**, 101 (1972) [*CA* **76**, 126873 (1972)].

⁵² A. Tomazic, A. Tisler, and B. Stanovnik, *Heterocycles* **12**, 1157 (1979).



A compound (40), isolated from the reaction between 2-chloro-5-nitropyridine and *tert*-butyl *N*-hydroxycarbamate, has been shown to react with benzaldehyde to give 6-nitro-2-phenyl-triazolopyridine (41)⁵³; 5-nitro-2-pyridone acts as a leaving group.

A number of mesoionic compounds of type 42 can be prepared by treating 2-pyridylcarbamoyl chlorides with sodium azide.⁵⁴ The reaction proceeds

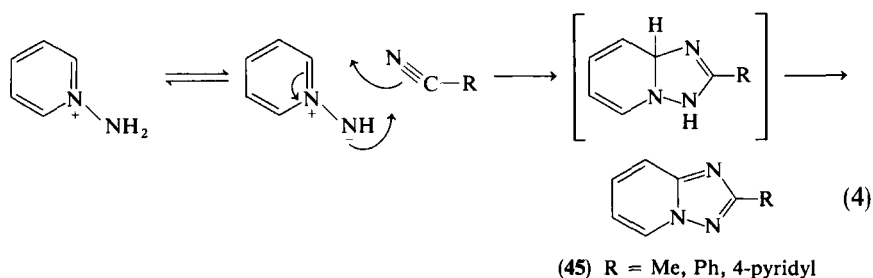


⁵³ T. Sheradsky, G. Saleminck, and Z. Nir, *Tetrahedron* **28**, 3833 (1972).

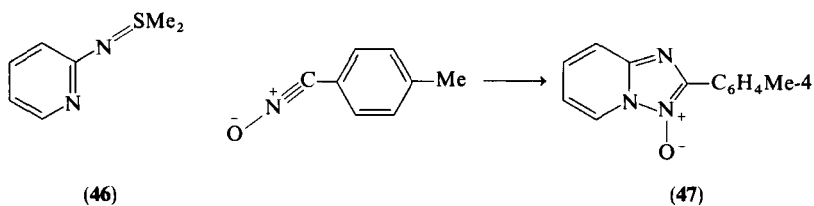
⁵⁴ G. Palazzo and L. Baiocchi, *Gazz. Chim. Ital.* **96**, 1020 (1966).

through an intermediate carbonyl azide, which has been isolated in one case,⁵⁵ although this is not necessary. Similar mesoionic compounds (**43** and **44**) are obtained when 1-amino-2-methyliminopyridine is treated with phosgene, thiophosgene, or cyanogen bromide.⁵⁶

Cyanides can react with 1-aminopyridinium salts to give 2-substituted triazolopyridines, possibly via the pyridinium ylide. With 1-aminopyridinium iodide and cyanide ion the intermediate 4-cyanopyridine reacts with the aminopyridinium salt to give 2-(4-pyridyl)triazolopyridine (**45**).⁵⁷ When acetonitrile or benzonitrile are used, 2-methyl- and 2-phenyltriazolopyridines are obtained.⁵⁸⁻⁶⁰ The reaction is thought to involve a dipolar cycloaddition of the *N*-iminopyridine with the nitrile, as shown in Eq. (4).



Another dipolar cycloaddition is that between the sulfimide **46** and *p*-toluonitrile oxide, giving the triazolopyridine 3-oxide **47**, which can be deoxygenated by phosphorus trichloride to give the 2-(*p*-tolyl)triazolopyridine.⁶¹



⁵⁵ T. Teraji and T. Kametani, Japanese Patent 71/27,466 [CA 75, 151806 (1971)].

⁵⁶ K. T. Potts, S. K. Roy, S. W. Schneller, and R. M. Huseby, *J. Org. Chem.* **33**, 2559 (1968).

⁵⁷ T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. Pharm. Bull.* **14**, 506 (1966).

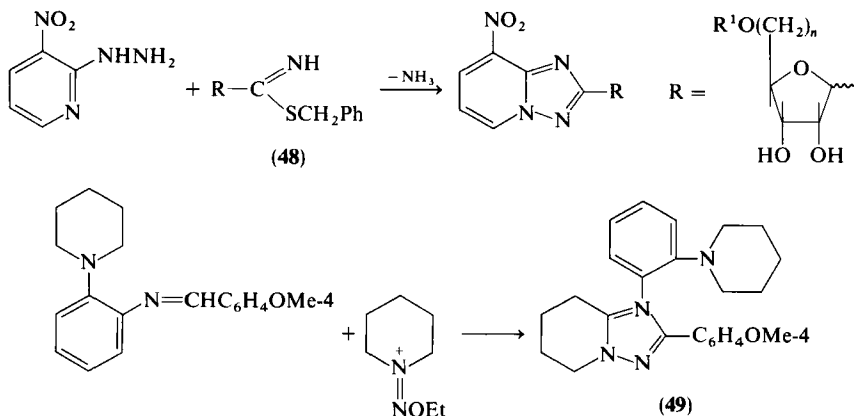
⁵⁸ K. Gewald, A. Schubert, and G. Martin, *J. Prakt. Chem.* **317**, 561 (1975).

⁵⁹ P. J. West and J. H. Parsons, Ger. Offen. 2,720,416 [CA 88, 136623 (1978)].

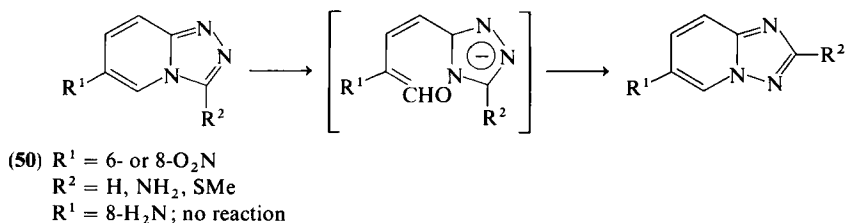
⁶⁰ T. Irikura and S. Suzue, Ger. Offen. 2,905,823 [CA 94, 121541 (1981)].

⁶¹ T. L. Gilchrist, C. J. Harris, C. J. Moody, and C. W. Rees, *J.C.S. Chem. Commun.*, 486 (1974).

Nucleosides based on [1,2,4]triazolo[1,5-*a*]pyridine can be prepared by reaction between 3-nitro-2-pyridylhydrazine and the thioformimidate **48** followed by ammonolysis.^{62,63} A tetrahydrotriazolopyridinium salt (**49**) results from a reaction between a diazenium salt and an anil.⁶⁴



c. *By Rearrangement from Other Heterocycles.* Isomerization of [1,2,4]triazolo[4,3-*a*]pyridines (**50**) by hot base can give [1,2,4]triazolo[1,5-*a*]pyridines.⁶⁵ The isomerization is greatly facilitated by electron-withdrawing groups and retarded by electron-donating groups.⁶⁶ The isomerization of 6-nitrotriazolopyridine (**50**; $\text{R} = \text{NO}_2$) is so easy that it occurs during attempts at synthesis.⁶⁶



⁶² T. Huynh-Dinh, J. Igolen, J. P. Marquet, E. Bisagni, and J.-M. L'hoste, *J. Org. Chem.* **41**, 3124 (1976).

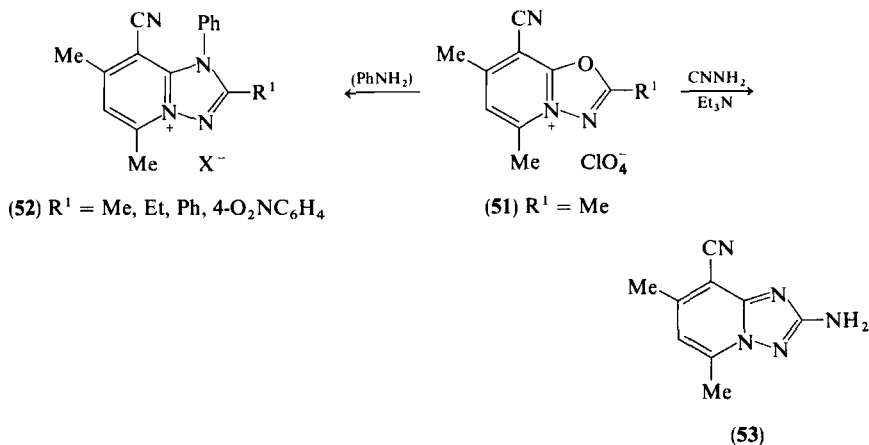
⁶³ J. Igolen, T. Huynh-Dinh, E. Bisagni, M. Gero, and E. De Maeyer, *Fr. Demande* 2,358,154 (1974).

⁶⁴ S. S. Mathur and H. Suschitzky, *J.C.S. Perkin I*, 2474 (1975).

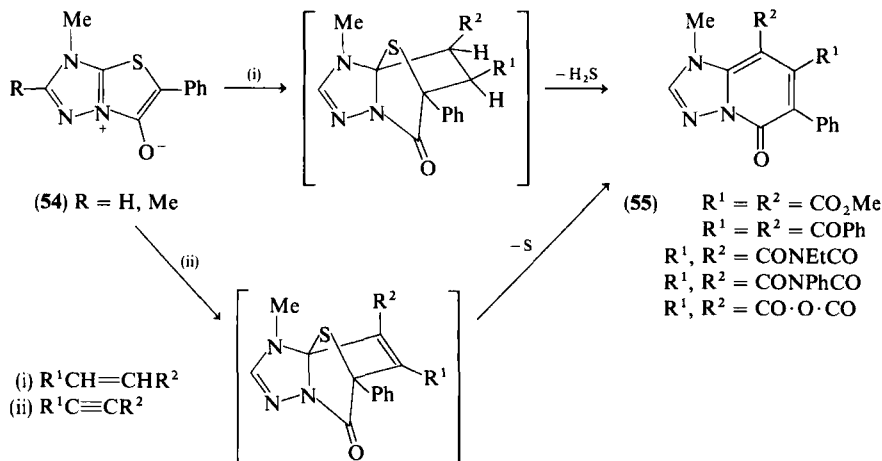
⁶⁵ K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.* **31**, 265 (1966).

⁶⁶ K. T. Potts and C. R. Surapaneni, *J. Heterocycl. Chem.* **7**, 1019 (1970).

Conversion of [1,3,4]oxadiazolo[3,2-*a*]pyridinium salts (**51**) to [1,2,4]-triazolo[1,5-*a*]pyridines can take two pathways: using aniline 1-phenyltriazolopyridinium salts (**52**) are obtained,⁶⁷ whereas using cyanamide and triethylamine, the 2-aminotriazolopyridine **53** is formed.⁶⁸



The mesoionic compound **54** reacts with acetylenic and olefinic dipolarophiles to give 1-methyltriazolopyridin-5-ones (**55**).⁶⁹ With the acetylenes sulfur is eliminated from the bridged intermediate, and with the alkenes hydrogen sulfide is eliminated.



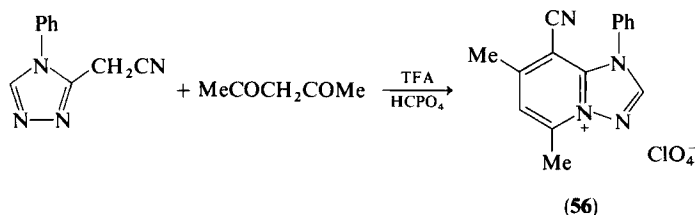
⁶⁷ G. V. Boyd and A. J. H. Summers, *J. Chem. Soc. C*, 409 (1971).

⁶⁸ G. V. Boyd and S. R. Dando, *J. Chem. Soc. C*, 3873 (1971).

⁶⁹ K. T. Potts and S. Kanemara, *J. Org. Chem.* **44**, 3803 (1979).

2. Synthesis from Triazoles

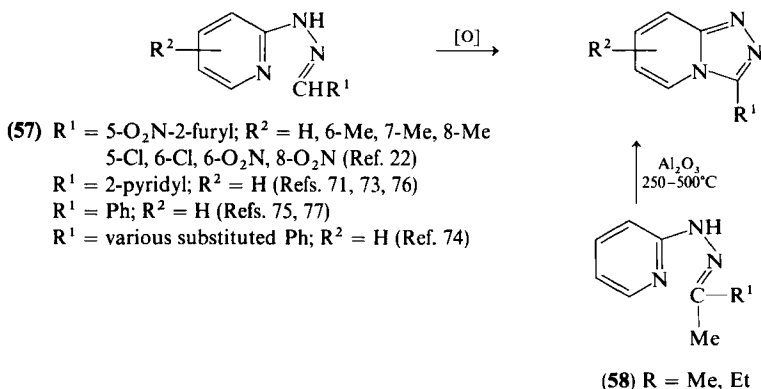
Condensation between pentan-2,4-dione and 4-phenyl[1,2,4]triazol-3-ylacetonitrile gives the highly substituted triazolopyridinium salt **56**.⁷⁰



C. SYNTHESIS OF [1,2,4]TRIAZOLO[4,3-*a*]PYRIDINES

Syntheses from Pyridines

a. *Formation of One Bond.* Most syntheses of [1,2,4]triazolo[4,3-*a*]pyridines are based on 2-pyridylhydrazine as a precursor. Oxidative cyclization of the hydrazones **57** gives 3-substituted triazolopyridines. The hydrazones have been oxidized by lead tetraacetate,^{71,72} nitrobenzene,^{73,74}



⁷⁰ V. A. Chuiguk and K. V. Fedotov, *Ukr. Khim. Zh. (Russ. Ed.)* **46**, 1306 (1980) [*CA* **94**, 208680 (1981)].

⁷¹ B. Stanovnik and M. Tisler, *Croat. Chem. Acta* **49**, 135 (1977).

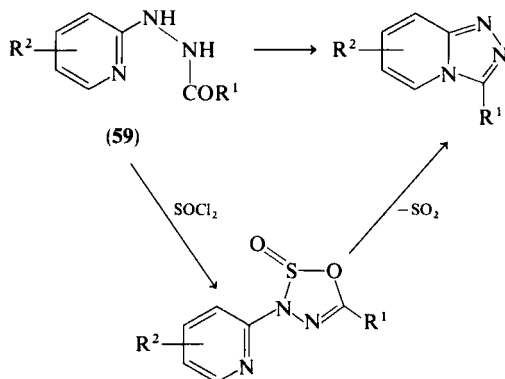
⁷² C. F. Boehringer and Soehne G. M. B. H., British Patent 1,131,590 (1968).

⁷³ S. Naqui and J. R. Srinivasan, *J. Sci. Ind. Res., Sect. B* **21**, 456 (1962).

⁷⁴ S. Naqui and V. R. Srinivasan, *Indian J. Chem.* **3**, 162 (1965).

ferric chloride,⁷⁴ bromination-dehydrobromination,⁷⁵ sulfur,⁷⁶ and by an electrochemical route.⁷⁷ High temperature cyclization of two ketone hydrazones (**58**) over alumina or fluorinated alumina gave 3-substituted triazolopyridines.⁷⁸

Hydrazides **59** can be cyclized by phosphoryl chloride,⁷² thionyl chloride,⁷⁹ boiling phenol,⁸⁰ by heating in the corresponding acid or acid chloride,⁸¹ by lead tetraacetate,⁸² or by heat.⁸³ The thionyl chloride reaction goes via the thioxadiazolone.

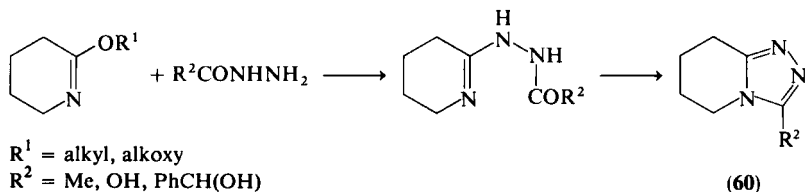


$R^1 = \text{Me, Ph, 2- and 4-pyridyl, 2-O}_2\text{NC}_6\text{H}_4$;

$R^2 = \text{H, 5- and 6-Cl (Ref. 79)}$

$R^1 = i\text{-Pr; } R^2 = \text{H (Ref. 83)}$

$R^1 = \text{H, Me, Et, Bu, OEt; } R^2 = 5\text{-Cl (Ref. 81)}$



⁷⁵ M. S. Gibson, *Tetrahedron* **19**, 1587 (1963).

⁷⁶ L. Kramsberger, P. Lorencek, S. Polanc, B. Vercek, B. Stanovnik, M. Tisler, and F. Povazanec, *J. Heterocycl. Chem.* **12**, 337 (1975).

⁷⁷ I. Tabakovic, M. Trkovnik, and D. Galijas, *J. Electroanal. Chem. Interfacial Electrochem.* **86**, 241 (1978) [*CA* **88**, 81015 (1978)].

⁷⁸ L. Yakhontov, N. N. Suvorov, E. V. Pronina, V. Ya. Kanterov, N. Ya. Podkhalyuzina, N. E. Starostenko, and U. N. Shkil'kova, *Khim. Geterosykl. Soedin.*, 1146 (1972) [*CA* **77**, 139986 (1972)].

⁷⁹ H. Reimlinger, J. J. M. Vandewalle, G. S. D. King, W. R. F. Lingier, and R. Merenyi, *Chem. Ber.* **103**, 1918 (1970).

⁸⁰ G. A. Reynolds and J. A. Van Allan, *J. Org. Chem.* **24**, 1478 (1959).

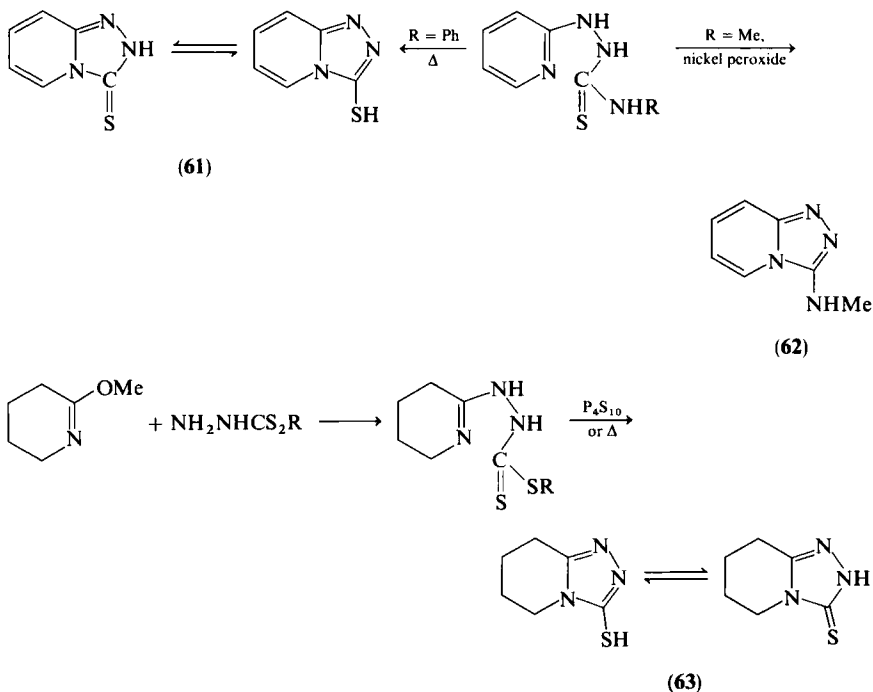
⁸¹ J. W. Schneller and D. G. Bartholomew, *J. Heterocycl. Chem.* **15**, 439 (1978).

⁸² J. D. Bower and F. P. Doyle, *J. Chem. Soc.*, 727 (1957).

⁸³ G. E. Ficken and J. D. Kendal, *J. Chem. Soc.*, 747 (1961).

Other examples of syntheses where a hydrazide is the probable intermediate appear in Section I,C,1,b. The hydrazide cyclization can be used to prepare tetrahydrotriazolopyridines (**60**), starting from cyclic iminoethers.⁸⁴⁻⁸⁷

Closely related are the syntheses from various sulfur-containing derivatives of 2-pyridylhydrazine by which it is possible to obtain the 3-thiol (or thione) **61**⁸⁰ or 3-methylaminotriazolopyridine (**62**).⁸⁸ By use of dithiocarbamates instead of acylhydrazines, the iminoether synthesis gives the tetrahydrotriazolopyridine-3-thiol (or thione) **63**.⁸⁹⁻⁹² Cyclization of the amidine **64** gives 3-anilinothiazolopyridine (**65**).⁹³



⁸⁴ S. Peterson, E. Tietze, and W. Wirth, U.S. Patent 2,913,454 (1959).

⁸⁵ Farbenfabriken Bayer Akt-Ges, British Patent 825,514 (1959).

⁸⁶ S. Peterson and E. Tietze, *Chem. Ber.* **90**, 909 (1957).

⁸⁷ H. Mohrle and H.-J. Hemmerling, *Arch. Pharm. (Weinheim, Ger.)* **310**, 588 (1977).

⁸⁸ H. Ogura, S. Mineo, and K. Nakagawa, *Heterocycles* **14**, 1125 (1980).

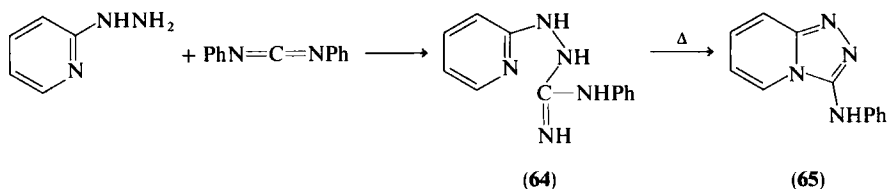
⁸⁹ Egyesult Gyogyszer es Tapszergyer (by J. Kerosi), Austrian Patent 258,289 [*CA* **68**, 165209 (1968)].

⁹⁰ Egyesult Gyogyszer es Tapszergyer, Neth. Patent Appl. 6,605,595 [*CA* **66**, 76012 (1967)].

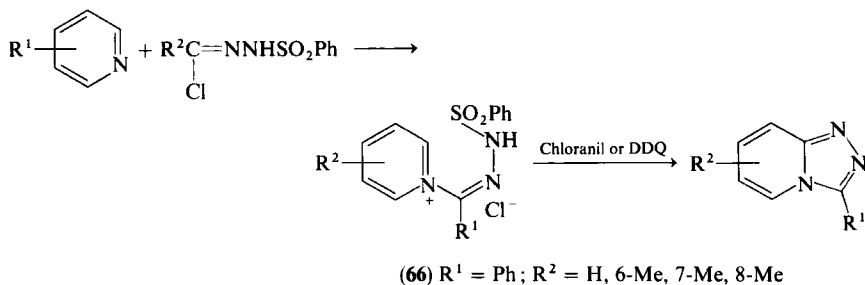
⁹¹ J. Korosi and P. Berenesi, *Magy. Kem. Foly.* **74**, 214 (1968) [*CA* **69**, 52114 (1968)].

⁹² J. Korosi and P. Berenesi, *Chem. Ber.* **101**, 1979 (1968).

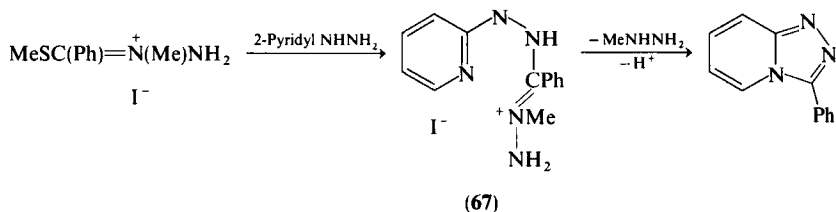
⁹³ H. Reimlinger, F. Billiau, and W. R. F. Lingier, *Synthesis*, 260 (1970).



There is a single example of formation of the 1,8a-bond. The pyridinium salts **66** can be cyclized by chloranil or by DDQ to give 3-substituted triazolo-pyridines.⁹⁴



The intermediate **67** obtained from a methylthiohydrazone salt and 2-pyridylhydrazine can cyclize with loss of a hydrazine to give 3-phenyltriazolopyridine.⁹⁵



b. Formation of Two Bonds. As shown in Section II,C,1,a, 2-pyridylhydrazones or -hydrazides are the commonest precursors for [1,2,4]triazolo[4,3-a]pyridines. There are also many reactions where the 2-pyridylhydrazines react with insertion of a single carbon fragment without isolation of intermediates. In the simplest examples formic acid⁹⁶⁻⁹⁹ or ethyl

⁹⁴ S. Ito, A. Kakehi, T. Matsuno, and J. Yoshida, *Bull. Chem. Soc. Jpn.* **53**, 2007 (1980).

⁹⁵ R. Grashey, M. Baumann, and H. Bauer, *Chem.-Ztg.* **96**, 225 (1972).

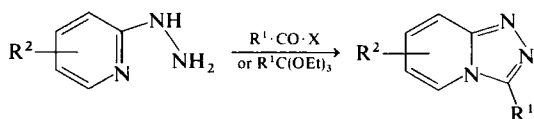
⁹⁶ R. G. Fargher and R. Furness, *J. Chem. Soc.*, 688 (1915).

⁹⁷ R. Graf, E. Lederer-Ponzer, V. Kopetz, R. Purbert, and P. Laszlo, *J. Prakt. Chem.* **138**, 244 (1934).

⁹⁸ S. Portnoy, *J. Heterocycl. Chem.* **7**, 703 (1970).

⁹⁹ W. Marckwald and K. Rudzik, *Ber. Dtsch. Chem. Ges.* **36**, 1111 (1903).

orthoformate^{100,101} produce triazolopyridines **68** without a substituent in position 3. A range of other acids, esters, or anhydrides has been used to give 3-substituted triazolopyridines **69**,^{51,102-109} 3-methyl-6-phenyl-¹¹⁰ and 3-methyl-6-(*p*-chlorophenyl)triazolopyridines.¹¹¹ Dicarboxylic acids give 3,3-ditriazolopyridine and various bis(3-triazolopyridyl)alkanes (**70**).¹⁰⁸



(3)

(**68**) $R^1 = \text{H}$; $R^2 = 5\text{-}, 6\text{-}, 7\text{-}, \text{ or } 8\text{-Me}$; 5,7-Me₂ (Ref. 108)

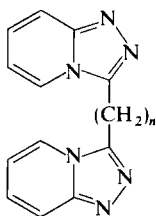
$R^1 = \text{H}$; $R^2 = 5\text{- or } 7\text{-CF}_3$ (Ref. 98)

$R^1 = \text{H}$; $R^2 = 6\text{-CO}_2\text{H}$; 7-Cl-6-CO₂H (Ref. 99)

$R^1 = \text{H}$; $R^2 = 6\text{-(}p\text{-ClC}_6\text{H}_4\text{)}$ (Ref. 100)

$R^1 = \text{H}$; $R^2 = 5\text{-Cl}$ (Ref. 101)

(**69**) $R^1 = \text{Me, Et, } n\text{-Pr, CH}_2\text{Ph, CF}_3, \text{CONEt}_2, \text{NHAc, PhCONHCH}_2, \text{pyridyl, furyl, thienyl, various R-C}_6\text{H}_4 \text{ (including Ph)}$;
 $R^2 = 5\text{-}, 6\text{-}, 7\text{-}, 8\text{-Me, 5,7-Me}_2, 6\text{-Cl}$



(**70**) $n = 0, 1, 2, 3, 8$

¹⁰⁰ J. D. Albright and R. I. Trust, U.S. Patent 4,209,626 (1980).

¹⁰¹ H. Reimlinger, J. J. M. Vandewalle, and W. R. F. Lingier, *Chem. Ber.* **103**, 1960 (1970).

¹⁰² J. Moragues, A. Vega, J. Prieto, M. Marquez, and D. J. Roberts, *Farmaco, Ed. Sci.* **31**, 126 (1976) [*CA* **84**, 180138 (1976)].

¹⁰³ J. Bickling, U.S. Patent 3,050,525 (1963).

¹⁰⁴ T. Kaufmann, H. Hacker, C. Kosel, and K. Vogt, *Z. Naturforsch. B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **14B**, 601 (1959).

¹⁰⁵ J. Bickling, U.S. Patent 2,917,511 (1959).

¹⁰⁶ L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, *Khim. Geterosikl. Soedin.* **2**, 186 (1970) [*CA* **73**, 14810 (1970)].

¹⁰⁷ T. Kaufmann, K. Vogt, S. Barck, and J. Schulz, *Chem. Ber.* **99**, 2593 (1966).

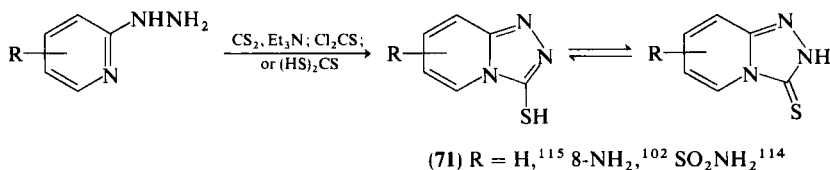
¹⁰⁸ K. T. Potts and H. R. Burton, *J. Org. Chem.* **31**, 251 (1966).

¹⁰⁹ A. Gallarde, Spanish Patent 400,725 [*CA* **83**, 114419 (1975)].

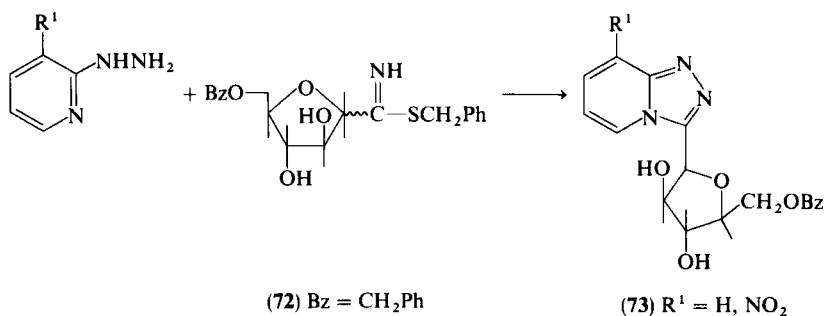
¹¹⁰ R. I. Trust and J. D. Albright, U.S. Patent 4,244,953 (1981).

¹¹¹ R. I. Trust and J. D. Albright, Eur. Patent Appl. 17438 [*CA* **94**, 139815 (1981)].

Triazolopyridine-3-thiols (or thiones) (**71**) are obtained from the hydrazine and carbon disulfide¹¹²⁻¹¹⁴, thiophosgene,¹⁰⁸ or trithiocarbonic acid.¹¹⁵



Other reagents that react with 2-pyridylhydrazines to give triazolopyridines (and the substituents thus introduced) are urea (3-hydroxy),^{104,107,108} ethyl allophanate (3-hydroxy),¹⁰⁸ cyanogen bromide (3-amino),^{104,107} [1,3,4]oxadiazoles (3-RCONHNH, from which 3-hydrazinotriazolopyridine was obtained),¹¹⁶ dichloromethylenebenzamide (3-benzoylamino),¹¹⁷ and the S-benzylthioamides **72**, giving the triazolopyridines **73**.¹¹⁸



If the 2-pyridylhydrazine carries a substituent on N-1, reaction with carbonyl chloride, thiocarbonyl chloride, or cyanogen bromide gives a mesoionic compound (**74**).^{56,114,119}

¹¹² G. A. Mokroshina, I. Ya. Postovskii, and S. K. Kotuskya, *Khim. Geterosikl. Soedin.* **3**, 411 (1977) [*CA* **87**, 53170 (1977)].

¹¹³ D. S. Tarbell, C. W. Todd, M. C. Paulson, E. G. Lindström, and V. P. Wystrach, *J. Am. Chem. Soc.* **70**, 1381 (1948).

¹¹⁴ I. Ya. Postovskii, S. K. Kotovskaya, and A. V. Polonyankin, *Khim. Farm. Zh.* **14**, 50 (1980) [*CA* **93**, 46529 (1980)].

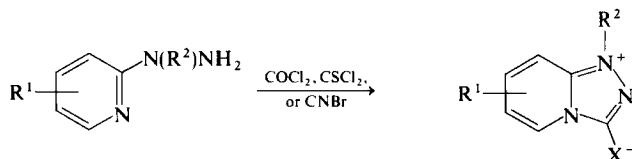
¹¹⁵ W. H. Mills and H. Schindler, *J. Chem. Soc.*, 312 (1923).

¹¹⁶ H. Gehlen and R. Neumann, *J. Prakt. Chem.* **311**, 71 (1969).

¹¹⁷ H. Reimlinger, W. R. F. Lingier, J. J. M. Vandewalle, and E. Goes, *Synthesis*, 433 (1970).

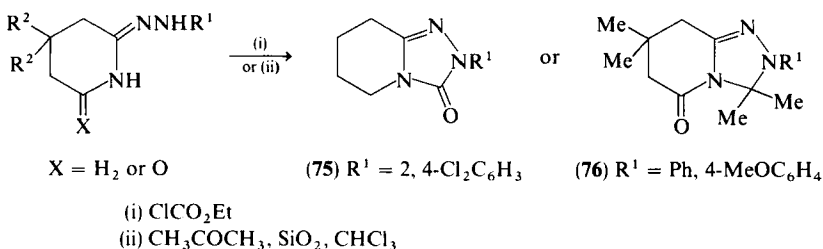
¹¹⁸ G. Doukhan, Huynh Dinh Tam, E. Bisagni, J.-C. Chermann, and J. Igolen, *Eur. J. Med. Chim. Ther.* **14**, 375 (1979) [*CA* **92**, 129221 (1980)].

¹¹⁹ G. Palazzo and L. Baiocchi, *Ann. Chim. (Rome)* **55**, 935 (1965).

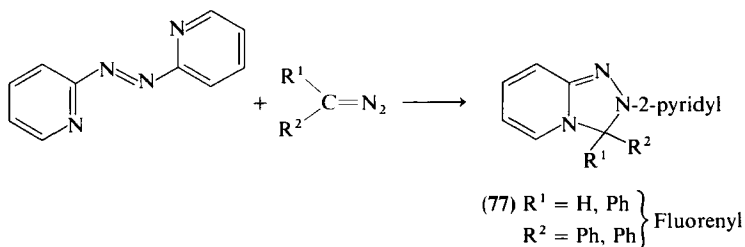


(74) $R^1 = \text{H}, 8\text{-SONH}_2$;
 $R^2 = \text{Me, Ph}$; $X = \text{O, S, NH}$

The reduced triazolopyridin-3-one **75** and triazolopyridin-5-one **76** are made by a superficially similar route from the hydrazones of suitable 2-piperidones. In the first case the additional carbon atom is provided by ethyl chloroformate¹²⁰; in the second, acetone is used.¹²¹



From azobis(2-pyridyl)- and diazoalkanes a series of 3,3-disubstituted [1,2,4]triazolo[4,3-*a*]pyridines (**77**) have been prepared.¹²² If one of the substituents at position 3 is a hydrogen atom, the triazolopyridinium salt can be obtained by treatment with trityl perchlorate.¹²²



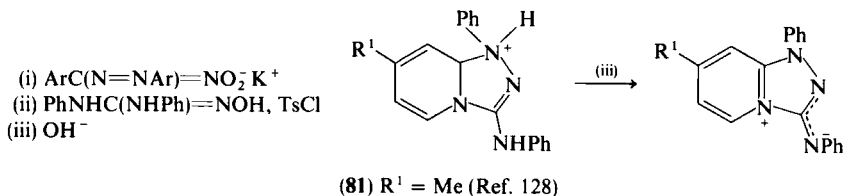
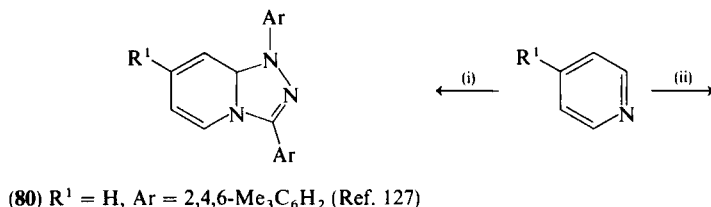
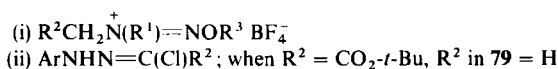
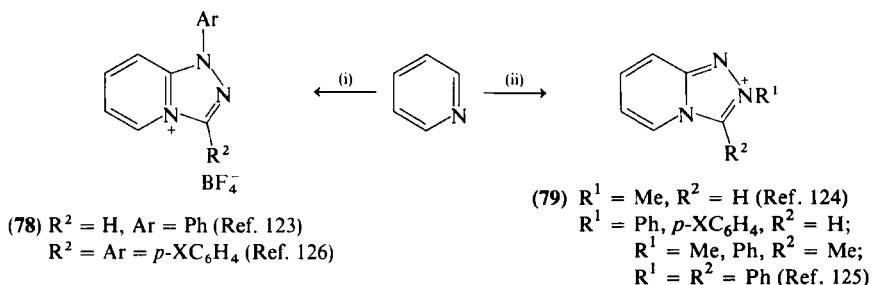
The other major approach to triazolo[4,3-*a*]pyridines is from pyridines or from 2-halogenopyridines, with the addition of a three-atom fragment to form the triazole ring. Reaction between pyridine or 4-methylpyridine and

¹²⁰ A. D. Wolf, Ger. Offen. 2,801,429 [CA **89**, 180006 (1978)].

¹²¹ T. Yamazaki, K. Matobe, S. Imoto, and M. Terashima, *Chem. Pharm. Bull.* **24**, 3011 (1976).

¹²² J. Markert and E. Fahr, *Tetrahedron Lett.*, 4337 (1967).

various azo or diazenium species gives triazolopyridinium salts **78**¹²³⁻¹²⁶ and **79** or 8aH-triazolopyridines **80** and **81**.^{127,128}



From 2-bromopyridines and thiosemicarbazide, 3-aminotriazolopyridine (**82**) is obtained,¹²⁹ and 2-chloropyridines react with 5-phenyl-[1,2,3,4]tetrazoles to give 3-phenyltriazolopyridines (**83**).^{130,131} A tetrahydro-

¹²³ R. Fusco, P. Dalla-Croce, and A. Salvi, *Gazz. Chim. Ital.* **98**, 511 (1968).

¹²⁴ T. Eicher, S. Hünig, and P. Nikolaus, *Angew. Chem., Int. Ed. Engl.* **6**, 699 (1967).

¹²⁵ T. Eicher, S. Hünig, H. Hansen, and P. Nikolaus, *Chem. Ber.* **102**, 3159 (1969).

¹²⁶ A. Gelleri, A. Messmer, I. Pinter, and L. Radics, *J. Prakt. Chem.* **318**, 881 (1976).

¹²⁷ C. Grundmann and K. Flory, *Justus Liebigs Ann. Chem.* **721**, 91 (1969).

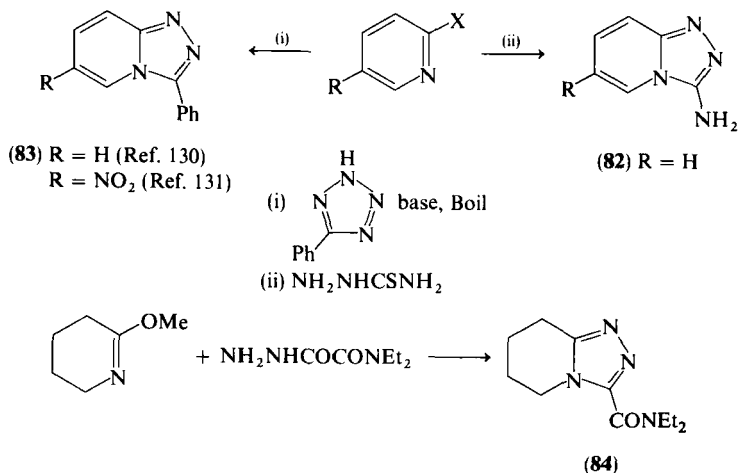
¹²⁸ R. J. Groot, T. J. King, and M. W. Partridge, *J. Chem. Soc. D*, 898 (1971).

¹²⁹ L. Heinisch, *Z. Chem.* **10**, 188 (1970).

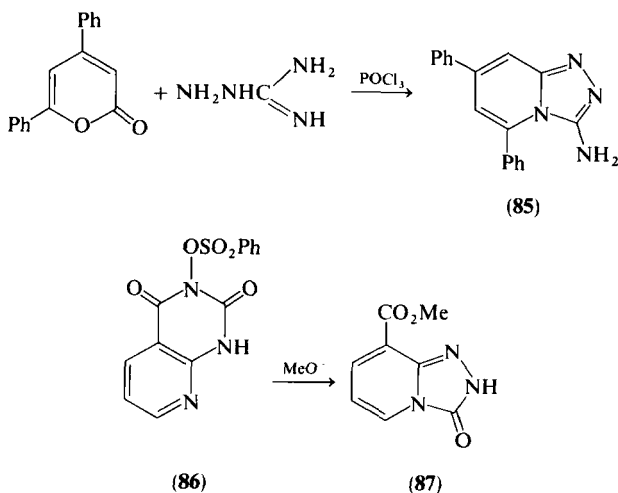
¹³⁰ A. Koennecke and E. Lippmann, *Z. Chem.* **18**, 175 (1978).

¹³¹ R. Huisgen, H. J. Sturm, and M. Seidel, *Chem. Ber.* **94**, 1555 (1961).

triazolopyridine is obtained when *O*-methylvalerolactim reacts with the hydrazide **84**⁵¹; other examples are reported.



c. *By Rearrangement from Other Heterocycles.* Aminoguanidine reacts with 4,6-diphenyl-2-pyrone in phosphoryl chloride to give the aminotriazolopyridine **85**.¹³² The pyridopyrimidinedione **86** undergoes ring contraction when treated with sodium methoxide to give the triazolopyridin-3-one **87**.¹³³



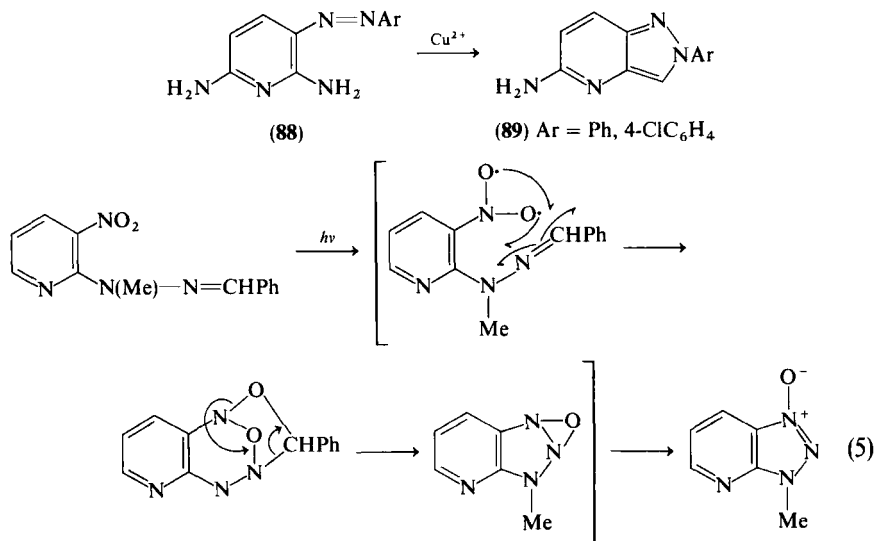
¹³² M. Alajorin, P. Molina, and A. Soler, *An. Quim., Ser. C* **76**, 207 (1980).

¹³³ K.-Y. Tserng and C. Bauer, *J. Heterocycl. Chem.* **11**, 163 (1974).

D. SYNTHESIS OF [1,2,3]TRIAZOLO[4,5-*b*]PYRIDINES AND OF [1,2,3]TRIAZOLO[4,5-*c*]PYRIDINES

1. Syntheses from Pyridines

a. *Formation of One Bond.* Oxidation of the 2-amino-3-(phenylazo)pyridines **88** by copper sulfate¹³⁴⁻¹³⁷ gives the 2-phenyltriazolo[4,5-*b*]pyridines **89**. Ammoniacal copper¹³⁸ has been used in a similar oxidation. Photochemical cyclization of the pyridylhydrazone **90** in benzene gives a triazolo[4,5-*b*]pyridine 1-oxide.¹³⁹ The suggested mechanism for the cyclization is shown in Eq. (5).



b. *Formation of Two Bonds.* Diazotization of a 2,3-diaminopyridine gives a triazolo[4,5-*b*]pyridine (**91a**), whereas diazotization of a 3,4-diaminopyridine gives a triazolo[4,5-*c*]pyridine (**91b**), and these routes have provided many examples for each system. The triazolopyridines of both types, carrying simple substituents, are summarized in Table I.

¹³⁴ B. G. Buell and R. S. Long, U.S. Patent 3,227,717 (1976).

¹³⁵ B. G. Buell and R. S. Long, U.S. Patent 3,058,989 (1962).

¹³⁶ G. M. Timmis, D. G. I. Felton, H. O. J. Collier, and P. L. Huskinson, *J. Pharm. & Pharmacol.* **9**, 46 (1957) [*CA* **51**, 10533 (1957)].

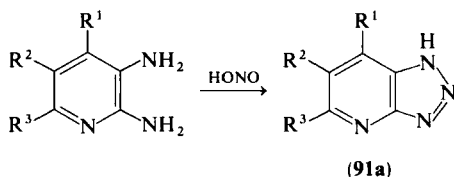
¹³⁷ G. Charrier and M. Jorio, *Gazz. Chim. Ital.* **68**, 640 (1958).

¹³⁸ G. Charrier and M. Jorio, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [6] **26**, 170 (1937) [*CA* **32**, 4583 (1938)].

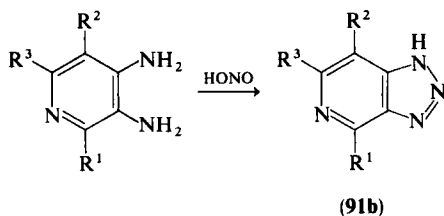
¹³⁹ Y. Maki, M. Suzuki, K. Izuta, and S. Iwai, *Chem. Pharm. Bull.* **22**, 1269 (1974).

TABLE I
 PRODUCTS **91a** AND **91b** PREPARED FROM DIAMINOPYRIDINES

R ¹	R ²	R ³	References for 91a	References for 91b
H	H	H	140	141
H	H	Me	142	143
Me	H	H	—	143
H	Me	H	—	144
H	Me	Me	145	—
H	Cl	H	146, 147	—
Cl	H	H	—	148
H	Br	H	142	—
H	NO ₂	H	142	149
Me	Br	Me	150	—
NH ₂	H	H	151	151
H	NH ₂	H	—	152
H	SH	H	142	—
Cl	H	NH ₂	153	—
Cl	H	NHCO ₂ Et	153	—
OH	H	NH ₂	154	—
OCH ₂ Ph	H	NH ₂	155	—

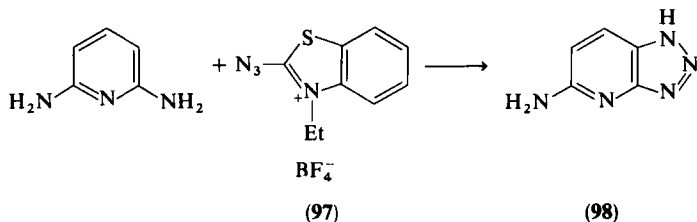


- ¹⁴⁰ A. E. Chichibabin and A. V. Kirsanov, *Ber. Dtsch. Chem. Ges.* **60**, 766 (1927).
¹⁴¹ O. Bremer, *Justus Liebigs Ann. Chem.* **518**, 274 (1935).
¹⁴² H. Graboyes and A. R. Day, *J. Am. Chem. Soc.* **79**, 6421 (1957).
¹⁴³ B. Brekiesz-Lewandowska and Z. Talik, *Rocz. Chem.* **44**, 69 (1970) [*CA* **73**, 45415 (1970)].
¹⁴⁴ B. Brekiesz-Lewandowska and Z. Talik, *Rocz. Chem.* **41**, 1887 (1967) [*CA* **69**, 2911 (1968)].
¹⁴⁵ A. Dornow and E. Rohe, *Chem. Ber.* **93**, 1093 (1960).
¹⁴⁶ J. R. Vaughan, Jr., J. Krapcho, and J. P. English, *J. Am. Chem. Soc.* **71**, 1885 (1949).
¹⁴⁷ J. R. Vaughan, Jr., U.S. Patent 2,637,731 (1953).
¹⁴⁸ Z. Talik and E. Plazek, *Rocz. Chem.* **30**, 1139 (1958) [*CA* **51**, 12089 (1957)].
¹⁴⁹ P. C. Jain and N. Anand, *Indian J. Chem.* **6**, 123 (1968).
¹⁵⁰ A. R. Dornow and O. Hahman, *Arch. Pharm. (Weinheim, Ger.)* **290**, 20 (1937).
¹⁵¹ K. B. De Roos and C. A. Saleminck, *Recl. Trav. Chim. Pays-Bas* **90**, 1166 (1971).
¹⁵² K. B. De Roos and C. A. Saleminck, *Recl. Trav. Chim. Pays-Bas* **88**, 1263 (1969).
¹⁵³ C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.* **38**, 1095 (1972).
¹⁵⁴ B. S. Gordon, J. M. Ravel, and W. Shine, *J. Biol. Chem.* **231**, 331 (1958).
¹⁵⁵ B. L. Cline, R. P. Panzica, and L. B. Townsend, *J. Heterocycl. Chem.* **13**, 1365 (1976).

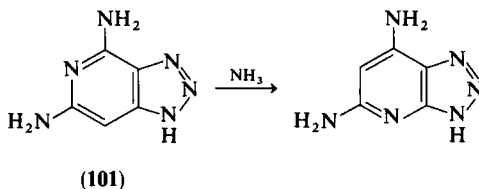
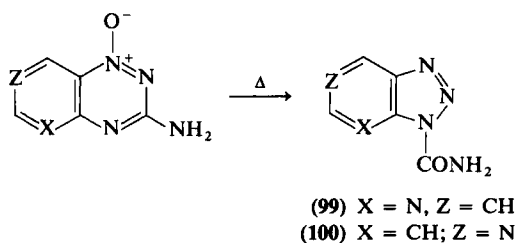


Other more complex examples are known,¹⁵⁶⁻¹⁶⁷ of which some are tranquilizing, antiasthmatic, or analgesic.^{156,157,165} The parent triazolo-[4,5-*b*]pyridine 4 has also been made from 1,2-diaminopyridine with *N*-nitrosodiphenylamine.¹⁶⁸ If *N*-substituted diaminopyridines are used, *N*-substituted triazolopyridines can be obtained.^{153,169-180} Examples are provided by

- ¹⁵⁶ R. L. Clark and A. A. Pessolano, Ger. Offen. 2,623,414 [CA 86, 106600 (1977)].
- ¹⁵⁷ B. Brickiesz-Lewandowska and Z. Talik, *Rocz. Chem.* **44**, 69 (1970) [CA 73, 45415 (1970)].
- ¹⁵⁸ K. Koda, A. Nakagawa, M. Hirano, and M. Ide, Japan Kokai 77 156,898 [CA 88, 152626 (1978)].
- ¹⁵⁹ Glaxo Labs Ltd., Fr. Demande 2,003,999 [CA 72, 111444 (1970)].
- ¹⁶⁰ T. Denzel and H. Hoehne, Ger. Offen. 2,506,234 [CA 83, 193340 (1975)].
- ¹⁶¹ G. A. Mokrushina, Yu A. Azev, and I. Ya Dostovskii, *Khim. Geterosikl. Soedin.* **7**, 100 (1975) [CA 83, 178947 (1975)].
- ¹⁶² H. Harnisch and A. Brack, Ger. Offen. 2,225,648 (1975) [CA 82, 87680 (1975)].
- ¹⁶³ S. Gati, Ger. Offen. 2,329,126 [CA 80, 134918 (1974)].
- ¹⁶⁴ B. L. Cline, R. P. Panzica, and L. B. Townsend, *Nucleic Acids, Chem.* **1**, 129 (1978).
- ¹⁶⁵ R. L. Clark, A. A. Pessolano, and T. Ying Shen, U.S. Patent 4,000,286 (1976).
- ¹⁶⁶ C. Temple, Jr., B. H. Smith, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.* **41**, 3784 (1976).
- ¹⁶⁷ K. Rufenacht, *Helv. Chim. Acta* **58**, 1521 (1975).
- ¹⁶⁸ H. Sieper, *Chem. Ber.* **100**, 1646 (1967).
- ¹⁶⁹ O. Bremer, *Justus Liebigs Ann. Chem.* **529**, 288 (1937).
- ^{169a} O. Bremer, *Justus Liebigs Ann. Chem.* **539**, 276 (1939).
- ^{169b} O. Bremer, *Justus Liebigs Ann. Chem.* **514**, 279 (1934).
- ¹⁷⁰ E. Koenigs and G. Jung, *J. Prakt. Chem.* **137**, 141 (1933).
- ¹⁷¹ B. W. Ashton and H. Suschitzky, *J. Chem. Soc.*, 4559 (1957).
- ¹⁷² P. Nantka-Namirski, *Acta Pol. Pharm.* **18**, 449 (1961).
- ¹⁷³ H. Bojarska-Dahlig and P. Nantka-Namirski, *Congr. Sci. Farm., Conf. Commun.*, 21st, 1961, 203 (1962) [CA 59, 6408 (1963)].
- ¹⁷⁴ P. Nantka-Namirski, *Acta Pol. Pharm.* **18**, 391 (1961); **19**, 229 (1962).
- ¹⁷⁵ M. M. Vohra, S. N. Pradhon, P. C. Jain, S. K. Chatterjee, and N. Anand, *J. Med. Chem.* **8**, 296 (1965).
- ¹⁷⁶ E. Bisagni, C. Ducrocq, C. Rivalle, P. Tambourin, F. Wendling, J.-C. Chermann, and L. Montagnier, Fr. Demande 2,387,229 [CA 88, 211396 (1978)].
- ^{176a} E. Bisagni, C. Ducrocq, C. Rivalle, P. Tambourin, F. Wendling, J.-C. Chermann, and L. Montagnier, Fr. Demande 2,422,662 [CA 93, 8153 (1980)].
- ¹⁷⁷ T. Denzel and H. Hoehne, Ger. Offen. 2,521,290 [CA 84, 105602 (1976)]; U.S. Patents 3,971,800, 3,971,801 (1976).



c. *By Rearrangement from Other Heterocycles.* Pyridotriazine *N*-oxides can be rearranged under basic conditions to give triazolopyridine-carboxamides **99**¹⁸⁸ or **100**.¹⁸⁹⁻¹⁹¹ The triazolo[4,5-*c*]pyridine **101** undergoes a Dimroth rearrangement at 150°C, giving the triazolo[4,5-*b*]pyridine.^{153,192}



2. Syntheses from Triazoles

When 3-substituted triazolo[4,5-*d*]pyrimidines **102** are treated with sulfuric acid and a compound containing an active methylene group, triazolo[4,5-*b*]pyridines **103** are formed, presumably via the 5-amino-4-formyltriazole.¹⁹³ Cyclization of the triazole **104** gives an aminocyanotriaz-

¹⁸⁸ J. A. Carbon and S. H. Tabata, *J. Org. Chem.* **27**, 2504 (1962).

¹⁸⁹ A. Lewis and R. G. Shephard, *J. Heterocycl. Chem.* **8**, 47 (1971).

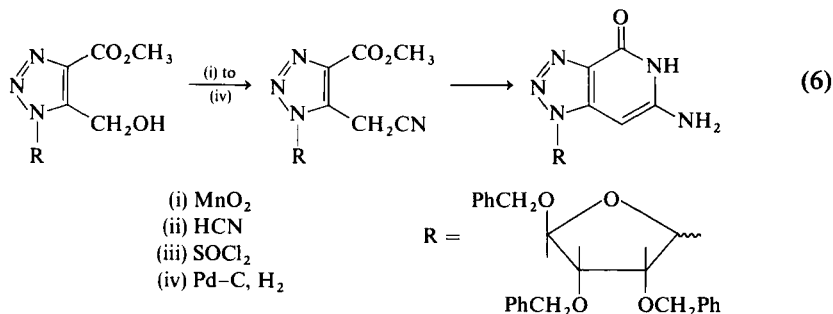
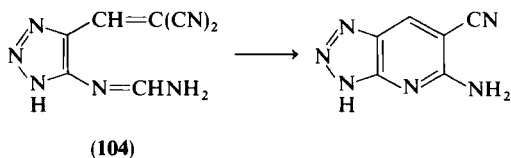
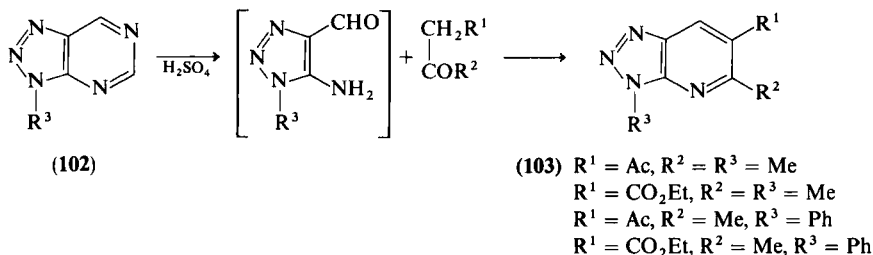
¹⁹⁰ P. Benko, E. Berenyi, A. Messmer, G. Hajos, and L. Pallos, *Magy. Kem. Foly.* **82**, 183 (1976) [*CA* **85**, 46593 (1976)].

¹⁹¹ P. Benko, E. Berenyi, A. Messmer, G. Hajos, and L. Pallos, *Acta Chim. Acad. Sci. Hung.* **90**, 405 (1976) [*CA* **86**, 139999 (1977)].

¹⁹² C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.* **37**, 3601 (1972).

¹⁹³ T. Higashino, T. Katori, and E. Hayashi, *Chem. Pharm. Bull.* **27**, 2861 (1979).

zolo[4,5-*b*]pyridine,¹⁹⁴ and the rather lengthy procedure shown in Eq. (6) has been used to prepare a nucleoside analog.^{195,196}



III. Physical Properties and Theoretical Chemistry

A. ELECTRONIC SPECTRA

The electronic spectra will be discussed in two groups, first those of compounds with bridgehead nitrogen and second those without.

In one study the spectra of triazolopyridines **1** and **3** were recorded and compared with that of the 2-methyl derivative **105** of compound **2**.¹⁹⁷ The spectrum of the parent system **2** has also been recorded.¹⁰⁸ Armarego has

¹⁹⁴ A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1620 (1973).

¹⁹⁵ R. A. Earl and L. B. Townsend, *Can. J. Chem.* **58**, 2550 (1980).

¹⁹⁶ R. B. Meyer, Jr., G. R. Revanker, P. Dan Cook, K. W. Ehler, M. Schweizer, and R. K. Robins, *J. Heterocycl. Chem.* **17**, 159 (1980).

¹⁹⁷ J. D. Bower, *J. Chem. Soc.*, 4510 (1957).

TABLE II
 ELECTRONIC ABSORPTION SPECTRA OF TRIAZOLOPYRIDINES 1-3

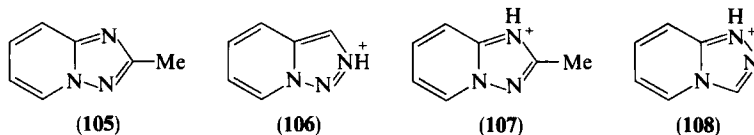
Compound	Solvent ^a	pH	$\lambda_{\max}(\text{nm})$ and $\log_{10} \epsilon^b$	References
1	C	—	213(4.38), 274(3.67), 283.5(3.66), 300(3.33), 306(3.34), <u>319</u> (3.25), 335.5(2.85)	197
1	W	4.0	<u>217</u> (4.05), 222.5(3.72), 278(3.81)	198
1	W	-2.0	223(3.72), <u>230</u> (3.47), 271(3.78), <u>288</u> (3.67), 299(3.36)	198
2	M	—	212(4.39), <u>273</u> (3.54), 277(3.56), 292(3.51), 299(3.5)	108
105	C	—	217.5(4.58), 273(3.57), <u>281</u> (3.52), <u>294</u> (3.2)	197, 199
105	W	7.0	<u>238</u> (3.45), 260(3.56), <u>273</u> (3.53), <u>283</u> (3.34)	198
105	W	0	237(3.67), <u>246</u> (3.62), 264(3.49), 268.5(3.52), 275(3.48), 291(3.1)	198
3 ^c	C	—	214(4.35), 259.5(3.32), 270(3.33), <u>293</u> (3.34), 299(3.36), 311(3.28), 326(2.93)	197
3	W	7.0	<u>238</u> (3.45), 260(3.56), <u>273</u> (3.53), <u>283</u> (3.34)	198
	W	0	237(3.67), <u>246</u> (3.62), 264(3.49), 268.5(3.52), 275(3.48), 291(3.1)	198

^a C = Cyclohexane, W = Water, M = Methanol.

^b Numbers underlined are inflections.

^c Hydrate.

made a more intensive study of the three compounds, using water as solvent and recording spectra both for neutral and protonated forms.¹⁹⁸ The values are grouped in Table II. The spectra for the protonated forms were thought (from other measurements) to be due to the cations **106**–**108**.¹⁹⁹



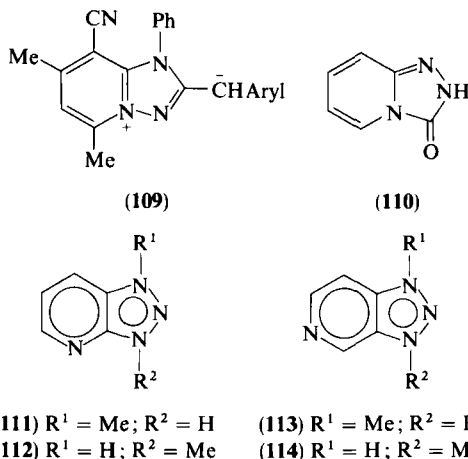
The only collection of UV spectral data for derivatives of compound **1** show the effect of a 3-acyl or 3-aryl substituent.²³ A bathochromic shift of the longest wavelength absorption band can reach 20 nm with an aryl substituent. The spectra of 2-phenyl-,¹⁹⁹ 2-benzyl-, 2-benzoyl-, and 2-benzhydryl[1,2,4]triazolo[1,5-*a*]pyridines,⁴² and of the mesoionic compounds **42**–**44**,⁵⁶ and **109**²⁰⁰ are reported. On the triazolopyridine **3**, substitu-

¹⁹⁸ W. L. F. Armarego, *J. Chem. Soc.*, 2778 (1965).

¹⁹⁹ G. M. Badger, P. J. Nelson, and K. T. Potts, *J. Org. Chem.* **29**, 2542 (1964).

²⁰⁰ G. V. Boyd and A. J. H. Summers, *J. Chem. Soc. B*, 1648 (1971).

tion by alkyl groups at position 3 changes the spectrum little,^{107,199} but a 3-phenyl substituent causes a bathochromic shift.^{80,199} Substituents on the pyridine ring can cause considerable bathochromic shifts, particularly an 8-nitro substituent.⁶⁶ Other substituted [1,2,4]triazolo[4,3-*a*]pyridines having absorption maxima at wavelengths greater than 300 nm are the 3-thiol (thione) **61**,⁸⁰ the triazolopyridin-3-one **110**,²⁰¹ and mesoionic compounds of type **74**.^{56,202} The fluorescence spectrum of compound **2** is recorded and is concentration dependent.²⁰³



For compound **4** there is no recorded spectrum, but compound **5** is reported²⁰⁴ to absorb at 258 nm ($\epsilon = 4300$) in methanol solution. Jain and Anand have reported spectra for the four *N*-methyl derivatives **111–114** in acid, neutral, and basic media¹⁴⁹; of the two compounds **113** and **114** the spectrum of compound **5** most resembles the former, leading to a 1*H*-tautomer as the predominant structure. A more recent report²⁰⁵ of the spectrum of compound **111** differs considerably from that given by Jain and Anand. Because of the similarity of systems **4** and **5** to purine (nucleosides from both have been prepared), there has been much interest in the spectra of the amino derivatives and of the triazolopyridinones. For the [1,2,4]triazolo-[4,5-*b*]pyridines, spectra are reported for the 5-amino derivatives **115**,¹⁸⁷ **116**,¹⁹⁴ **117**,¹⁵³ and **118**¹⁶⁶; for the 3-amino derivatives **119** and **120**¹⁸¹; and for

²⁰¹ B. M. Lynch and S. C. Sharma, *Can. J. Chem.* **55**, 831 (1977).

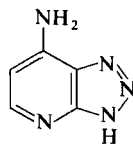
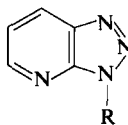
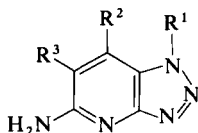
²⁰² A. Saito and B. Shimizu, *Bull. Chem. Soc. Jpn.* **50**, 1596 (1977).

²⁰³ T. Nagano, M. Hirobe, M. Itoh, and T. Okamoto, *Tetrahedron Lett.*, 3815 (1975).

²⁰⁴ J. A. May, Jr. and L. B. Townsend, *J. Org. Chem.* **41**, 1449 (1976).

²⁰⁵ K. B. De Roos and C. A. Saleminck, *Recl. Trav. Chim. Pays-Bas* **90**, 1181 (1971).

the 7-amino derivatives **121**.¹⁹² Triazolopyridin-5-ones **122** and **123**,^{182,183} **124** and the 2*H*-tautomers **125** and **126**,¹⁸⁴ the triazolopyridin-7-one **127**,¹⁹² and the -7-thione **128**¹⁶⁶ have also been studied.



(115) R¹ = R² = R³ = H

(116) R¹ = R² = H; R³ = CN or CONH₂

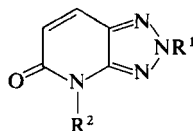
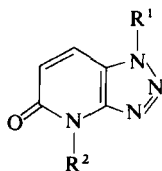
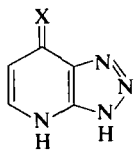
(117) R¹ = R³ = H; R² = Cl, N₃ (also 5-NHCO₂Et)

(118) R¹ = R³ = H; R² = SMe

(119) R = NH₂

(120) R = N = CHPh

(121)



(127) X = O

(122) R¹ = R² = H

(125) R¹ = R² = Me

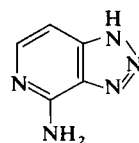
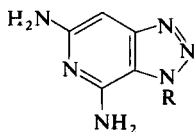
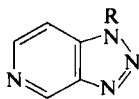
(128) X = S

(123) R¹ = H; R² = Me

(126) R¹ = Me; R² = β-D-ribofuranosyl

(124) R¹ = R² = Me

Fewer spectra of [1,2,4]triazolo[4,5-*c*]pyridines have been recorded. Amino derivatives where the amine is at position 1, (**129** and **130**),¹⁸¹ at positions 4 and 6 (**131** and **132**),¹⁵³ at position 4 only (**133**),¹⁹² and at position 6 only (**134**)¹⁵² have been reported with UV absorption data, some at several pH values. The triazolopyridin-4-one **135**¹⁹² and the 2*H*-triazolopyridine



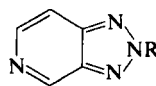
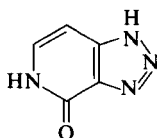
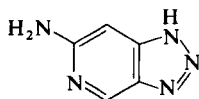
(129) R = NH₂

(131) R = H

(133)

(130) R = N = CHPh

(132) R = CHPh₂, 6-NHCO₂Et



(134)

(135)

(136) R = ribofuranosyl

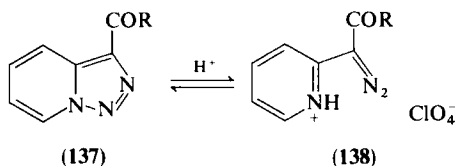
136²⁰⁶ are of interest, the latter absorbing at 396 nm. In all these compounds where tautomerism is possible we record the formulas given by the authors, although in many cases there is no proof as to their correctness.

B. INFRARED SPECTRA

Detailed IR spectra are available for the 3-(2-pyridyl) derivative of compound **1** (see **15**),¹⁸ for compound **2**,⁶⁵ and for the 3-isopropyl derivative of compound **3**.⁸³ Additionally, an absorption at 1631 cm⁻¹ in the spectrum of compound **1** is assigned to C=C and C=N stretching.²⁰⁷ No complete assignments are available for any of the parent compounds **1-5**, most interest centering on substituent group frequencies. Formyl³² and acyl or aroyl groups²³ in position 3 of triazolopyridine **1** give C=O absorption at 1650–1680 cm⁻¹; Regitz and Liedhegener²³ report the development of diazo group absorption at 2121–2139 cm⁻¹ when compounds **137** are treated with 60% perchloric acid, indicating the presence of the ring-opened species (**138**).

Other recorded IR spectra are

1. Of system **1**, a 3-cyano derivative,²⁷ $\nu_{\max} = 2240 \text{ cm}^{-1}$
2. Of system **2**, some 2-substituted derivatives,⁴² all with C=N stretch at 1640 cm⁻¹
3. Of system **3**, a trialkyl derivative and a 3-carbamoyl derivative,¹⁰⁸ the latter having amide bands at 1675 and 1623 cm⁻¹, 5-chloro-3-amino- and 7-thiol derivatives²⁰⁸, 5-substituted trifluoromethyl derivatives,⁹⁸ and 5-chloro-3-substituted (including 3-amino) derivatives⁸¹



No detailed IR spectra are reported for systems **4** and **5**. Some absorption bands are reported for derivatives of compound **4**, 2-phenyl-5-amino-2*H*-triazolopyridine (**89**),²⁰⁹ 6-acetyl-3,5-dimethyl-3*H*-triazolopyridine,¹⁹³ triazolopyridin-7-one (**127**)¹⁹² and its 5-amino derivative,¹⁶⁶ the 7-amino and

²⁰⁶ J. A. May, Jr. and L. B. Townsend, *J. Org. Chem.* **41**, 1449 (1976).

²⁰⁷ J. H. Boyer and L. T. Welford, *J. Am. Chem. Soc.* **80**, 2741 (1958).

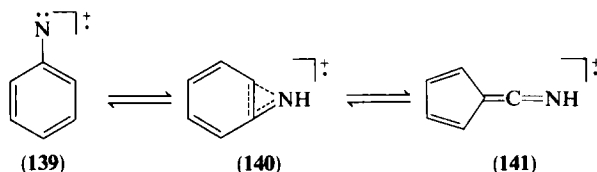
²⁰⁸ K. T. Potts and S. Husain, *J. Org. Chem.* **35**, 808 (1970).

²⁰⁹ W. Baeyens, G. A. Bens, P. De Moerloose, and L. De Taeye, *Pharmazie* **35**, 86 (1980).

7-chloro derivatives,¹⁹² and 5-amino-7-methylthiotriazolopyridine.¹⁶⁶ There are even fewer IR data for derivatives of compound 5. Some absorptions were reported for the 4-amino- **133**¹⁵³ and the 6-aminotriazolopyridine **134**,¹⁵² for the 4-chloro derivative, and for triazolopyridin-4-one **135**.¹⁵³

C. MASS SPECTRA

The mass spectrum of compound **1** and of its 3-deutero derivative has been reported.³⁵ Apart from a strong molecular ion, the principal feature is a peak at 91 m.u. due to a C_6H_5N radical ion. This ion or interconverting ions **139–141**, which are obtained from many other compounds, heterocyclic and nonheterocyclic, have been studied by the technique of collision-induced decomposition (CID).²¹⁰ A study of some triazolopyridine-7-methanols has shown that other pathways, notably loss of the CHN_2 fragment, can become important.²⁵



Potts *et al.*²¹¹ have reported detailed fragmentation pathways for [1,2,4]triazolo[4,3-*a*]pyridine (**3**) and for simple derivatives **142** and **143** and of [1,2,4]triazolo[1,5-*a*]pyridine, where the substituents are in the five-membered rings. Major ions are the molecular ions in most cases. The major pathway in both series is loss of HCN (or RCN) to give a common ion at 92 m.u. The exceptions are compounds of type **142** where R is amino, hydroxyl, or thiol (3-thione) when elimination of the substituent with part of the five-membered ring is favored. For the derivatives of compound **3**, nitrogen loss makes a minor alternative pathway. Other [1,2,4]triazolo[4,3-*a*]pyridines studied are chloro derivatives,²⁰⁸ nitro and amino derivatives,⁶⁶ and 2-substituted triazolopyridin-3-ones related to Trazodone.²¹² In the latter, McLafferty rearrangements involving the side chains on N2 lead to the most important fragmentations.

The ionization potentials have been recorded for compounds **4** (9.20 ± 0.05 eV) and **5** (9.70 ± 0.05 eV).²¹³

²¹⁰ A. Maquestia, Y. Van Haverbeke, R. Flammang, A. Menu, and C. Wentrup, *Org. Mass Spectrom.* **13**, 518 (1978).

²¹¹ K. T. Potts, E. Brugel, and U. P. Singh, *Org. Mass Spectrom.* **5**, 1 (1971).

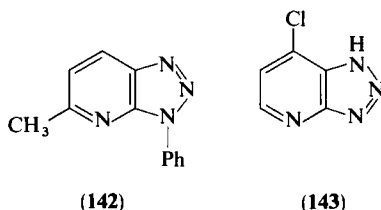
²¹² L. Baiocchi, A. Frigerio, M. Giannangeli, and L. Secchi, *Boll. Chim. Farm.* **114**, 206 (1975).

²¹³ O. Thorstad and K. Undheim, *Chem. Scr.* **6**, 222 (1974).

D. NUCLEAR MAGNETIC RESONANCE SPECTRA

1. ¹H-NMR Spectra

The chemical shifts and coupling constants for compounds 1–3 are shown in Table III. In this table a uniform numbering is adopted for all compounds, as shown in the formula of indolizine at the head of the table. No spectrum is available for compound 4, although that of compound 5 is reported.²⁰⁴ From the figures available for the simple derivatives 142 and 143, chemical shifts and coupling constants for compound 4 can be included in Table III.



There are substantial collections of ¹H-NMR spectra of substituted [1,2,3]triazolo[1,5-*a*]pyridines (mainly 3- and 7-substituted¹⁴) and of [1,2,4]triazolo[1,5-*a*]- and -[4,3-*a*]pyridines (including solvent effects and a discussion of steric effects).²¹⁴ Other papers contain spectral details on some simple [1,2,4]triazolo[1,5-*a*]pyridines,^{39,42,47,62,69,203} and one deals with the spectra of some 3-oxides.⁴⁴ Some simple [1,2,4]triazolo[4,3-*a*]pyridines have data recorded.^{62,79,208} There are two reports of the effect of quaternization, one at position 2²¹⁷ and one for positions 1 or 2.²¹⁸ A correlation has been observed between electron density and chemical shift for a number of aza- and polyazaindolizines, including compounds 2 and 3.²¹⁹

With the exception of those quoted in Table III, the derivatives of compounds 4 and 5 for which NMR data are available are heavily substituted. A number of the compounds related to system 4 are related to nucleosides, particularly amino^{155,166,192,220} and oxo derivatives.^{155,166,184,220} Similarly, apart from a 1-aryl derivative of compound 5,^{179a} interest has centered on compounds related to purines^{153,192,196} and nucleosides.²⁰⁴

²¹⁴ K. T. Potts, H. R. Burton, T. H. Crawford, and S. W. Thomas, *J. Org. Chem.* **31**, 3522 (1966).

²¹⁵ T. Higashino, T. Katori, and E. Hayashi, *Chem. Pharm. Bull.* **27**, 2861 (1979).

²¹⁶ K. B. DeRoos and C. A. Salemink, *Recl. Trav. Chim. Pays-Bas* **90**, 1181 (1971).

²¹⁷ T. Eicher, S. Hünig, H. Hansen, and P. Nikolaus, *Chem. Ber.* **102**, 3159 (1966).

²¹⁸ W. W. Paudler and R. J. Brumbaugh, *J. Heterocycl. Chem.* **5**, 29 (1968).

²¹⁹ E. Kleinpeter, R. Borsdorf, G. Fischer, and H. J. Hoffman, *J. Prakt. Chem.* **314**, 515 (1972).

²²⁰ B. L. Cline, R. P. Panzica, and L. B. Townsend, *J. Org. Chem.* **43**, 4910 (1978).

TABLE III
¹H-NMR DATA FOR TRIAZOLOPYRIDINES^a

Compound	H1	H2	H3	H5	H6	H7	H8	Solvent	<i>J</i> values (Hz)	References
1	8.05	—	—	8.7	7.2	7.2	7.7	CDCl ₃	<i>J</i> _{3,7} 0.8; <i>J</i> _{5,6} 7.0; <i>J</i> _{5,7} 1.0 <i>J</i> _{6,7} 6.5; <i>J</i> _{6,8} 1.25; <i>J</i> _{7,8} 9.0	35
2	—	8.35	—	8.62	7.04	7.52	7.82	CDCl ₃	<i>J</i> _{5,6} 6.6; <i>J</i> _{5,7} 1.3; <i>J</i> _{6,7} 6.6; <i>J</i> _{6,8} 1.2; <i>J</i> _{7,8} 8.8; <i>J</i> _{5,8} 1.2	214
3	—	—	8.86	8.21	6.88	7.28	7.79	CDCl ₃	<i>J</i> _{5,6} 6.7; <i>J</i> _{5,7} 1.2; <i>J</i> _{6,7} 6.7 <i>J</i> _{6,8} 1.2; <i>J</i> _{7,8} 9.0; <i>J</i> _{5,8} 1.2	214
4 ^b	—	—	—	—	8.66	7.22	8.35	DMSO	<i>J</i> _{6,7} 5.1; <i>J</i> _{7,8} 8	192, 215, 216
5	15.0	—	—	9.55	—	8.57	7.96	DMSO	<i>J</i> _{5,7} 1.0; <i>J</i> _{7,8} 6.0	204

^a In ppm from TMS (δ).

^b Deduced from spectra of compounds **142**,²¹⁵ and **143**.^{192,216}

TABLE IV
¹³C CHEMICAL SHIFTS FOR COMPOUNDS 1–3

Compound	Solvent	C1	C2	C3	C5	C6	C7	C8	C8a	References
1	Acetone	118.7	—	—	126.1	116.1	126.1	116.1	134.5	221
1	CDCl ₃	125.2 ^a	—	—	124.7	115.1	125.0	117.6	133.3	25
2	Acetone	—	154.6	—	129.7	114.7	130.4	117.2	151.4	221
3	Acetone	—	—	137.1	125.8	114.5	128.9	115.9	149.7	221

^a Spectrum in CD₃COCD₃ very similar to that reported in Ref. 221.

2. ^{13}C -NMR Spectra

A detailed study of ^{13}C -NMR shifts for a number of aza- and diazaindolizines has been published and includes discussion of compounds 1–3.²²¹ The spectra were determined for acetone solutions; the assignments were based on a regression analysis for the eight systems used, incorporating previous assignments on the four monoazaindolizines having the second nitrogen in the five-membered ring. The assignments are shown in Table IV (numbered as for indolizine). However, examination of the ^{13}C -NMR spectrum of compound 1, using specific deuteration and substitution by alkyl groups to establish the position of absorptions for C-3 and C-4–C-7²⁵ has led to different assignments, (also given in Table IV), and there must therefore be some doubt as to the validity of the assignments for compounds 2 and 3. There are INDO calculations of total electron densities in the paper by Witanowski *et al.*,²²¹ and these are plotted against the chemical shifts. Chemical shifts have been reported for the quaternary carbons in some substituted [1,2,4]triazolo[4,5-*a*]- and -[4,3-*a*]pyridines⁶² and for some [1,2,4]triazolo[4,3-*a*]pyridinones.²⁰¹

The major uses of ^{13}C -NMR spectra of derivatives of compounds 4 and 5 have been for assignment of site of attachment of sugar residues (N-1, N-2, or N-3). A detailed discussion of the spectra of some [1,2,3]triazolo[4,5-*b*]pyridines, including principal coupling constants, has been provided by Townsend *et al.*²²² Less detailed reports are available for 2,5-disubstituted [1,2,3]triazolo[4,5-*b*]pyridin-5-ones,¹⁸⁴ for compound 5, for D-ribosyl derivatives (enabling assignment of site of ribosylation),²⁰⁴ for similar derivatives of compound 4,²²⁰ and for some [1,2,3]triazolo[4,5-*c*]pyridin-4-ones.¹⁹⁶

3. ^{14}N - and ^{19}F -NMR Spectra

Witanowski *et al.* have reported²²³ the ^{14}N chemical shifts for compounds 1–3. The values for compound 1 (relative to CH_3NO_2) are $+40.9 \pm 3.2$ (N-2), -30.6 ± 3.9 (N-3), and $+119.9 \pm 0.2$ (N-4); for compound 2 $+150.0 \pm 1.0$ (N-1), $+94.1 \pm 2.2$ (N-3), and $+140.7 \pm 0.3$ (N-4); and for compound 3 $+61.0 \pm 4.2$ (N-1), $+118.1 \pm 9.0$ (N-2), and $+185.5 \pm 0.2$ (N-4). All numberings given are as for indolizine (bridgehead N is N-4). The

²²¹ M. Witanowski, L. Stefaniak, W. Sicinska, and G. A. Webb, *J. Mol. Struct.* **64**, 15 (1980).

²²² B. L. Cline, P. E. Fagerness, R. P. Panzica, and L. B. Townsend, *J.C.S. Perkin II*, 1586 (1980).

²²³ M. Witanowski, L. Stefaniak, S. Szymanski, Z. Grabowski, and G. A. Webb, *J. Magn. Res.* **21**, 185 (1976).

results are discussed in terms of INDO calculations, and the bridgehead nitrogen nuclei are said to reflect the electronic charge distribution in the molecules. The ^{19}F -NMR spectrum of compound **21** has been reported.³¹

E. DISSOCIATION CONSTANTS

Armarego has measured the $\text{p}K_a$ values of compounds **1**, the 2-methyl derivative of compound **2** and compound **3** by a spectrophotometric method.¹⁹⁸ Compound **1** is by far the weakest base, with a $\text{p}K_a$ of 0.42; compound **3** and the 2-methyl derivative of compound **2** are similar at 3.18 and 2.96. Without firm evidence the protonated forms were suggested to be **106–108**.

F. THEORETICAL CHEMISTRY

Calculations of electron density and of bond orders for compounds **1–3** have been performed, using the SCF-LCAO-MO method of Roothaan, as modified by Pariser, Parr, and Pople.²²⁴ The π -electron densities are shown for each of the three molecules in Fig. 1; in the case of compound **3**, values

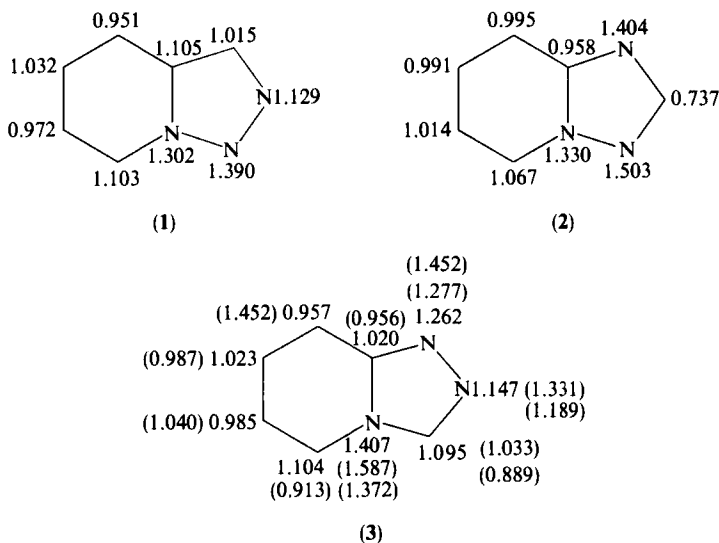


Fig. 1. π -Electron densities calculated for compounds **1–3**.²²⁴ Values in parentheses are from Ref. 225.

²²⁴ V. Galasso, G. De Altì, and A. Bigotto, *Theor. Chim. Acta* **9**, 222 (1968).

due to Reimlinger *et al.*²²⁵ calculated by HMO methods are included. Calculated values for the lowest excited states of compounds **2** and **3** have been compared with observed values.²²⁶ Several groups have attempted to correlate NMR shifts with electron density calculations.^{219,221,223} Electron density and dipole moment calculations have been performed on the mesoionic compound **74** ($R^1 = H$; $R^2 = Me$; $X = O$).²²⁷

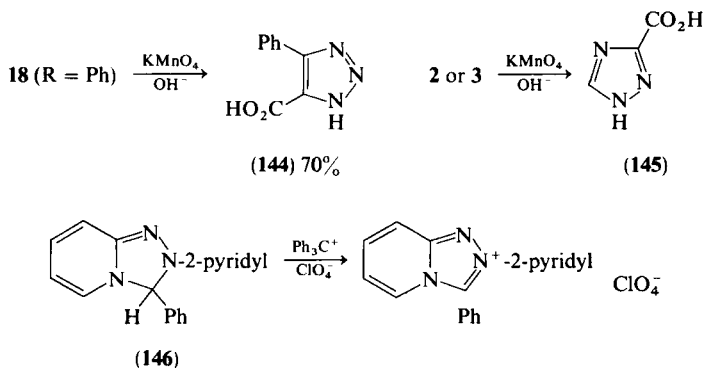
IV. Chemical Properties

Chemical reactions are grouped under reaction types (oxidation, reduction, etc.), and each of the five systems is dealt with sequentially in each subsection.

A. OXIDATION

1. Oxidation of the Ring

Oxidation of compounds **8** ($R = Ph$),²⁰ (**2**),⁴⁹ and (**3**),⁶⁵ using alkaline permanganate, gives triazolecarboxylic acids **144** and **145**, respectively, indicating the greater stability of the triazole ring. The 3*H*-triazolo[4,3-*a*]pyridine **146** can be dehydrogenated by triphenylmethyl perchlorate to give the quaternary salt.²²⁸



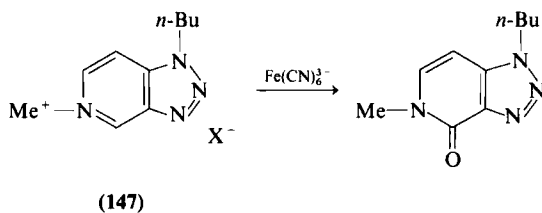
²²⁵ H. Reimlinger, J.-M. Gilles, E. Anthoine, J. J. M. Vandewalle, W. R. F. Lingier, E. De Ruiter, R. Merenyi, and A. Lubert, *Chem. Ber.* **104**, 3925 (1971).

²²⁶ J. Feitelson, *J. Chem. Phys.* **43**, 2511 (1965).

²²⁷ L. Paolini and A. Ciampi, *J. Heterocycl. Chem.* **5**, 7 (1968).

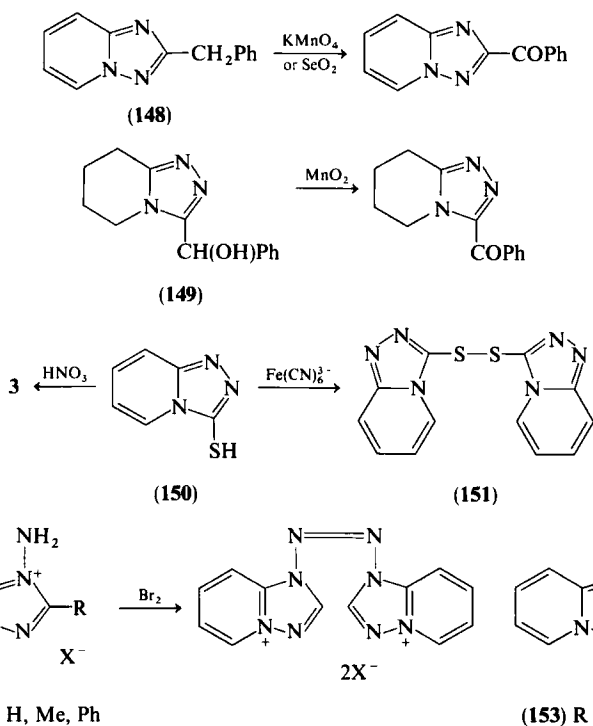
²²⁸ E. Fahr, J. Markost, N. Pelz, and T. Erlenmaier, *Ann. Chim.*, 2088 (1975).

The quaternary [1,2,3]triazolo[4,5-*c*]pyridinium salt **147** is oxidized by ferricyanide to the triazolopyridin-5-one.¹⁶⁹



2. Oxidation of Substituents

Alkyl groups can be oxidized, as for example the benzyl group in compound **(148)**, to a benzoyl group by permanganate or (better) by selenium dioxide.⁴² Similarly, the benzyl alcohol in compound **149** is oxidized by manganese dioxide.⁸⁷ The thiol **150**, treated with ferricyanide, gives the disulfide **151**.⁶⁵ Oxidation of thiol **150** with nitric acid is thought to

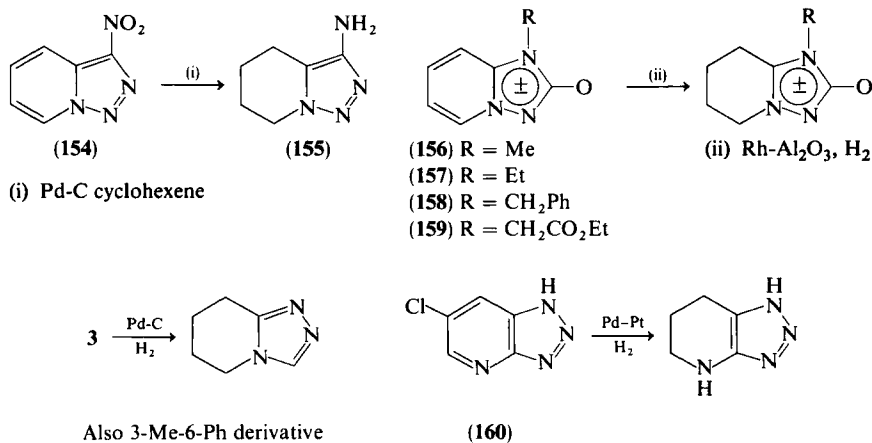


proceed through the sulfone with subsequent loss of SO_2 to give the parent **3**, although the net result is an apparent reduction.⁶⁵ Oxidation of the *N*-aminotriazolopyridinium salt **152** gives an azo compound, whereas the isomeric salts **153** are oxidatively deaminated by the same reagent.⁴⁶

B. REDUCTION AND ADDITION REACTIONS

1. Reduction of the Ring

Catalytic reduction of the derivatives of triazolopyridines invariably attacks the pyridine ring, leaving the triazole. There is no report of reduction of compound **1**, but 3-nitrotriazolopyridine (**154**) gives as major product the tetrahydrotriazolopyridinamine **155**.²²⁹ Reduction with palladium–charcoal takes a different course (see Section IV,F). The mesoionic derivatives of [1,2,4]triazolo[1,5-*a*]pyridine **156–158**⁵⁴ and **159**²³⁰ are reduced to py-tetrahydro derivatives, as is compound **3**,²³¹ although it had previously been reported that 3-substituted derivatives of compound **3** were not reduced.⁶⁵ Chloro[1,2,3]triazolo[4,5-*b*]pyridine (**160**) is reductively dehalogenated with reduction of the pyridine ring by platinum or palladium catalysts.¹⁴⁶ By addition of base the reduction can be stopped at compound **4** (see Section

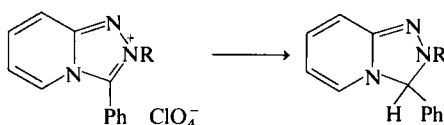


²²⁹ G. Jones, D. R. Sliskovic, B. Foster, J. Rogers, A. K. Smith, M. Y. Wong, and A. C. Yarham, *J.C.S. Perkin I*, 78 (1981).

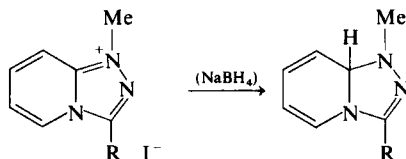
²³⁰ T. Kametani and T. Teraika, Japanese Patent 71/21,034 and 71/21,035 [*CA* 75, 129814 and 129815 (1971)].

²³¹ M. Kac, F. Kovac, B. Stanovnik, and M. Tisler, *Gazz Chim. Ital.* **105**, 1291 (1975).

IV,B,2). Successful reduction by sodium borohydride has been reported only for quaternary salts **161**²²⁸ and **162**⁶⁵; the reported sites of reduction differed.

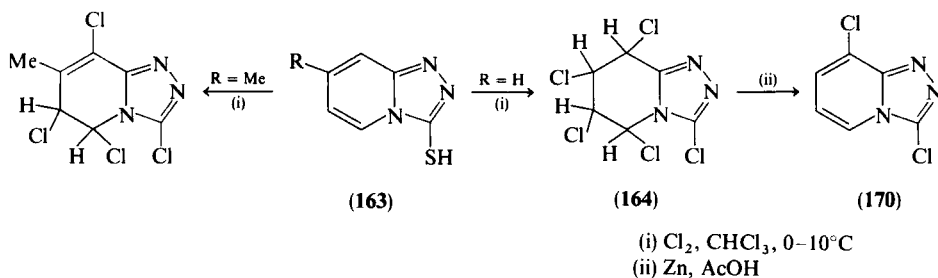


(161) R = 2-pyridyl



(162) R = H, NH₂

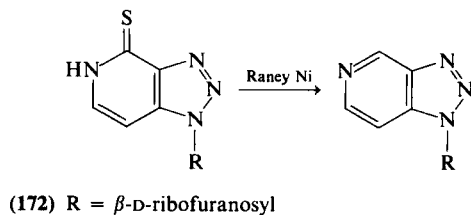
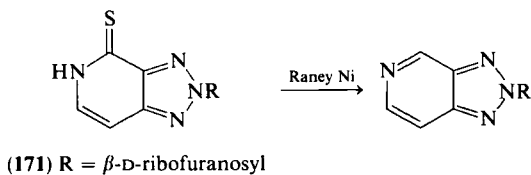
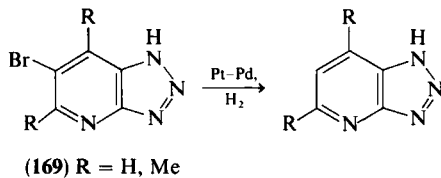
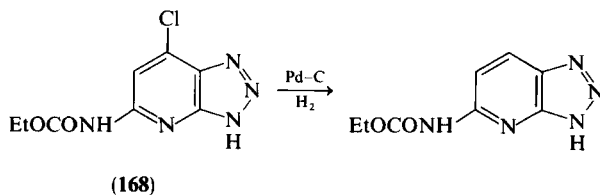
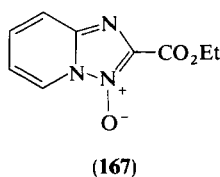
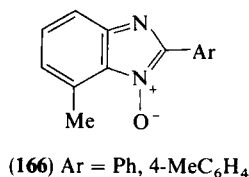
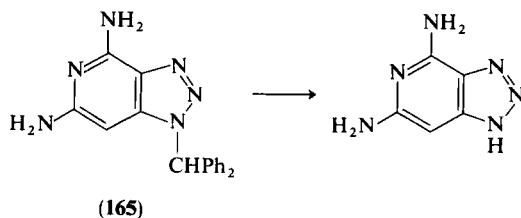
The only other additions to the ring are of chlorine to the [1,2,4]triazolo[4,3-*a*]pyridine-3-thiols **163**.²⁰⁸ The compound with no substituent on the pyridine ring takes up two molecules of chlorine (as well as undergoing substitution at position 3 to give compound **164**), whereas the 7-methyl derivative takes up one molecule.



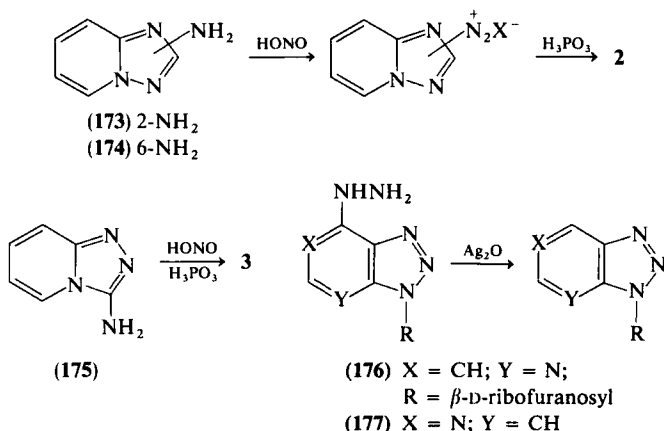
2. Reduction of Substituent Groups, Including Reductive Replacement

The only alkyl group reported as reductively removed is the diphenylmethyl substituent from N3 in compound **165**.¹⁵³ Deoxygenation of *N*-oxides can be done thermally (heating in toluene with oxygen transfer to solvent) for compounds of type **166**,⁴⁴ or more commonly by use of phosphorus derivatives, as described for compounds **32**,⁴⁴ **33**,⁴⁵ **166**,⁴⁴ and **167**.⁶¹ Halogens can be reductively removed from [1,2,3]triazolo[4,5-*b*]pyridines **160**,¹⁴⁶ **168**,²²⁰ and **169**,¹⁴² and from pentachloro derivative **164**, giving dichloro compound **170**.²⁰⁸ Removal of thiol groups by reduction

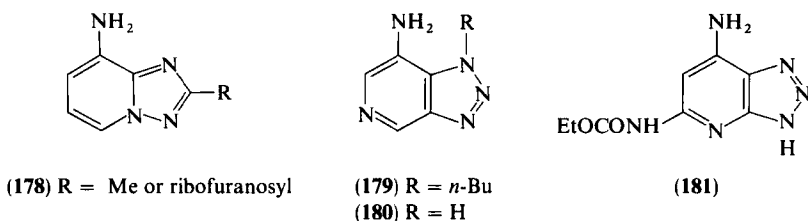
with Raney nickel has been achieved from *2H*-[1,2,3]triazolo[4,5-*c*]pyridine **171** and the *3H* isomer **172**,²⁰⁶ and a methylthio substituent from the *S*-methyl derivative of compound **172**.²⁰⁶



Two noncatalytic methods have been used to remove amino or hydrazino groups. Diazotization and reduction of the diazonium salt by hypophosphorous acid removes amino groups from aminotriazolopyridines **173**,⁶⁵ **174**,⁶⁶ and **175**,⁶⁵ whereas silver oxide treatment removes hydrazino groups from compounds **176**²¹⁶ and **177**.²⁰⁶



Aminotriazolopyridines can be prepared by reduction of nitro groups, using hydrogen and a catalyst, as in examples **178**⁶² and **179**^{169a} or by stannous chloride and hydrochloric acid, as in example **180**.¹⁴² Stannous chloride has also been used to reduce a *p*-nitrophenyl to a *p*-aminophenyl substituent.^{169b} Amine **181** is obtained by reduction of the corresponding azide.¹⁵³ Catalytic reductive debenzoylation of 7-benzyloxy[1,2,3]triazolo[4,5-*b*]pyridines^{155,220} gives triazolopyridin-7-ones. Borohydride reduction of 2-benzoyl[1,2,4]-triazolo[1,5-*a*]pyridine gives the corresponding benzyl alcohol.⁴²

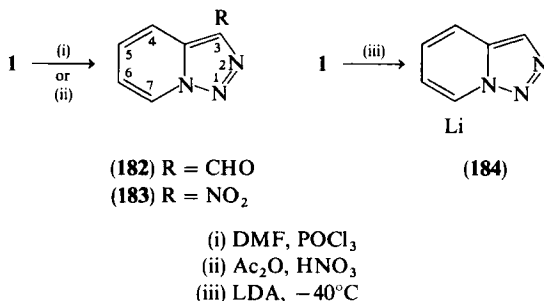


C. REACTIONS WITH ELECTROPHILES

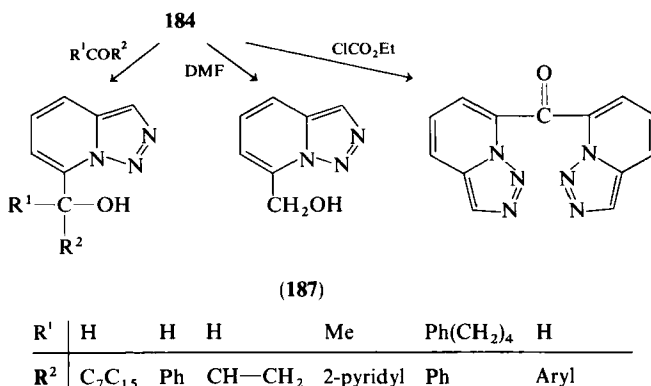
Not unexpectedly, polyazaheterocycles have been frequently treated with alkylating agents. In this section all other electrophiles are dealt with first, then all alkylations in the second subsection.

1. *Electrophiles Other than Alkylating Agents*

Compound **1** reacts with electrophiles in two contrasting ways. Vilsmeier formylation³² and nitration²²⁸ give the 3-substituted triazolopyridines **182** and **183**; other electrophiles give products resulting from ring opening, and these are shown in Section IV,F. There is some doubt as to the mechanism of deuteration of compound **1**; reaction with deuterium oxide at 100°C gives

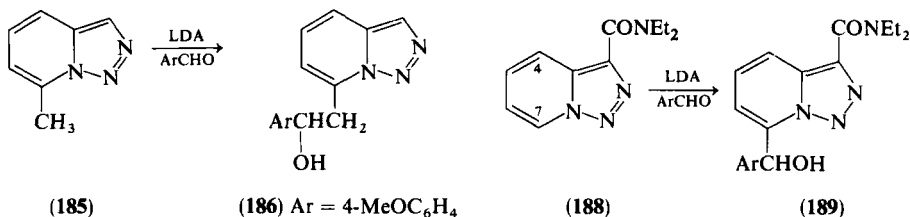


the 3-deutero derivative and then more slowly the 3,7-dideuteriotriazolopyridine.³⁵ The reaction is not accelerated by deuteriosulfuric acid but is accelerated by base, and it has been suggested that it may proceed via the pyridyldiazomethane tautomer. Triazolopyridine **1** is protonated by anhydrous hydrogen bromide, forming an isolable hydrobromide²⁵; by analogy with Armarego's experiments¹⁹⁸ this would be protonated on N-2. The directed lithiation of triazolopyridine **1** at -40°C, gives a 7-lithio derivative (**184**), from which the 7-deutero derivative is obtained by reaction with deuterium oxide.¹⁴ The reactions of this 7-lithio derivative (**184**) that do not result in ring opening are summarized in Scheme 1. Lithiation of

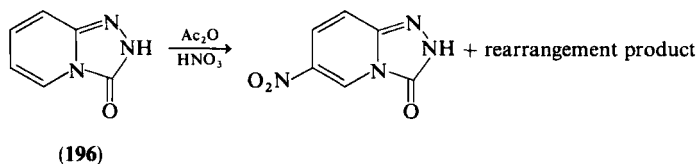
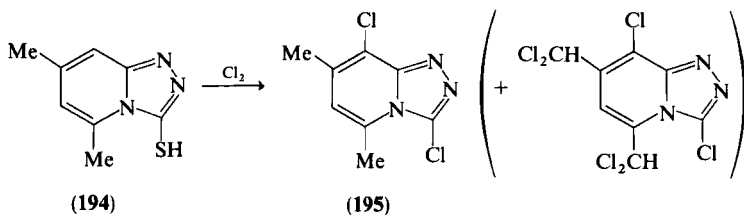
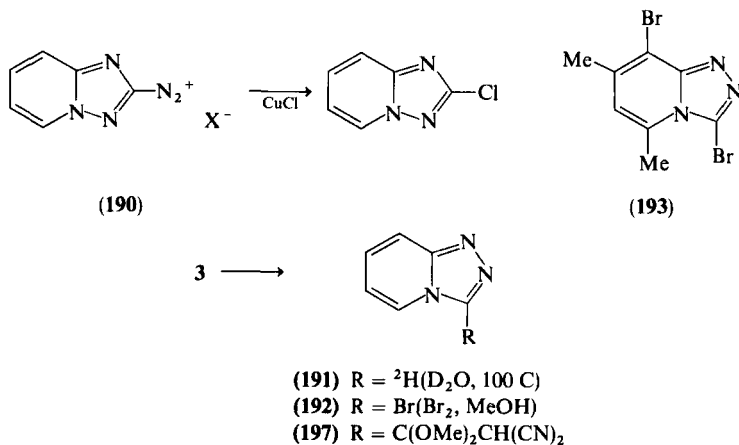


SCHEME 1

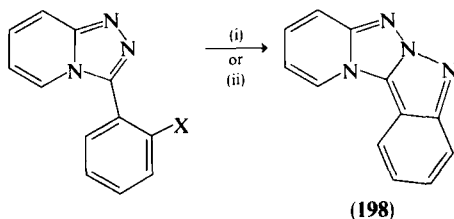
7-methyltriazolopyridine **185** gives the 7-lithiomethyl derivative, which reacts with anisaldehyde to give the alcohol **186** and with oxygen to give the hydroxymethyl derivative **187**.¹⁴ Diethylamide **188** is dilithiated (at positions 4 and 7), but reacts with anisaldehyde at position 7, giving the alcohol **189**.²⁵



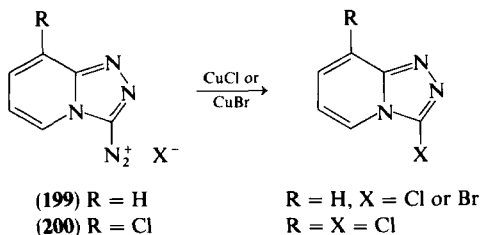
There appear to be no direct electrophilic substitutions of compound **2**; it is unreactive toward bromine, *N*-bromosuccinimide, or nitrating agents.⁴⁹ The sole electrophilic substitution (excluding alkylation) is that of the diazo group in compound **190** by chlorine in a Sandmeyer reaction.⁶⁵ By contrast,



there are many reports of attack by electrophiles on triazolopyridine **3** and its derivatives. Protonation is thought to give cation **108**,¹⁹⁸ but deuterium exchange with deuterium oxide gives the 3-deutero derivative **191**.²¹⁷ Bromination of compound **3** and its derivatives has been thoroughly examined. With bromine in methanol the 3-bromo derivative **192** was obtained,⁶⁵ whereas aqueous bromine gave only a perbromide and hence the hydrobromide. Substituents in position 3 prevented bromination, but 5,7-dimethyltriazolopyridine gave the 3,8-dibromo derivative **193**.⁶⁵ Other derivatives of triazolopyridine **3** brominated in position 3 are the 5-chloro⁸¹ and 7-phenyl²³² compounds. Chlorine reacts with compound **163** by addition.²⁰⁸ The dimethyl derivative **194** gives a dichloro derivative (**195**), but the mechanism is uncertain and may involve radical substitution at position 3, although the substitution at position 8 appears likely to be electrophilic. Triazolopyridine **3** was said to be inert to the other normal electrophilic reagents (nitration, sulfonation, Vilsmeier formylation, and Friedel-Crafts reactions),⁶⁵ but the 3-methyl derivative may be nitrated prior to rearrangement (see Section IV,F).⁶⁶ Triazolopyridin-3-one **196** is nitrated, again with some rearrangement.²⁰¹ The parent **3** reacts with tetracyanoethylene in methanol to give the 3-substituted derivative **197**; cyanide-methoxyl exchange preceded electrophilic attack.⁶⁵ An intramolecular attack by a nitrene (generated from an azide or a nitro compound) gives the tetracyclic compound **198**.²³³ Sandmeyer reactions on the diazo compound **199** give the



(i) $X = \text{NO}_2, (\text{EtO})_3\text{P}$
(ii) $X = \text{N}_3, \text{heat}$

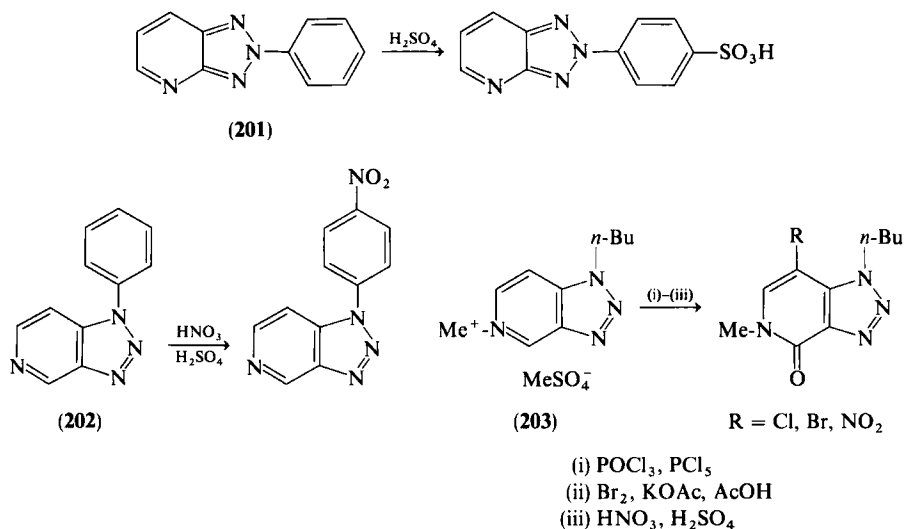


²³² S. Yusrugi, A. Miyabe, and T. Fushima, *Yakugaku Zasshi* **93**, 642 (1973) [*CA* **79**, 42417 (1973)].

²³³ P. Sai Ram and V. R. Srinivasan, *Indian J. Chem., Sect B* **15B**, 85 (1977).

3-chloro or 3-bromo derivatives⁶⁵; from 8-chlorotriazolopyridine **200** the 3,8-dichloro derivative is similarly prepared.²⁰⁸

Compounds **4** and **5** would be expected to be inert toward electrophilic substitution, and, in fact, sulfonation of the 2-phenyl derivative **201**²³⁴ and nitration of the 1-phenyl derivative **202**^{169b} lead to substitution on the phenyl rings. A series of electrophilic substitutions on the product (**203**) from 1-(*n*-butyl)[1,2,3]triazolo[4,5-*c*]pyridine and dimethyl sulphate give 7-bromo-, 7-nitro-, and 7-chlorotriazolopyridin-4-ones; the electrophilic attack may, in each case, be on the triazolopyridinone.¹⁶⁹

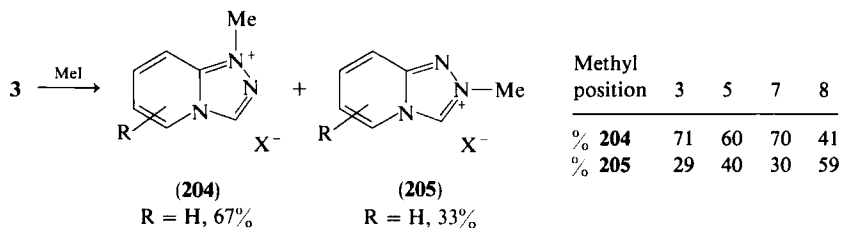


2. Alkylation

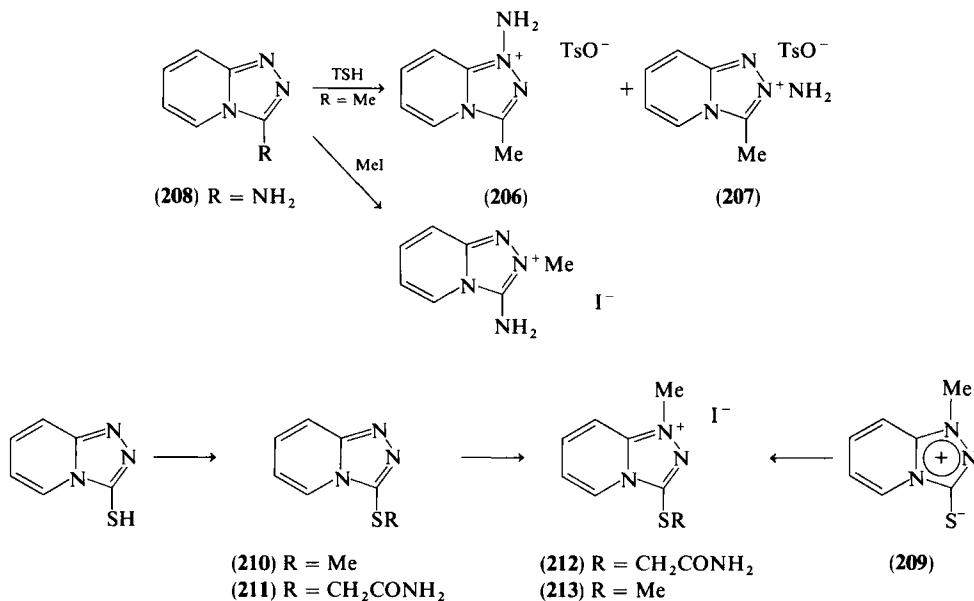
There is only one report of an alkylation of compound **1** to give a methiodide of unspecified structure.¹⁰ There are no reports of alkylation of compound **2** or of its derivatives but many reports of alkylation of derivatives of compound **3**, particularly in the preparation of Trazadone (**6**) and related compounds. Methylation of the parent **3** and its *C*-methyl derivatives has been thoroughly examined by Paudler and Brumbaugh.²¹⁸

In summary, methylation on N-1 predominates, giving quaternary salts **204**, unless an 8-methyl group presents a steric obstruction, when the N-2 methylation product **205** slightly predominates. Both methiodides are demethylated at 225°C, but on heating in a sealed tube the 1-methyltriazolo-

²³⁴ G. Charrier and M. Jorio, *Ann. Chim. Farm.* **1**, 39 (1938).

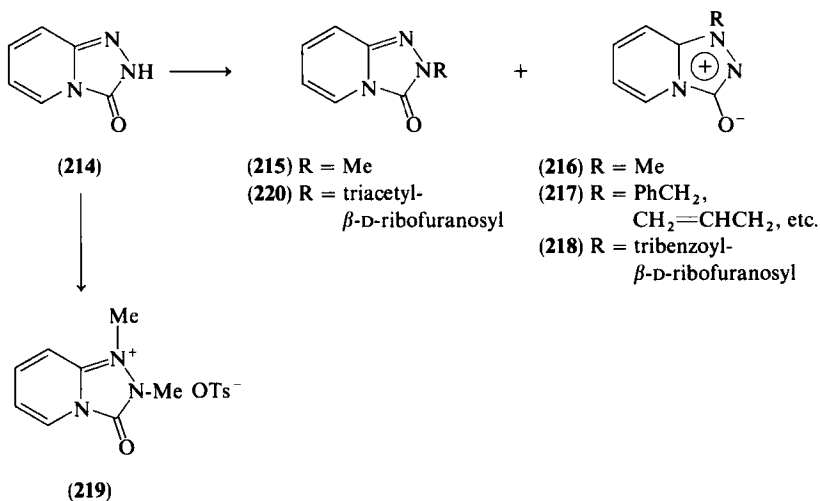


pyridinium salt rearranges to the isomer. A similar product ratio of methiodides is obtained from 3-methyltriazolo[4,3-*a*]pyridine (N-1/N-2 = 65:35), and the ratio for N-amination is more extreme, compounds **206** and **207** being formed in a ratio of 87:13.⁴⁶ The other exception to this pattern (excluding triazolo[4,3-*a*]pyridin-3-one) is 3-aminotriazolo[4,3-*a*]pyridine **208**, which presumably because of its amidine structure is methylated exclusively on N-2.⁶⁵ The 3-thione or thiol (both formulas are given by different authors) and the related mesoionic compound **209** are alkylated on sulfur, giving S-alkyl derivatives **210**,⁶⁵ **211**,²³⁵ and **212**.²³⁵ Further methylation of the methylthio derivative **210** or methylation of the mesoionic compound **209** gives the same dimethyl derivative **213**.⁶⁵



²³⁵ D. J. Brown, W. C. Dunlap, G. W. Grigg, L. Danckwerts, and T. Nagamatsu, *Aust. J. Chem.* **31**, 397 (1978).

The importance of Trazodone has led to much interest in the alkylation of triazolopyridin-3-one **214**. The original report⁶⁵ that methylation with dimethyl sulfate gave only the 2-methyl derivative **215** (also obtained with diazomethane) has been modified. Some rearrangement to a [1,2,4]triazolo[1,5-*a*]pyridinone has been reported,²⁰¹ whereas yet another report mentions the formation of the mesoionic 1-methyl derivative **216**.²³⁶ Similar mesoionic compounds (**217** and **218**) are reported as the major products when the TMS derivative of compound **214** is treated with mercuric bromide and an alkyl halide, the intermediate mercury salt being decomposed by hydrogen sulfide or on Dowex.^{237,238} Saito and Shimizu suggest²³⁷ that the sequence of alkylation may be first on oxygen, with migration to N-1 and



N-2. Alkylation with methyl tosylate (2 equivalents) gives the 1,2-dimethyl derivative **219**.²³⁹ Friedel-Crafts catalyzed glycosylation of compound **214** gives a mixture of the 2-glycosyl derivative **220** and rearranged product.²⁰¹ Trazodone (**6**) has been directly synthesized by alkylation of compound **214**, using sodium hydride,^{240,241} and by a two-stage process.²⁴¹ Analogs **221** and **222** have been obtained by alkylative modifications of existing side chains.^{241,242}

²³⁶ G. Palazzo and L. Baiocchi, *Ann. Chim. (Rome)* **56**, 190 (1966).

²³⁷ A. Saito and B. Shimizu, *Bull. Chem. Soc. Jpn.* **50**, 1596 (1977).

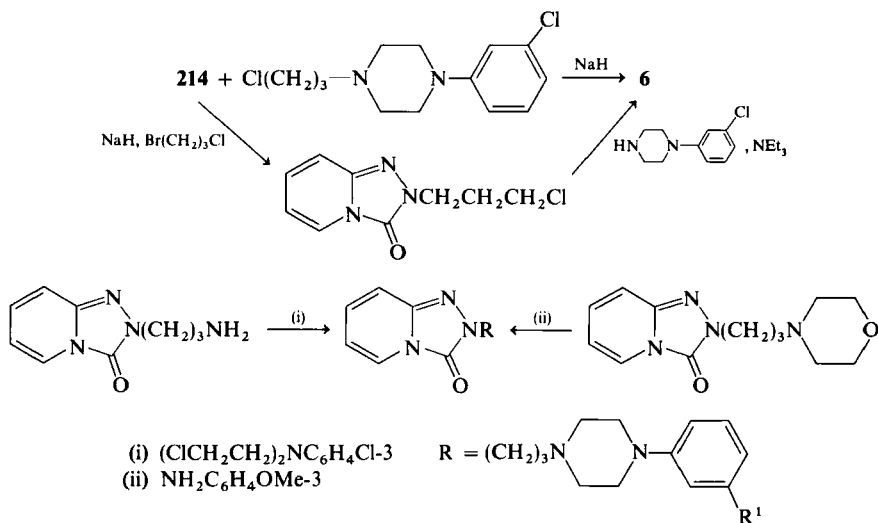
²³⁸ B. Shimizu and A. Saito, Japan Kokai 73/36,190 [*CA* **78**, 111329 (1973)].

²³⁹ B. Shimizu and A. Saito, Japan Kokai 73/36,191 [*CA* **79**, 42511 (1973)].

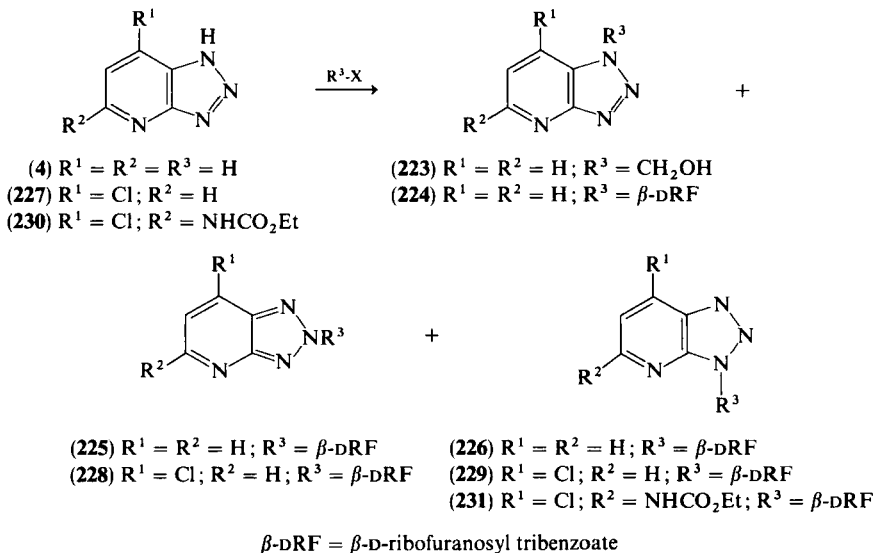
²⁴⁰ A. C. R. A. F. S. p. A. *Fr. M.* 8135 (1970) [*CA* **76**, 144855 (1972)].

²⁴¹ G. Palazzo and B. Silvestrini, U.S. Patent 3,381,009 (1968).

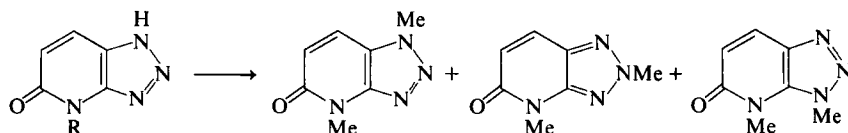
²⁴² G. Palazzo, South African Patent 72/06,070 [*CA* **80**, 3530 (1974)].

(221) $\text{R}^1 = \text{OMe}$ (222) $\text{R}^1 = \text{H}$

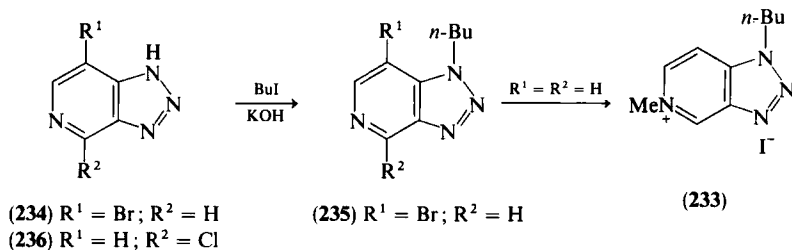
Much of the interest in alkylation of compounds **4** and **5** and their derivatives is centered on the formation of D-ribofuranosyl derivatives. Compound **4** reacts with formaldehyde to give the 1-hydroxymethyl derivative **223**¹⁶⁷ and with mercuric chloride and tribenzoyl-D-ribofuranosyl chloride to give the three *N*-glycosides **224–226**,²¹⁶ with the *N*-3 isomer predominating. The



7-chloro derivative (**227**) gives, with the same chloride and potassium cyanide in nitromethane, only N-2 and N-3 glycosides **228** and **229** in 27 and 33% yields;²¹⁶ and the 5-ethoxycarbonylamino-7-chloro derivative (**230**), as silyl derivative, gives almost entirely the N-3 glycoside **231** in 81% yield.²²⁰ The triazolopyridin-4-one **232** gives three dimethyl derivatives: 1,4, 2,4, and 3,4 in the ratio 0.27:1:0.02¹⁸⁴; other similar compounds gave also predominantly N-2 substitution. The 1-(*n*-butyl) derivative of compound **5** is methylated on the pyridine nitrogen to give the quaternary salt **233**.^{169b} The 7-bromotriazolopyridine **234** reacts with *n*-butyl iodide and base to give the 1-(*n*-butyl) derivative **235**,^{169a} whereas the 4-chlorotriazolopyridine **236** has been alkylated by a β -D-ribofuranosyl bromide under a variety of conditions, giving all three *N*-glycosides, although the proportion of N-1 isomer can be increased.²⁰⁶



(232) R = H or Me



(234) R¹ = Br; R² = H

(236) R¹ = H; R² = Cl

(235) R¹ = Br; R² = H

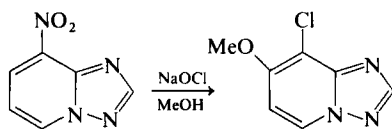
(233)

D. REACTIONS WITH NUCLEOPHILES GIVING SUBSTITUTION PRODUCTS

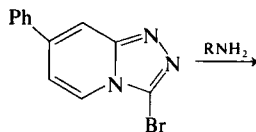
1. Substitutions on the Ring

No nucleophilic substitutions are reported for compound **1** or its derivatives. The only nucleophilic substitution of a derivative of compound **2** is the "haloalkoxylation" of the 8-nitro derivative to give compound **237**.⁶⁶ Nucleophilic replacement of halogen in position 3 of the 7-phenyl derivative of compound **3** by a number of amines gives the amines **238**,^{232,243} and the triazolopyridin-3-one **214** reacts with phosphoryl chloride to give the

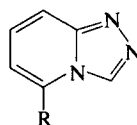
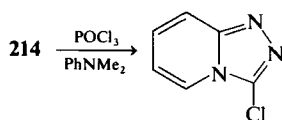
²⁴³ S. Yusurgi, T. Fushima, and A. Miyabe, Japanese Patent 72/47,391 [CA 78, 111329 (1973)].



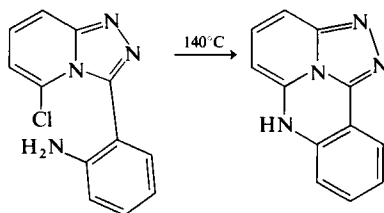
(237)

(238) R = H, *i*-Pr, Ph, etc.

3-chloro derivative.⁶⁵ Halogen in position 5 of triazolopyridine **3** is also replaceable by nucleophiles, as shown by the formation of the 5-ethoxy (**240**) and 5-ethylthio (**241**) derivatives⁸¹ from compound **239** and by the intramolecular replacement that occurs to give a tetracyclic compound when the aminophenyltriazolopyridine **242** is heated.²⁴⁴ Formation of the 5-hydroxy derivative **243** occurs when the 5-ethylsulfonyl derivative is treated with potassium hydroxide.⁸¹



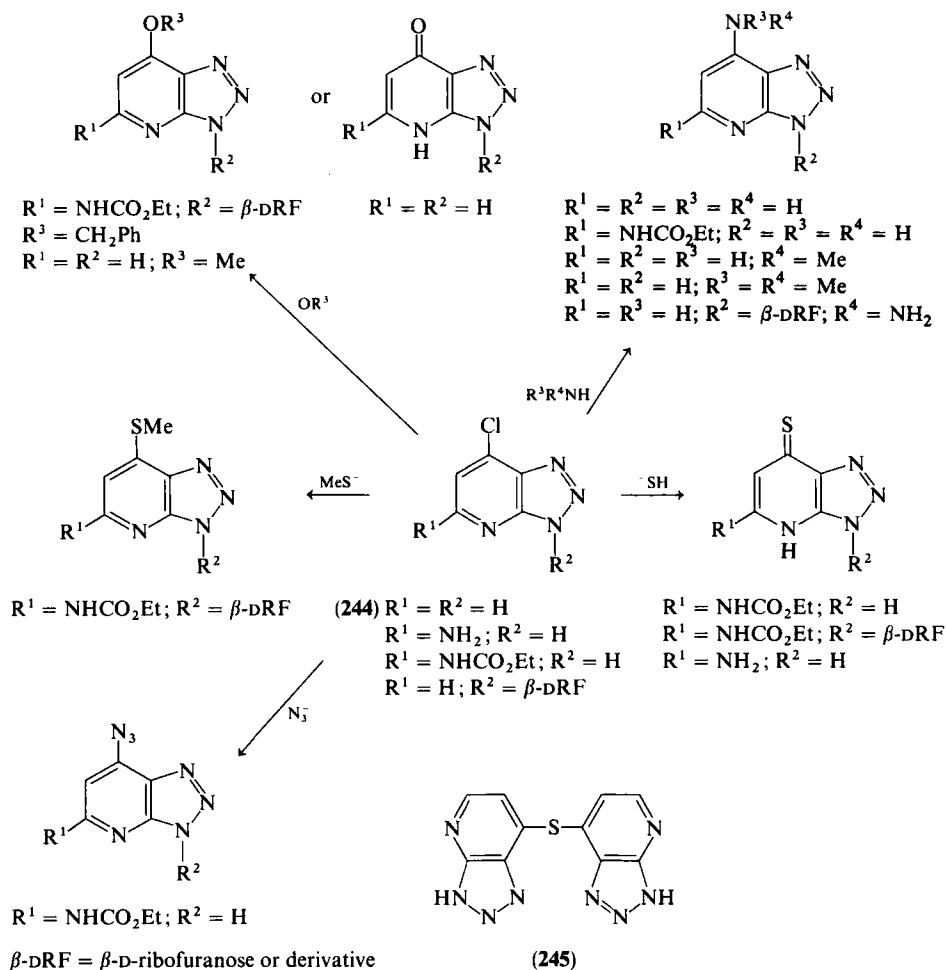
- (239) R = Cl
 (240) R = OEt
 (241) R = SEt
 (243) R = OH, from R = SO₂Et



(242)

All nuclear nucleophilic substitutions on derivatives of compound **4** have involved the replacement of a substituent at position 7 (the equivalent of the γ -position in pyridine). In the 7-chloro derivative **244**, replacement is possible by methoxide ion,¹⁵¹ by ammonia (with some rearrangement)¹⁹² and by amines,¹⁵¹ and by thiourea to give the sulfide (**245**).¹⁵¹ Substituted 7-chloro derivatives undergo replacement by benzyl oxide ion to give a 7-benzyloxy derivative^{155,220} and by azide,¹⁵³ hydrazine,²¹⁶ hydrosulfide (to give the 7-thione¹⁶⁶), and methyl thiolate.²²⁰ Some of these compounds carry D-ribofuranosyl benzoate substituents on N-2 or N-3, and methoxide ion

²⁴⁴ H. Reimlinger and W. R. F. Lingier, *Chem. Ber.* **108**, 3787 (1975).



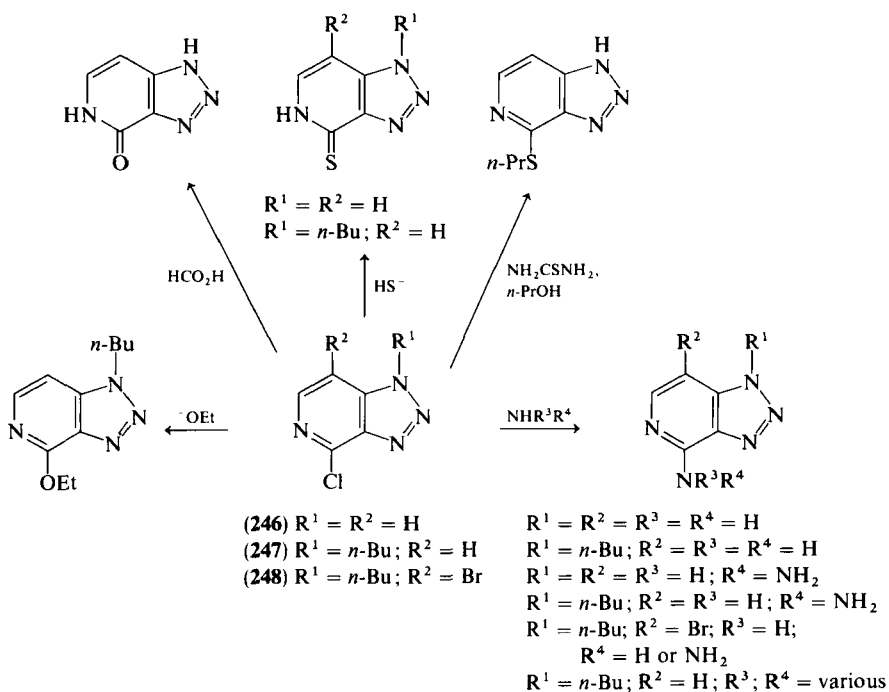
SCHEME 2

attack (which can give the triazolopyridone¹⁵³) can also cause debenzoylation.²¹⁶ These replacements are summarized in Scheme 2.

A similar series of nucleophilic substitutions has been performed on 4-chloro[1,2,3]triazolo[4,5-c]pyridine (**246**) and some of its simple substituted derivatives. On compound **246** itself formic acid gives the triazolopyridin-4-one,¹⁹² ammonia gives the 4-amino compound,¹⁹² and hydrazine the 4-hydrazino derivative;²⁴⁵ hydrosulfide gives the 4-thione¹⁹² and thiourea in propanol, at first reported¹⁵¹ to give the 4-thione, has subsequently been

²⁴⁵ Z. Talik and B. Brekiesz, *Rocz. Chem* **38**, 887 (1964) [*CA* **62**, 5271 (1965)].

shown to give a mixture of the 4-propylthio derivative with some rearranged pyridothiadiazole.¹⁹² The 1-*n*-butyl derivative **247** of compound **246** undergoes replacement by ethoxide, hydrosulfide, ammonia, and many amines;^{169a} and 7-bromo-1-*n*-butyl-4-chlorotriazolopyridine (**248**) undergoes exclusive replacement of the 4-chloro substituent in reactions with ammonia or hydrazine.^{169a} The only other substantial series of substitutions have been done on the three isomeric glycosides formally formed from compound **246** and the tribenzoate of β -D-ribofuranose.²⁰⁶ These undergo thione formation (N-1, N-2, and N-3), replacement by ammonia and methyl thiolate (N-3 only), and reaction with hydrazine (N-1 only). The reactions of compounds **246–248** are summarized in Scheme 3.

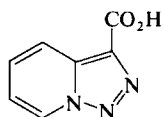


SCHEME 3

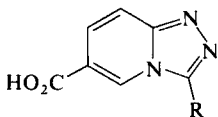
2. Side-Chain Substitutions and Transformation of Substituents

Carboxylic acids attached to the ring, as in compounds **249**²⁵ and **250**,⁷² can be converted to acid chlorides, and hence to amides,^{25,72} esters,⁷² or azides.⁷²

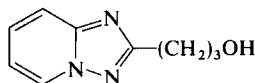
Similarly, side-chain alcohols such as those in compounds **251**²⁴⁶ and **252**¹⁶⁷ can give chlorides, and these can react with piperazines²⁴⁶ or thiophosphates.¹⁶⁷ The side-chain phosphorus derivatives **253**²⁴⁷ and **254**^{248,249} are prepared by nucleophilic displacement, respectively, of hydroxide and chloride ions. The dichloromethyl derivative **255** gives the dimethylaminomethyl derivative **256** on treatment with *N,N*-dimethylhydrazine.²⁵⁰



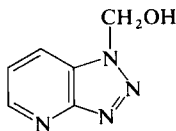
(249)



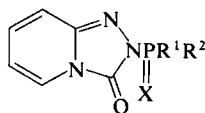
(250)



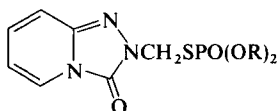
(251)



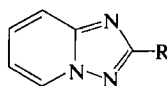
(252)



(253)



(254)

(255) R = CHCl₂(256) R = CH₂NMe₂

E. HOMOLYTIC REACTIONS

There are virtually no reports of homolytic reactions on the triazolo-pyridines. Unsuccessful attempts have been made to treat triazolopyridine (**1**) with methyl radicals,²⁵ and a free radical mechanism is suggested as a possibility in the replacement of the methylthio group by chlorine (Section IV,C).²⁰⁸

²⁴⁶ T. Irikura, Ger. Offen. 2,449,270 (1975) [CA **83**, 97308 (1975)].

²⁴⁷ W. Lorenz, I. Hamman, and B. Homeyer, Ger. Offen. 2,438,789 [CA **85**, 33022 (1976)].

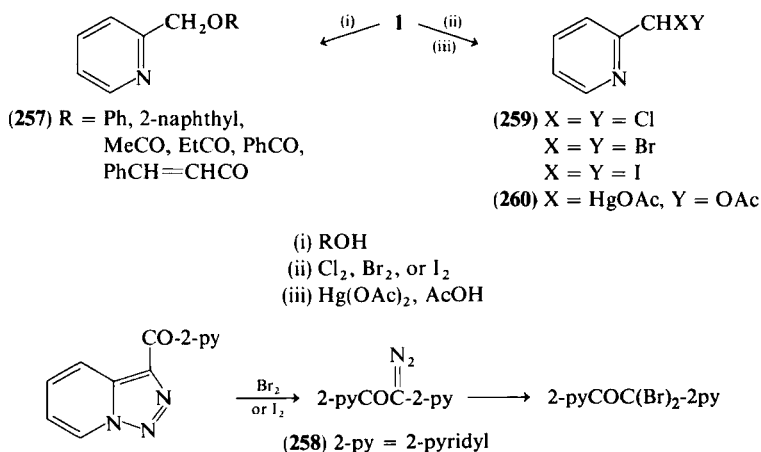
²⁴⁸ W. Lorenz, I. Hamman, and B. Homeyer, U.S. Patent 3,980,783 (1976).

²⁴⁹ W. Lorenz, I. Hamman, and B. Homeyer, Ger. Offen. 2,424,571 [CA **84**, 74274 (1976)].

²⁵⁰ K. Suzue, Japan Kokai 79/39,092 [CA **91**, 175355 (1979)].

F. RING-OPENING REACTIONS AND REARRANGEMENTS

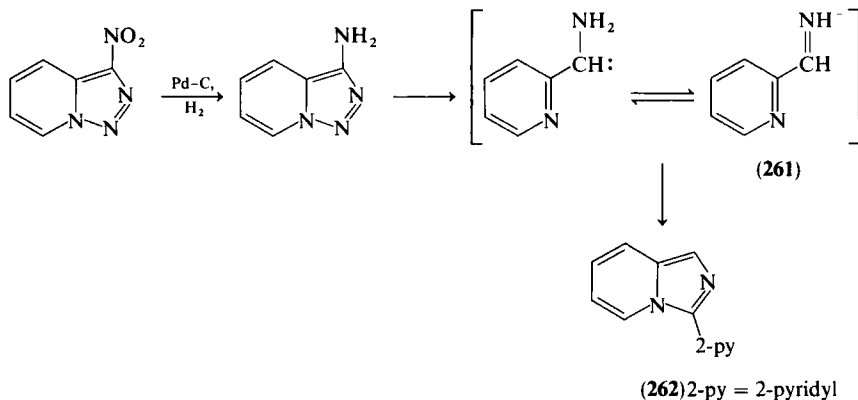
The triazolopyridines undergo a number of interesting ring-opening reactions, some of which lead, by recyclization, to other heterocycles. The reactions of this type of triazolopyridine (**1**) and its derivatives can be subdivided into those that can occur at reasonably low temperatures and those that involve considerable heat or pyrolysis. All appear to depend on the equilibrium between the triazolopyridine and the pyridyldiazoalkane, the simplest example being the protonation of 3-acyltriazolopyridines to give isolated diazoketones (described in Section III,B).²³ Boyer and Welford²⁰⁷ first described the reaction of compound **1** with acids (including phenols) to produce 2-pyridylmethanol derivatives (**257**) and also the production of dipyridyl ketones **258** or their derivatives when 3-aryltriazolopyridines reacted with halogens. Jones *et al.*^{14,25,229} have shown that triazolopyridine **1** and derivatives with a free 3-position react with halogens to give 2-dihalogenomethylpyridines (**259**) in excellent yield; mercuric acetate gives the related pyridine derivative **260**.²²⁹ In combination with the specific



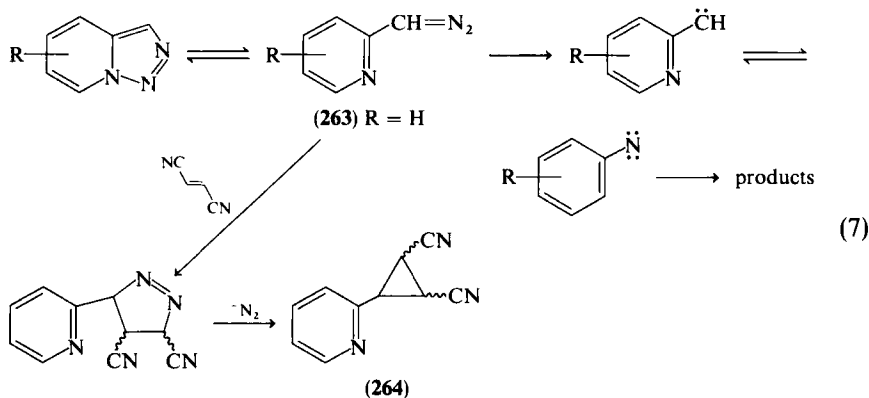
lithiation of compound **1** at position 7 (Section IV,C), the ring opening with bromine can lead to a number of 6-substituted pyridine-2-carboxaldehydes.¹⁴ The same group have reported²²⁹ that catalytic hydrogenation of 3-nitrotriazolopyridine gives as major product the imidazopyridine **262**, probably via the intermediate **261**. Compound **262** has subsequently been reported as formed from 3-aminotriazolopyridine by treatment with acid or base.⁸

The pyrolysis of triazolopyridine **1** was first investigated by Crow and Wentrup²⁵¹ and has subsequently been extensively studied by them and their

²⁵¹ W. D. Crow and C. Wentrup, *Tetrahedron Lett.*, 6149 (1968).



co-workers.²⁵²⁻²⁵⁵ At high temperatures the products are aniline and azobenzene, characteristic of the intermediacy of phenylnitrene, in turn formed by rearrangement of pyridylcarbene, as in Eq. (7).²⁵¹ Pyrolysis of 3-methyltriazolopyridine gives 2-vinylpyridine and of 3-phenyltriazolopyridine gives carbazole.²⁵¹ The last reaction has been used to prepare carbazoles.²⁵⁶ The details of the rearrangement have been well reviewed,²⁵⁷ but of interest are the identification by IR spectroscopy of the diazoalkylpyridine intermediate **263**,²⁵⁷ and the trapping of this intermediate by fumaronitrile when the decomposition was performed at 180–220°C,³⁵ giving compound **264**.



²⁵² W. D. Crow, M. N. Paddon-Row, and D. S. Sutherland, *Tetrahedron Lett.*, 2239 (1972).

²⁵³ C. Wentrup, C. Mayor, and R. Gleiter, *Helv. Chim. Acta* **55**, 2628 (1972).

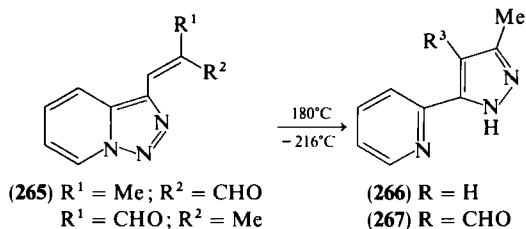
²⁵⁴ C. Wentrup, *Helv. Chim. Acta* **55**, 1613 (1972).

²⁵⁵ C. Wentrup, *Tetrahedron* **30**, 1301 (1973).

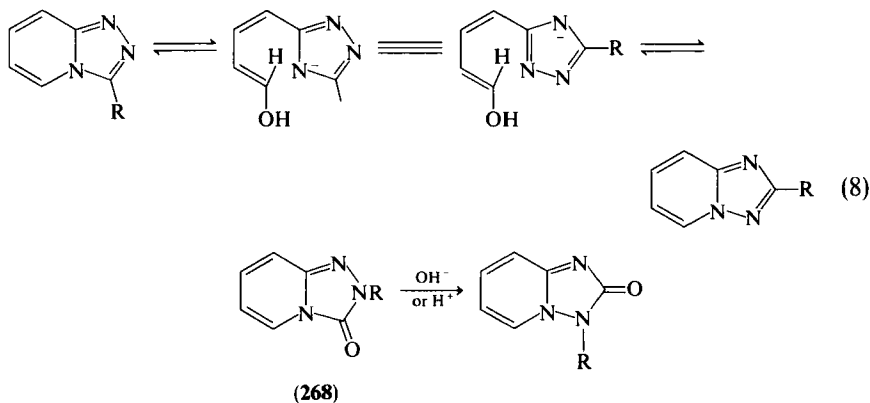
²⁵⁶ C. Mayor and C. Wentrup, *J. Am. Chem. Soc.* **97**, 7467 (1965).

²⁵⁷ C. Wentrup, *Adv. Heterocycl. Chem.* **28**, 231 (1981).

Thermolysis of the (*Z*)-acraldehyde **265** gives a mixture of the pyridyl-pyrazoles **266** and **267**.²⁵⁸ From the (*E*)-acraldehyde only compound **266** was obtained. In this reaction the diazoalkane is presumably trapped by the side-chain double bond, with subsequent formyl migration.



[1,2,4]Triazolo[1,5-*a*]pyridine (**2**) is the most stable of the three systems with bridgehead nitrogen atoms, being produced by rearrangement from the triazolo[4,3-*a*]pyridine **3**. The rearrangement of derivatives of compound **3** has been well studied.^{66,259} The rearrangement can be achieved by acid, base, or simple heat, and is facilitated by electron-withdrawing and is retarded by electron-donating substituents on the pyridine ring.⁶⁶ The mechanism (in essence a Dimroth rearrangement) is shown in Eq. (8). The triazolo-pyridin-3-ones **268** rearrange similarly.²⁰¹

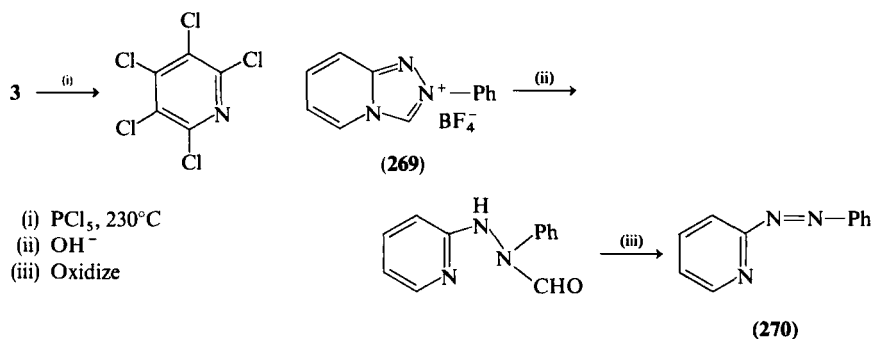


There are two examples where compound **3** or a derivative (**269**) opens without recyclization. With excess phosphorus pentachloride at 230°C compound **3** reacts to give pentachloropyridine.²⁶⁰ Treatment of 2-phenyl-triazolopyridinium fluoroborate with a base gives an *N*-formylpyridyl-hydrazine, which on oxidation gives the azo compound **270**.

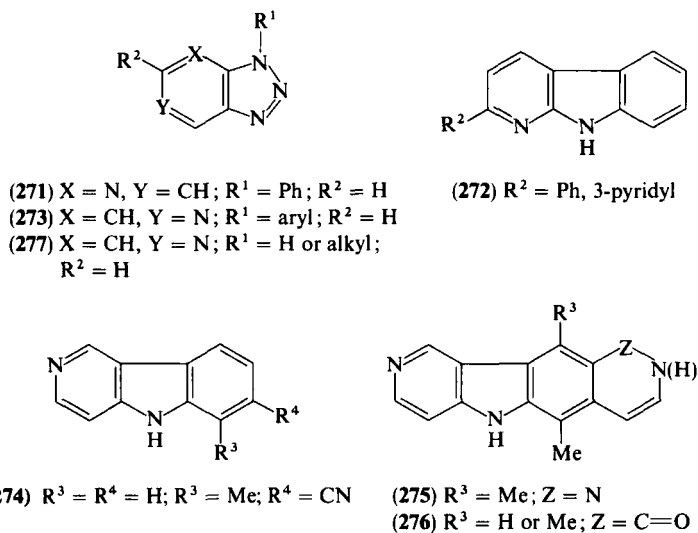
²⁵⁸ L. S. Davies and G. Jones, *J. Chem. Soc. C*, 759 (1971).

²⁵⁹ K. T. Potts and H. R. Burton, *Proc. Chem. Soc., London*, 420 (1964).

²⁶⁰ M. F. De Pompeii and W. W. Paudler, *J. Heterocycl. Chem.* **13**, 139 (1976).



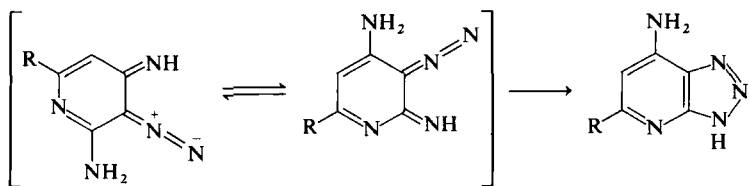
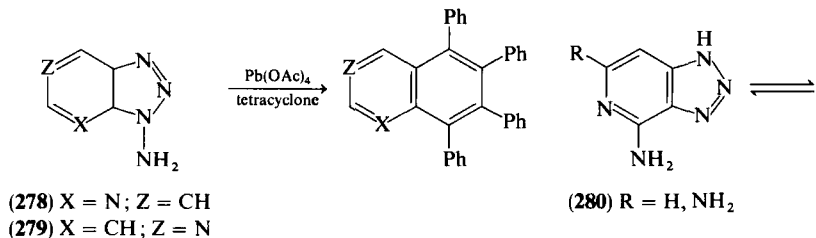
The derivatives of compounds **4** and **5** are very similar in behavior and will be dealt with together. The only direct pyrolytic ring opening of triazolo[4,5-*b*]pyridines related to compound **4** are those of compounds **271** which give pyridoindoles **272** when heated in polyphosphoric acid.²⁶¹ Pyrolysis of derivatives of compound **5** have been more thoroughly examined because they provide a route to azaellipticine (**275**) and related compounds. Thus pyrolysis of the 3-aryl derivatives **273** in paraffin or boiling phenanthrene give polycycles **274–276**, including azaellipticine.^{141,176,179,179a} The 1-alkyl derivatives **277** give 4-aminopyridines.¹⁷¹



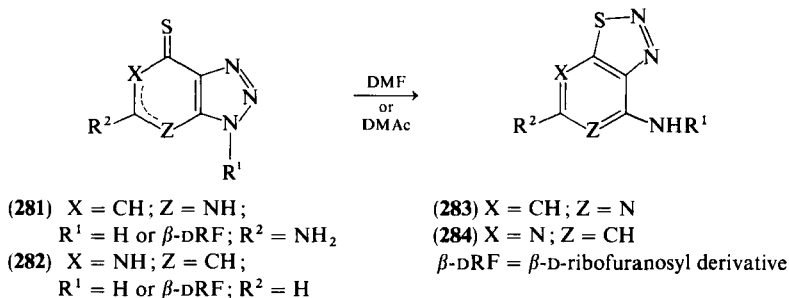
A number of ring-opening reactions involve aminotriazolopyridines. Oxidation of the *N*-amino derivatives **278** and **279** leads, via loss of nitrogen,

²⁶¹ P. Nantka-Namirskii and L. Kaczmarek, *Pol. J. Pharmacol. Pharm.* **30**, 569 (1978) [*CA* **91**, 20373 (1979)].

to the 2,3- and 3,4-pyridyne, respectively. The pyridynes can be trapped by tetracyclone,¹⁸¹ but if the trapping agent is absent then various other "pyridyne" products [2-acetoxypyridine, *N*-(3- or 4-pyridyl)pyridin-4-one] are formed.²⁶² The 4-aminotriazolopyridines **280** are unstable in the presence



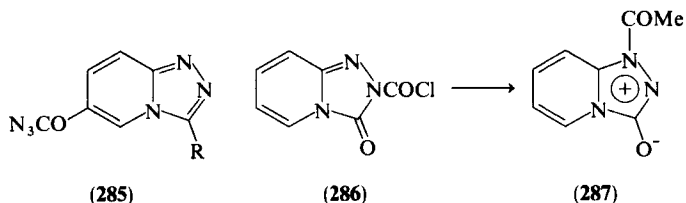
of ammonia, undergoing ring opening-ring closing to give the isomeric compounds of the [4,5-*b*] series.^{153,192} The thiones **281** or **282** rearrange on heating in DMF or dimethylacetamide, giving pyridothiadiazoles **283** or **284**.^{166,192,206,220} Compounds of type **283** and **284** are formed during attempts to convert chlorotriazolopyridines to the thiones.



There are two rearrangements that do not involve ring opening. The azides **285** undergo Curtius rearrangement on heating; in dioxane the amine is formed, in acetic anhydride the *N*-acetylamine.⁷² The acid chloride **286** is reported to be converted to the mesoionic compound **287** when treated with acetic acid and triethylamine at room temperature.²⁶³

²⁶² G. W. J. Fleet, I. Fleming, and D. Phillippides, *J. Chem. Soc. C*, 3948 (1971).

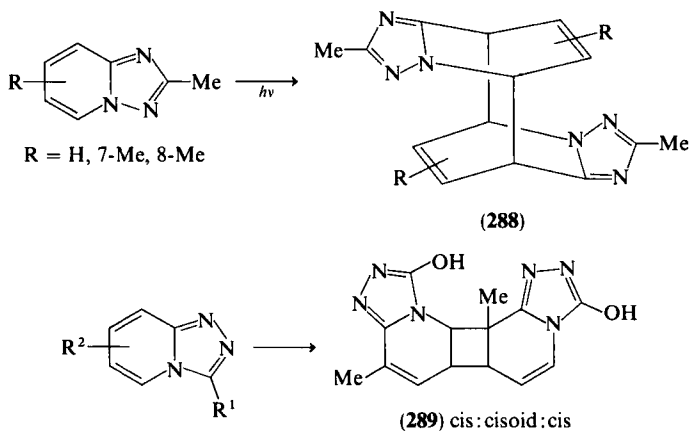
²⁶³ B. Shimizu and A. Saito, Japan Kokai 73/62,795 [*CA* **80**, 27265 (1974)].



G. PHOTOCHEMICAL REACTIONS

1. Reactions Involving the Ring

Irradiation of triazolopyridine **1** in methanol²⁶⁴ or acetic acid²⁶⁵ gives a mixture of 2-substituted pyridines. The 2-methyl derivative of compound **2** and the 2,7- and 2,8-dimethyl derivatives photodimerize in a $\pi_4 + \pi_4$ mode with light of ~ 263 nm, the dimers **288** being decomposed by light of < 220 nm.²⁰³ The dimerization is suggested to proceed through an excimer. By contrast a number of derivatives of compound **3** photodimerize by a $\pi_2 + \pi_2$ process, the 5,6-bond in one molecule reacting with the 7,8-bond in the second molecule.²⁶⁶ A typical structure is shown in compound **289**. When an alkyl chain connects the 3-positions of two molecules of compound **3**, the only $\pi_2 + \pi_2$ reaction possible is that between the two 5,6-bonds, giving compounds of type **290**; in the case where the alkyl bridge has three carbon atoms, a cage compound (**291**) is also formed.²⁶⁷

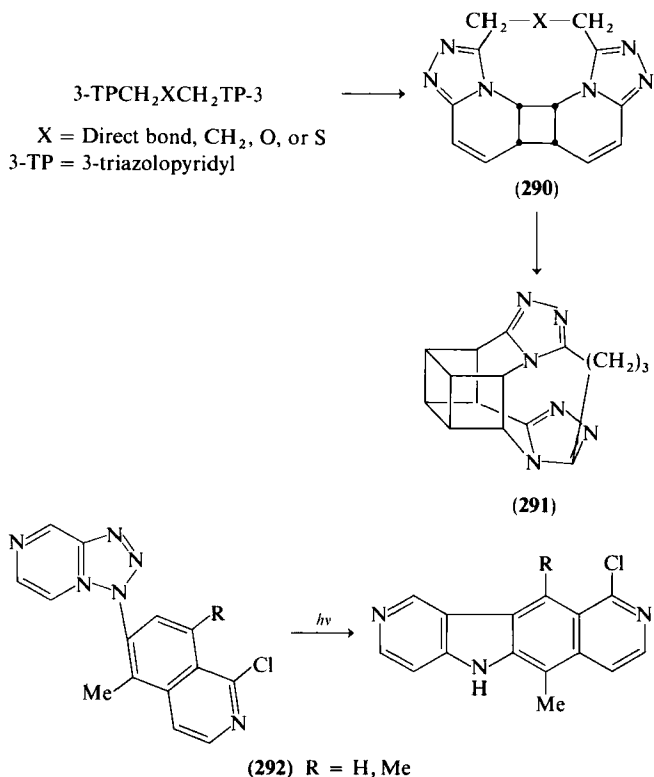


²⁶⁴ J. H. Boyer and R. Selverajan, *J. Heterocycl. Chem.* **6**, 503 (1969).

²⁶⁵ T. Miyasaki, *Iyo Kizai Kenkyusho Hokoku (Tokyo Ika Shika Daigaku)* **2**, 67 (1968).

²⁶⁶ K. T. Potts, E. G. Brugel, and W. C. Dunlap, *Tetrahedron* **33**, 1247 (1977).

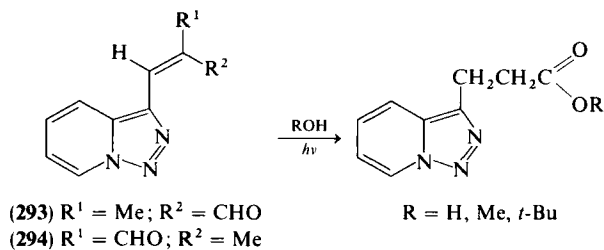
²⁶⁷ K. T. Potts, E. G. Brugel, and W. C. Dunlap, *Tetrahedron* **33**, 1253 (1977).



Photolysis of the 1-aryltriazolopyridines **292** gives an ellipticine analog (see also Section IV,F).¹⁷⁹

2. Side-Chain Reaction

The triazolopyridylacetaldehydes **293** and **294** take up water, methanol, or *tert*-butanol when irradiated in the appropriate solutions, giving triazolopyridylpropionic acid or its esters.²⁶⁸

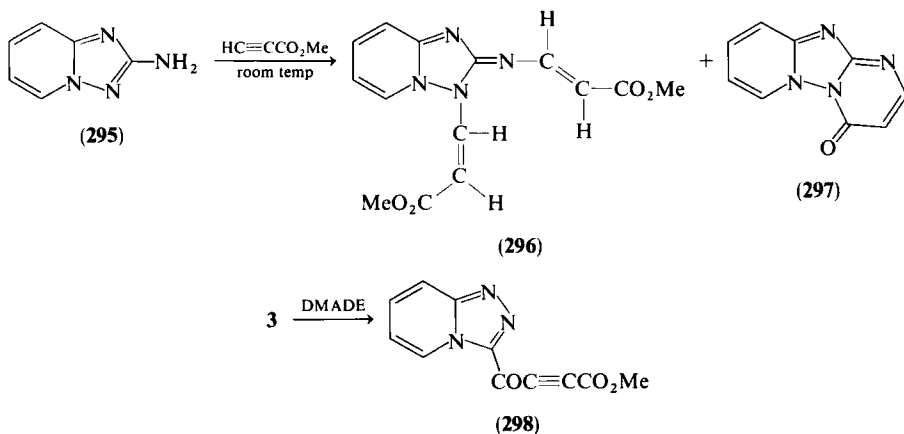


²⁶⁸ L. S. Davies and G. Jones, *J. Chem. Soc. C*, 2572 (1971).

H. OTHER REACTIONS

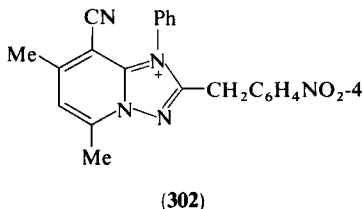
1. Reaction with Acetylenedicarboxylates

Compound **1** fails to react with dimethyl acetylenedicarboxylate (DMADE) even after two years.²⁵ At room temperature, 2-aminotriazolo-pyridine **295** gives a diadduct (**296**) with methyl propiolate and a tricyclic compound (**297**), which becomes the only isolated product on heating.²⁶⁹ Compound **3** reacts with DMADE to give the 3-substituted derivative **298**.⁶⁵



2. Reactions of Methyl and Methylene Groups

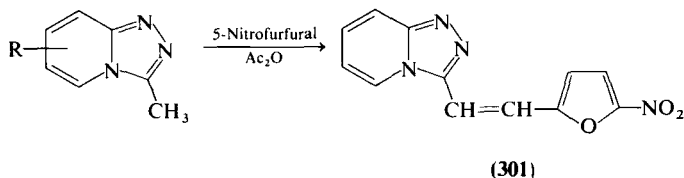
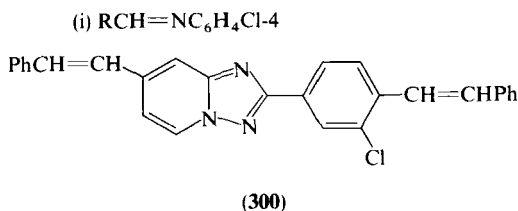
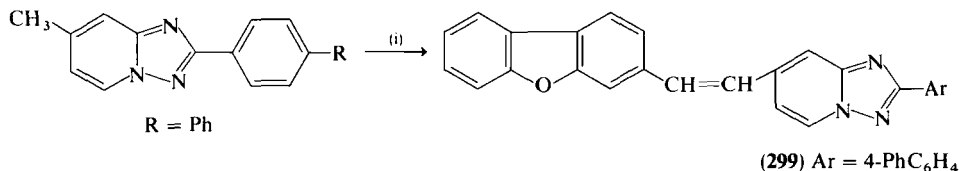
Methyl groups in position 7 of triazolopyridines of type **2** are sufficiently reactive to condense with anils, giving diarylakenes such as compound **299**.^{270,271} Methyl groups in positions 6 and 8 are not reactive in condensation, but a bis adduct (**300**) has been obtained by using a reactive 2-tolyl group. A methyl group in position 3 of system **3** is also sufficiently active to condense



²⁶⁹ H. Reimlinger, M. A. Peiren, and R. Merenyi, *Chem. Ber.* **105**, 794 (1972).

²⁷⁰ J.-P. Pauchard and A. E. Siegrist, *Helv. Chim. Acta* **61**, 142 (1978).

²⁷¹ A. E. Siegrist and J.-P. Pauchard, *Ger. Offen.* 2,750,570 [*CA* **90**, 2598 (1979)].



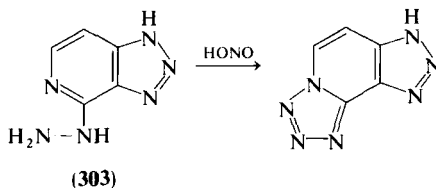
with 5-nitrofurfural in hot acetic anhydride, giving diarylalkenes of type **301**.²⁷² The methylene group in the quaternary salt **302** is sufficiently acidic to form a stable ylide with sodium hydroxide.²⁰⁰

3. Hydrolysis of Substituents

Esters can usually be hydrolyzed without attack on the nucleus, as can carbamates¹⁵³ (giving amines). The 8-[1,2,4]oxadiazol-3-yl substituent in compound **29** is hydrolyzed by sodium hydroxide giving the amide.⁴¹

4. Reactions of Hydrazino Substituents

Hydrazine substituents attached to triazolo[4,5-b]pyridines undergo normal reactions (for oxidative removal see Section IV,A,3). Treatment with nitrous acid gives an azide²¹⁶ except in the case of compound **303** when cyclization occurs.^{169a}



²⁷² C. F. Boehringer and Soehne, G. M. B. H. British Patent 1,130,909 (1968).

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Pyrans, Thiopyrans, and Selenopyrans*

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Technology, Prague, Czechoslovakia*

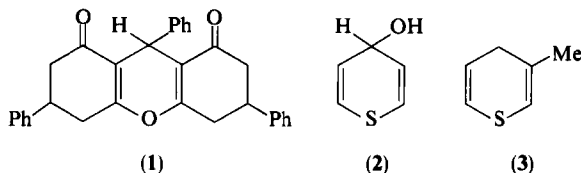
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**In memory of my friend Ulli Eisner, who died prematurely.*

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I. Introduction

Current knowledge of pyran, heteropyrans, and their derivatives has developed relatively slowly. The first pyran (**1**) was prepared^{1,2} in 1896 whereas a preparation³ of the first authentic^{4,5} thiopyran **2** appeared only in 1940. An earlier report⁶ on **3** must be considered with caution due to a lack of structure proof.^{6,7} Organic chemists paid little attention to pyrans until 1950 but the number of papers has gradually increased, exceeding the previous production in the following 10 years.



Except for several chapters found in monographs⁸⁻¹⁰ and in special articles¹¹⁻¹³ appearing in less commonly used languages,¹⁴⁻¹⁷ no exhaustive

¹ D. Vorländer and J. Erig, *Justus Liebigs Ann. Chem.* **294**, 302 (1886).

² D. Vorländer and F. Kalkow, *Justus Liebigs Ann. Chem.* **309**, 348, 356 (1899); D. Vorländer and O. Strauss, *ibid.*, 375.

³ N. I. Putokhin and V. G. Egorova, *Zh. Obshch. Khim.* **10**, 1873 (1940).

⁴ N. I. Putokhin and V. G. Egorova, *Dokl. Akad. Nauk SSSR* **96**, 293 (1954).

⁵ J. Degani, R. Fochi, and C. Vincenzi, *Tetrahedron Lett.*, 1167 (1963).

⁶ K. Krekeler, *Ber. Dtsch. Chem. Ges.* **19**, 3266 (1886).

⁷ J. Degani and C. Vincenzi, *Boll. Sci. Fac. Chim. Ind. Bologna* **25**, 51 (1967) [*CA* **68**, 29543 (1968)].

⁸ J. Fried, In "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. II, Chapter VII, Wiley, New York (1950).

review on pyrans and heteropyrans is available. This review is an attempt to discuss the literature up to 1981 as covered by *Chemical Abstracts*. Only isolable or spectroscopically identifiable pyrans as well as their thia, seleno, and telura analogs (heteropyrans) without exocyclic double bonds are considered. All benzo derivatives such as chromenes, thiochromenes, xanthenes, and thioxanthenes including all their heteroanalogs containing other than the heteroatoms mentioned are also excluded.

II. Structure

The term *pyran structure* used in this chapter applies to a six-membered ring possessing one oxygen, sulfur, selenium, or tellurium heteroatom singly bonded in a cyclic system of two double bonds and one tetrahedral atomic center. According to the position of the saturated carbon atom, the heterocycles can be classified as *2H* and *4H* isomers or more systematically as 2- and 4-oxines, and 2- and 4-thiines. Of the parent oxygen compounds, *2H*-pyran (**4**) and *4H*-pyran (**5**), and the sulfur analogs, *2H*-thiopyran (**6**) and *4H*-thiopyran (**7**), only **4** has not been synthesized.¹⁸⁻²⁴ *4H*-Selenopyran (**8**)^{22,25} and

⁹ K. Dimroth and K. H. Wolf, "New Methods of Preparative Organic Chemistry," Vol. 3, pp. 357, 388. Academic Press, New York, 1964.

¹⁰ "Rodd's Chemistry of Carbon Compounds," 2nd ed., Vol. IV, Part E, pp. 2, 347. Elsevier, Amsterdam, 1977.

¹¹ K. Dimroth, *Angew. Chem.* **72**, 331 (1960).

¹² R. D. Thompson, *Rev. Pure Appl. Chem.* **14**, 127 (1964).

¹³ H. D. Schweiger, *Pharm. Ztg.* **120**, 1253 (1975).

¹⁴ V. G. Kharchenko, S. N. Chalaya, and T. M. Konovalova, *Khim. Geterotsikl. Soedin.*, 147 (1975).

¹⁵ V. G. Kharchenko, S. N. Chalaya, and T. M. Konovalova, "Thiopyrans and Pyrylium Salts." Izd. Saratovsk. Universiteta, Saratovsk, 1975.

¹⁶ K. Fukui, *Yuki Gosei Kagaku Kyokaihi* **24**, 741 (1966) [*CA* **65**, 16931 (1966)].

¹⁷ V. G. Kharchenko, S. N. Chalaya, and T. M. Konovalova, *Khim. Geterotsikl. Soedin.*, 1155 (1974) [*CA* **82**, 16622 (1975)].

¹⁸ S. Masamine and N. T. Castellucci, *J. Am. Chem. Soc.* **84**, 2452 (1962).

¹⁹ J. Strating, J. H. Keijer, E. Molenaar, and L. Brandsma, *Angew. Chem.* **74**, 465 (1962).

²⁰ J. Degani, R. Fochi, and C. Vincenzi, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 241 (1965) [*CA* **63**, 13197 (1965)].

²¹ D. Schuijl-Laros, P. J. W. Schuijl, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **91**, 785 (1972).

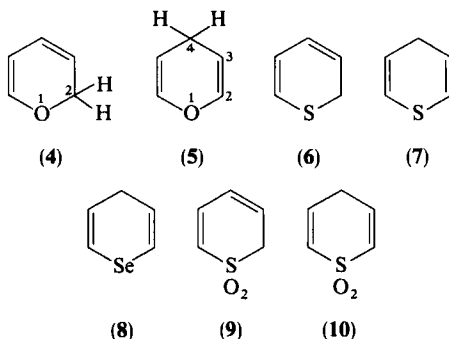
²² V. G. Kharchenko, S. K. Klimenko, and T. I. Krupina, *Zh. Org. Khim.* **3**, 1344 (1967).

²³ L. Brandsma and P. J. W. Schuijl, *Recl. Trav. Chim. Pays-Bas* **88**, 30 (1969).

²⁴ J. Strating and E. Molenaar, *Org. Prep. Proced.* **1**, 21 (1969).

²⁵ J. Degani, R. Fochi, and G. Spunta, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 243 (1965).

sulfones **9**^{26,27} and **10**²⁶ are known. All attempts to prepare **4** have been unsuccessful, evidently due to its lability associated with the valence isomerization to *cis*-2,4-pentadienal (see Section V,E).²⁸ Simple alkyl and halogen derivatives of **4** except the 2,2-disubstituted ones are also unstable.²⁸⁻³² 4*H*-Pyran (**5**) and its alkyl, alkoxy, and halogen derivatives^{29,33} also are labile substances.^{18,19}



4*H*-Pyran (**5**) seems to be thermodynamically somewhat more stable than **4** according to semiempirical CNDO/2 and nonempirical *ab initio* MO calculations.³⁴ A stability increase may be achieved by the introduction of substituents into suitable positions of the heterocyclic ring. Although no systematic studies have been carried out, the literature discussed here enables one to conclude that increasing substitution, especially by π -conjugating groups on trigonal centers, results in an enhancement in the stability of the pyran. Compounds like **1**,² **11**,³⁵ **12**,³⁶ and **13**³⁷ are typical examples of stabilized pyrans. Similar factors evidently operate in corresponding thiopyrans, which can be sometimes transformed to more stable sulfones (see Section V,A).³⁸⁻⁴⁰ Case **12** also demonstrates the preferential stability of

²⁶ E. Molenaar and J. Strating, *Recl. Trav. Chim. Pays-Bas* **86**, 436 (1967).

²⁷ E. Molenaar and J. Strating, *Recl. Trav. Chim. Pays-Bas* **86**, 1047 (1967).

²⁸ P. Schiess and H. L. Chia, *Helv. Chim. Acta* **53**, 485 (1970).

²⁹ S. Sarel and J. Rivlin, *Tetrahedron Lett.*, 821 (1965).

³⁰ P. Schiess, R. Seeger, and C. Suter, *Helv. Chim. Acta* **53**, 1713 (1970).

³¹ T. A. Gosink, *J. Org. Chem.* **39**, 1942 (1974).

³² A. Roedig and T. Neukam, *Justus Liebigs Ann. Chem.*, 240 (1975).

³³ S. M. McElvain and G. R. McKay, *J. Am. Chem. Soc.* **77**, 5601 (1975).

³⁴ S. Böhm and J. Kuthan, *Collect. Czech. Chem. Commun.* **46**, 759 (1981).

³⁵ J. Kuthan, J. Paleček, and L. Vavruška, *Collect. Czech. Chem. Commun.* **39**, 855 (1974).

³⁶ Z. Rappoport and D. Ladkani, *J.C.S. Perkin I*, 2595 (1974).

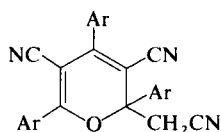
³⁷ G. Vanags and L. Geita, *Zh. Obshch. Khim.* **27**, 977 (1957) [*CA* **52**, 3802 (1958)].

³⁸ G. Suld and C. C. Price, *J. Am. Chem. Soc.* **83**, 1770 (1961).

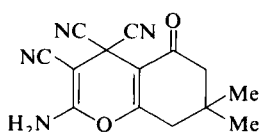
³⁹ G. Suld and C. Price, *J. Am. Chem. Soc.* **84**, 2090 (1962).

⁴⁰ V. G. Kharchenko and V. I. Kleimenova, *Zh. Org. Khim.* **7**, 613 (1971) [*CA* **75**, 5634 (1971)].

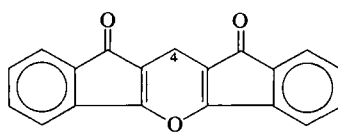
2-aminopyrans with respect to their imino tautomers, contrary to the behavior of analogous hydroxypyran, which exist exclusively as tautomeric oxo forms and are not considered here.^{36,41}



(11)

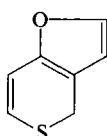


(12)

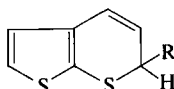
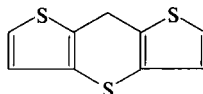


(13)

The classification of some rare bicyclic systems, e.g., **14**,⁴² **15a**,⁴³ and **16**⁴⁴ as pyrans or thiopyrans may be questioned. Nevertheless, such compounds are included.



(14)

(15a) R = H
(15b) R = Me

(16)

Limited knowledge exists with respect to detailed molecular structures of simple pyrans and heteropyrans. The semiempirical CNDO/2 calculations, using a full geometry optimization procedure, predict **4** and **5** to exhibit small deviations of the heterocyclic rings from the planar conformations.³⁴ Unfortunately, similar calculated data for thiopyrans **6**, **7**, and **9** were not presented.⁴⁵ Accounts of several X-ray diffraction investigations on compounds possessing pyran or thiopyran fragments are available.⁴⁶⁻⁵¹

Structurally complex derivative **17** has two hexasubstituted 2*H*-pyran rings A and B.⁴⁹ The data in Table I show that bond distances and angles for nonhydrogen atoms of fragments A and B exhibit quite similar features. Both double bonds C-3-C-4 and C-5-C-6 possess expected lengths but the

⁴¹ M. Quintero, C. Seoane, and J. L. Soto, *Tetrahedron Lett.*, 1835 (1877).

⁴² M. Dolci and R. Fochi, *J. Heterocycl. Chem.* **13**, 365 (1976).

⁴³ L. Brandsma and H. J. T. Bos, *Recl. Trav. Chim. Pays-Bas* **88**, 732 (1969).

⁴⁴ J. Ashby, M. Ayad, and O. Meth-Cohn, *J.C.S. Perkin I*, 1104 (1973).

⁴⁵ A. F. Pronin and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, 1206 (1977).

⁴⁶ E. Boelema, G. J. Visser, and A. Vos, *Recl. Trav. Chim. Pays-Bas* **86**, 1275 (1967).

⁴⁷ M. Haque and C. N. Caughlan, *Chem. Commun.*, 34 (1967).

⁴⁸ M. Haque and C. N. Caughlan, *J. Org. Chem.* **32**, 3017 (1967).

⁴⁹ A. Furlani, P. Bicev, S. Francoso, A. C. Villa, A. G. Manfredotti, and C. Guastini, *J.C.S. Perkin II*, 1011 (1977).

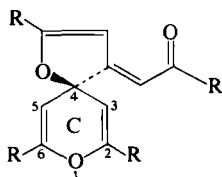
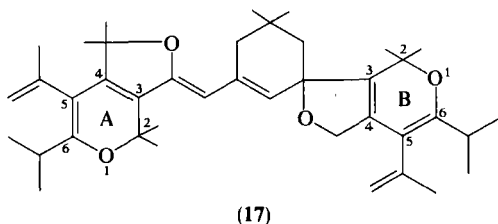
⁵⁰ S. A. Chawdhury, *Acta Crystallogr., Sect. B* **B32**, 1065 (1976).

⁵¹ M. Haque and C. N. Caughlan, *J. Org. Chem.* **32**, 3017 (1967).

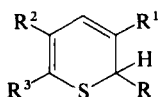
TABLE I
BOND DISTANCES (pm) AND ANGLES ($^{\circ}$) IN PYRANS **17**⁴⁹ AND **18**⁵²

Distance	Ring			Angle	Ring		
	A	B	C		A	B	C
O-1-C-2	147.2	147.1	135	O-1-C-2-C-3	107.6	108.0	119
C-2-C-3	151.0	151.2	133	C-2-C-3-C-4	121.3	120.2	123
C-3-C-4	134.2	132.9	152	C-3-C-4-C-5	121.6	121.4	121
C-4-C-5	146.3	146.5	148	C-4-C-5-C-6	116.0	116.5	112
C-5-C-6	134.8	133.5	131	C-5-C-6-O-1	122.4	121.7	122
C-6-O-1	136.3	138.1	141	C-6-O-1-C-2	120.4	117.8	122

formal single bond C-4-C-5 is somewhat shortened. Rings A and B are non-planar and "envelope shaped" with significant deviations of tetragonal C-2 centers from the approximate plane of the other ring atoms.



(18) R = *t*-Bu



(19a) R = R³ = Ph; R¹ = PhCH₂; R² = CHO

(19b) R = N(C₂H₄)₂O; R¹ = CO₂CH₂C₆H₄Br-*p*, R² = Me; R³ = MeS

The 4*H*-pyran ring C in spirocyclic derivative **18** is almost planar with maximum deviations about 4 pm and is somewhat distorted by nonbonded interactions due to the bulky 2,6-*tert*-butyl groups⁵² (see Table I).

A 2*H*-thiopyran ring may be seen in the X-ray diffraction results on aldehyde **19a**^{50,51} and derivative **19b**.⁵³ Data given in Table II demonstrate the

⁵² L. Yu. Ukhin, U. U. Bessonov, A. I. Yanovskii, T. V. Timofeeva, N. G. Furmanova, and Yu. T. Struchkov, *Khim. Geterotsikl. Soedin.*, 461 (1980) [*CA* 93, 168061 (1980)].

⁵³ R. Kalisch, A. E. Smith, and E. J. Smutny, *Tetrahedron Lett.*, 2241 (1971); A. E. Smith, R. Kalish, and E. J. Smutny, *Acta Crystallogr., Sect. B* **B28**, 3494 (1972).

TABLE II
BOND DISTANCES (pm) AND ANGLES (°) FOR THIOPYRAN RINGS IN **9**, **19**, AND **22**

Bond	Distances					Bonds	Angles			
	9	19a	19b	22			9	19a	22	
S-1-C-2	176.4	188.0	182.7	181.0	177.2	C-2-S-1-C-6	102.6	106.3	104.5	102.1
C-2-C-3	149.4	157.0	150.8	151.9	132.9	S-1-C-2-C-3	112.6	107.8	111.2	120.7
C-3-C-4	132.5	133.0	136.4	134.3	149.0	C-2-C-3-C-4	123.1	123.6	123.2	122.6
C-4-C-5	145.0	150.0	141.7	145.5	152.5	C-3-C-4-C-5	123.2	128.4	123.2	113.4
C-5-C-6	133.8	138.0	136.9	136.3	133.5	C-4-C-5-C-6	123.8	117.7	123.0	120.0
S-1-C-6	173.0	174.0	157.9	171.2	174.8	C-5-C-6-S-1	120.3	123.6	121.7	122.8
References	46	51	50	53	54		46	51	50	54

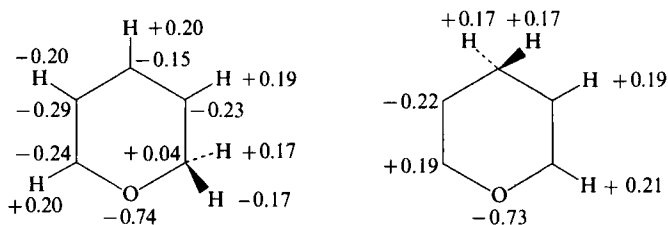
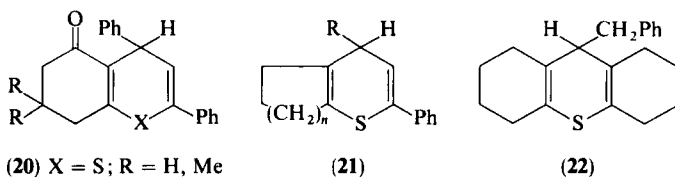


FIG. 1. Gross charge densities at atomic centers of *2H*- and *4H*-pyran.

location of double bonds between atoms C-3 and C-4 as well as C-5 and C-6. The observed distances indicate, however, that the C—C single bonds are shortened. The S-1—C-2 bond length is normal but S-1—C-6 exhibits a partial double bond character. The “frozen” ring conformation is slightly nonplanar and “boat shaped,” in which carbons C-2 and C-5 are situated 52.3 and 11.9 pm above the plane C-3—C-4—C-6 and above center S-1. The X-ray diffraction analysis of simple sulfone **9** also indicates a nonplanar conformation of the heterocycle.⁴⁶ Similarly, analogous X-ray investigation of condensed derivative **22** shows that the *4H*-thiopyran ring has a compressed, somewhat distorted boat conformation.⁵⁴



The interpretation of the ¹H-NMR spectra of *2H*-pyrans **20** and **21** in different solvents has been based on the assumption that the rings are boat shaped as in **19** and that the 4-substituent prefers the axial conformation.⁵⁵

Figure 1 shows gross charge densities at all atomic centers of molecules **4** and **5** calculated by split-valence 4-31G basis set of atomic orbitals.⁵⁶ Typical of both **4** and **5** is the location of a negative charge at neighboring positions C-3, C-4, and C-5 as well as at oxygen centers O-1. Possible consequences of the electronic structures of **4** and **5** for the relative lability have been also discussed in terms of partial charges and molecular orbital energies.⁵⁶ Similar calculated data on thiopyrans **6** and **7** are lacking, although the importance of *d*-orbital participation in their electronic structures was noted.⁴⁵

⁵⁴ A. A. Shcherbakov, G. G. Aleksandrov, Yu. T. Struchkov, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, 1470 (1979) [*CA* **92**, 163810 (1980)].

⁵⁵ I. A. Evtushenko, S. K. Klimenko, B. I. Ionin, and V. G. Kharchenko, *Zh. Org. Khim.* **11**, 2417 (1975).

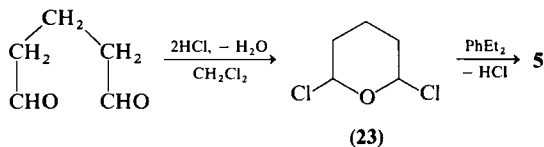
⁵⁶ S. Böhm and J. Kuthan, *Collect. Czech. Chem. Commun.* **46**, 759 (1981).

III. Synthesis from Acyclic Precursors

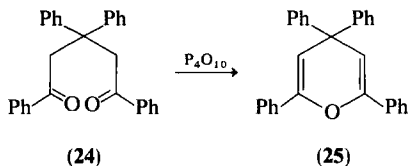
The expressions "acyclic" or "cyclic" precursors used in this section indicate whether a pyran ring closure does or does not occur during synthesis. No importance is attributed to the fact that reactants may already contain a ring.

A. PYRANS FROM 1,5-DICARBONYL COMPOUNDS

The best approach to unsubstituted 4*H*-pyran (**5**) is from glutaric dialdehyde and hydrogen chloride, which gives up to a 40% yield of **5**. Intermediate **23** is not isolated.^{9,19,57} This procedure was successfully extended to the preparation of 4-methyl-4*H*-pyran.⁷



Similar cyclodehydrations of simple 1,5-diketones may require more reactive agents. Thus **24** undergoes dehydration with P_4O_{10} to 2,4,4,6-tetraphenyl-4*H*-pyran (**25**, 68%).⁵⁸



The ring closure of **26** to **27** proceeds with *p*-toluenesulfonic acid in boiling benzene.⁵⁹ The same reaction products (**27**) were obtained from ketols **28** with acetic anhydride in acetic acid.⁶⁰

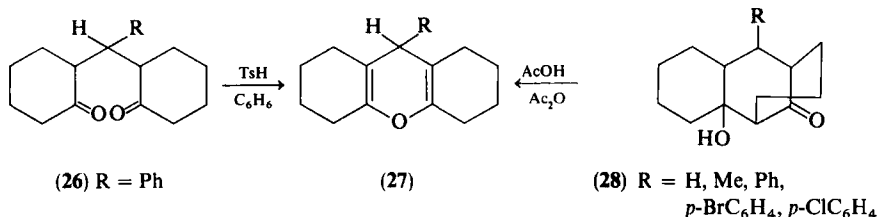
If two cyclic 1,3-dioxo fragments are connected via a monocarbon 2,2'-bridge, only one undergoes cyclodehydration. Thus bicyclic 4*H*-pyran systems **20b** (R = H or Ph) were obtained after the reaction of triketone **53**

⁵⁷ L. Brandsma and J. Strating, in "Houben-Weyl Methoden der organischen Chemie" (E. Müller, ed.), 4th ed., Vol. VI, Chapter 4, p. 109. Thieme, Stuttgart, 1966.

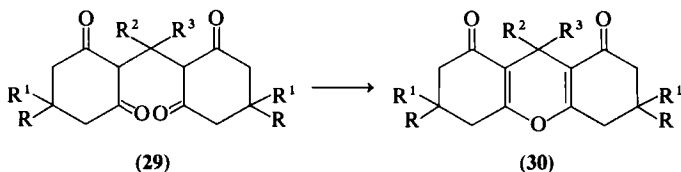
⁵⁸ A. Peres de Carvalho, *Ann. Chim. (Paris)* [11] **4**, 449 (1935).

⁵⁹ V. I. Vysotskii, N. V. Verishinina, M. N. Tilichenko, V. V. Isakov, and T. M. Belokon, *Zh. Org. Khim.* **9**, 2427 (1973) [*CA* **80**, 47783 (1974)].

⁶⁰ V. G. Kharchenko and A. F. Blinokhvatov, *Khim. Geterotsikl. Soedin.*, 1615 (1978) [*CA* **90**, 103768 (1979)].



with acetic anhydride.⁶¹ Similarly, 3-ethynyl-2,4-diformyl-1,5-dienal undergoes dehydrations with acetic or maleic anhydrides to 3,5-diformyl-4-ethynyl-4H-pyran (**85d**).⁶² Tricyclic 4H-pyran-3,5-diones **30** were thus prepared from readily available tetraketones **29** on heating with acetic anhydride, acetic acid, sulfuric acid, *p*-toluenesulfonic acid, or on melting.^{1,2,63-67}



- (a) $R = R^1 = R^2 = H$; $R^3 = H, Ph, p\text{-}ClC_6H_4, p\text{-}NO_2C_6H_4, o\text{-}Me\text{-}p\text{-}N(CH_2CH_2Cl)_2C_6H_3$
 (b) $R = Ph$; $R^1 = R^2 = H$; $R^3 = H, o\text{-}Me\text{-}p\text{-}N(CH_2CH_2Cl)_2C_6H_3$
 (c) $R = R^1 = Me$; $R^2 = H$; $R^3 = H, Me, Et, Ph, o\text{-}HOC_6H_4, o\text{-}AcOC_6H_4, o\text{-}MeOC_6H_4, o\text{-}Me\text{-}p\text{-}N(CH_2CH_2Cl)_2C_6H_3$
 (d) $R = R^1 = R^2 = R^3 = Me$
 (e) $R, R^1 = (CH_2)_4$; $R^2 = H$; $R^3 = H, Ph, o\text{-}HOC_6H_4$

The same procedure was explored in the synthesis of polycondensed 4H-pyran (**13**)³⁷ as well as several of its more complex 4,4-disubstituted derivatives⁶⁸⁻⁷⁰ from 1,3-indandione precursors.

⁶¹ V. G. Kharchenko, L. I. Markova, and K. M. Korshunova, *Zh. Org. Khim.* **12**, 663 (1976).

⁶² F. Wille and W. Schwab, *Monatsh. Chem.* **108**, 929 (1977).

⁶³ E. C. Horning and M. G. Horning, *J. Org. Chem.* **11**, 95 (1946).

⁶⁴ H. Antaki, *J. Chem. Soc.*, 4877 (1963).

⁶⁵ J. Lielbriedis and E. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 198 (1964) [*CA* **61**, 6984 (1964)].

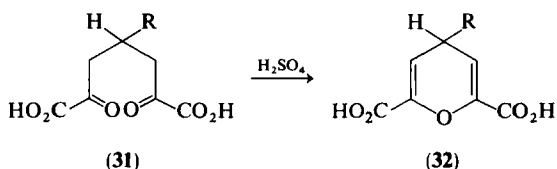
⁶⁶ S. Inayama and K. Mamoto, Japan Kokai 74, 125,364 (1974) [*CA* **83**, 9788 (1975)].

⁶⁷ R. Desai, *J. Indian Chem. Soc.* **10**, 663 (1933).

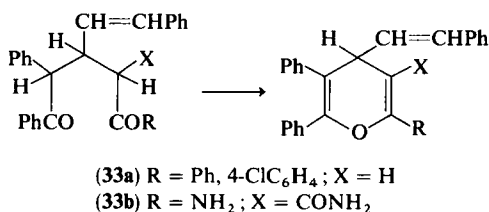
⁶⁸ G. I. Vanag and L. S. Geita, *Zh. Obshch. Khim.* **26**, 1746 (1956); *Dokl. Akad. Nauk SSSR* **95**, 277 (1954).

⁶⁹ G. Vanags and L. Geita, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 153 (1955) [*CA* **50**, 4945 (1956)].

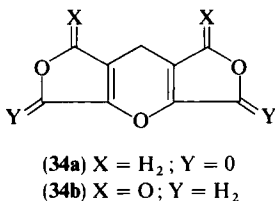
Analogously stable 4*H*-pyran-2,6-dicarboxylic acids **32** were available by cyclodehydration of α, α' -diketo diacids **31** with sulfuric acid.⁷¹⁻⁷³



Similar cyclocondensations were described with more complex 1,5-dicarbonyl precursors (**33a,b**).⁷⁴ Other examples of the ring closure accompanied by hydrolysis of substituent X = CO₂Et will be mentioned in Section V,K.



Bislactones **34** were prepared similarly from the corresponding methylene bisketolactones.^{75,76}



Biscoumarin derivative **36** was obtained from **35** with POCl₃ in pyridine or by heating **37** with acetic acid.⁷⁷ (Scheme 1).

⁷¹ E. Blaise and H. Gault, *Bull. Soc. Chim. Fr.* [4] 1, 129 (1907).

⁷² J. C. Lewis and R. M. Seifert, *Org. Prep. Proced. Int.* 3, 243 (1971).

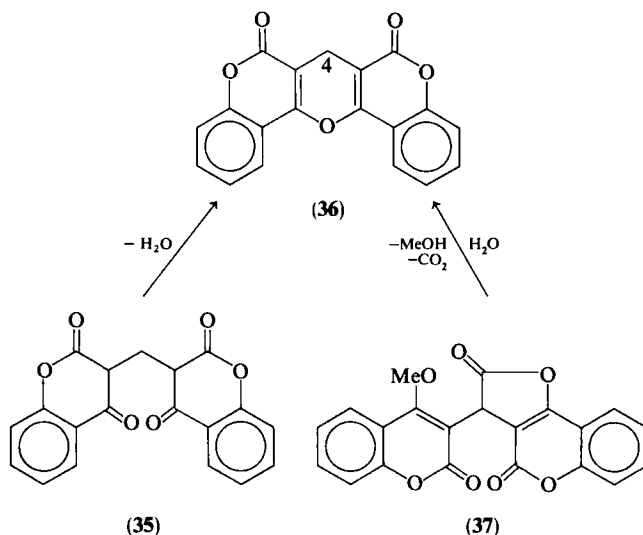
⁷³ A. Cope and A. Fournier, *J. Am. Chem. Soc.* 79, 3896 (1957).

⁷⁴ A. Sammour, A. Raouf, M. Elkasaby, and M. A. Hassan, *Acta Chim. Acad. Sci. Hung.* 83, 209 (1974).

⁷⁵ V. V. Feofilaktov, *J. Russ. Phys. Chem. Soc.* 61, 1145 (1929) [CA 24, 832 (1929)].

⁷⁶ I. Butula and D. Grguric, *Synthesis*, 808 (1979).

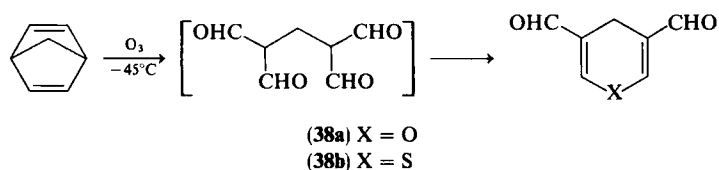
⁷⁷ E. Zieger and T. Kappe, *Monatsh. Chem.* 96, 77 (1965).



SCHEME 1

Several other 4-substituted 4H-pyrans (36) were synthesized analogously.⁷⁸⁻⁸⁴

As follows from the preceding examples, the dehydrative 4H-pyran ring closure is facilitated when a condensed ring system is formed. Otherwise the formation of 4H-pyrans may be difficult. Only a small amount of 3,5-diformyl-4H-pyran (38a) was found after the ozonolysis of norbornadiene, followed by decomposition of the primary ozonides with zinc and acetic acid.⁸⁵



⁷⁸ K. Fučík, Ž. Procházka, L. Láblér, F. Kanhäuser, and F. Jančík, *Chem. Listy* **43**, 53 (1949).

⁷⁹ K. Fučík and R. Láblér, *Chem. Listy* **45**, 497 (1951).

⁸⁰ K. Fučík and Ž. Procházka, *Bull. Soc. Chim. Fr.*, 932 (1951).

⁸¹ K. Fučík, Ž. Procházka, and J. Štrof, *Chem. Listy* **45**, 488 (1951).

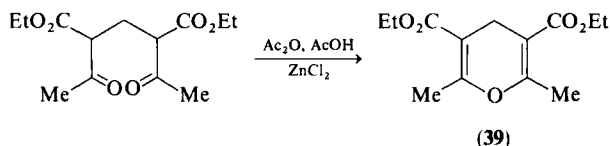
⁸² K. Fučík, Ž. Procházka, and J. Štrof, *Collect. Czech. Chem. Commun.* **16**, 305 (1951).

⁸³ E. Ziegler, H. Junek, and G. Wildtgrube, *Monatsh. Chem.* **87**, 386 (1956).

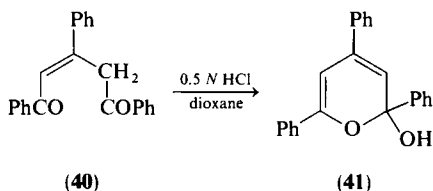
⁸⁴ H. Pazdro, *Diss. Pharm.* **15**, 29 (1963) [*CA* **59**, 11458 (1963)].

⁸⁵ J. M. Brown and F. Sondheimer, *Angew. Chem.* **86**, 346 (1974).

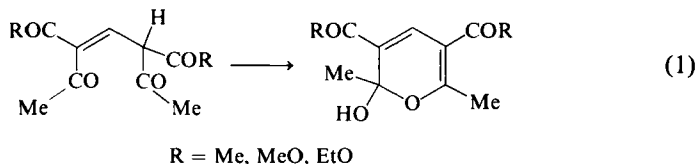
Cyclodehydration of methylenebisacetoacetic ester to **39** requires ZnCl_2 catalysis. Attempts to accomplish the reaction with methylenebisbenzoylacetic ester failed.⁸⁶



Insufficient information concerning the transformation of unsaturated 1,5-dicarbonyl precursors to 2*H*-pyrans is available. A reinvestigation of an earlier report⁸⁷ on a possible 2-hydroxy-2*H*-pyran sodium salt formation after the decomposition of 1-benzoylpyridinium ion with hydroxide ion would be desirable. The formation of 2-hydroxy-2,4,6-triphenyl-2*H*-pyran (**41**) from the appropriate 1,5-diketone (**40**) was also reported.⁸⁸



A similar cyclization shown in Eq. (1) proceeds spontaneously in chloroform.⁸⁹



B. THIOPYRANS FROM 1,5-DICARBONYL COMPOUNDS

The synthesis of 4*H*-thiopyrans from 1,5-dicarbonyl compounds consists of the cyclization of 1,5-dioxo precursors with hydrogen sulfide in the presence of protic acids or with various phosphorus polysulfides.

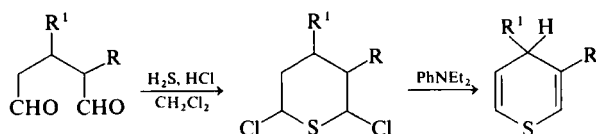
⁸⁶ J. Wolinsky and H. S. Hauer, *J. Org. Chem.* **34**, 3169 (1969).

⁸⁷ H. Freytag, *Ber. Dtsch. Chem. Ges. B* **67**, 1995 (1934).

⁸⁸ J. P. Griot, J. Royer, and J. Dreux, *Tetrahedron Lett.*, 2195 (1969).

⁸⁹ L. Crombie, D. E. Games, and A. W. G. James, *J.C.S. Perkin I*, 464 (1979).

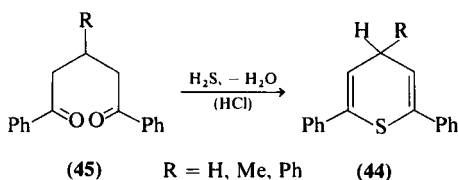
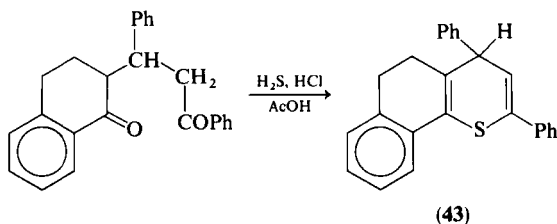
The first synthesis starting with glutaric dialdehydes and involving intermediates **42** succeeded in preparing unsubstituted 4*H*-thiopyran (**7**)^{19,24} as well as alkylated derivatives.^{7,90,91}



(42) R = H or Me; R¹ = H, Me, or *i*-Pr

In the case of R = R¹ = H this procedure gives 20 to 45% of 7 98% pure.²⁴

Analogous cyclizations with 1,5-diketones show that ring closure readily occurs in protic solvents such as acetic acid⁹²⁻⁹⁴ or alcohols.⁹⁴⁻⁹⁶ Typical examples include the preparations of 4*H*-thiopyran derivatives **43**, **45**, and **47a** from the corresponding 1,5-diphenyl-1,5-diones **44** and **46**, respectively.^{92,93}



(45) R = H, Me, Ph (44)

⁹⁰ J. Degani, R. Fochi, and C. Vincenzi, *Gazz. Chim. Ital.* **94**, 203 (1964).

⁹¹ J. Degani and C. Vincenzi, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 245 (1965) [*CA* **63**, 13197 (1965)].

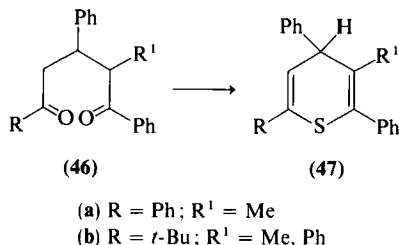
⁹² V. G. Kharchenko, V. I. Kleimenova, and A. R. Yakoreva, *Khim. Geterotsikl. Soedin.*, 900 (1970) [*CA* **74**, 76272 (1971)]; V. G. Kharchenko, S. K. Klimenko, V. I. Kleimenova, and N. M. Kupranets, *Zh. Org. Khim.*, 1711 (1969).

⁹³ V. G. Kharchenko, N. M. Kupranets, V. I. Kleimenova, A. A. Rassudova, M. E. Stankevich, and N. M. Yartseva, *Zh. Org. Khim.* **6**, 1119 (1970).

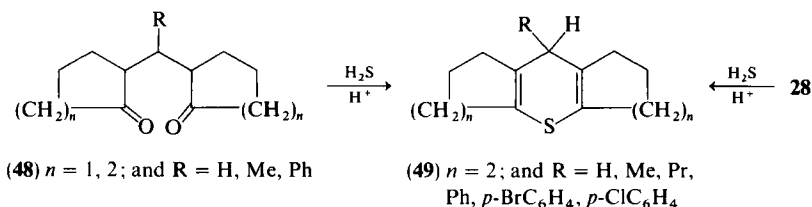
⁹⁴ O. V. Fedotova, L. K. Kulikova, B. A. Shenderov, A. P. Kharchenko, and G. M. Shub, *Khim.-Farm. Zh.* **11**, 72 (1977) [*CA* **88**, 62264 (1978)].

⁹⁵ V. G. Kharchenko and S. K. Klimenko, *Khim. Geterotsikl. Soedin.*, 630 (1967) [*CA* **68**, 29544 (1968)].

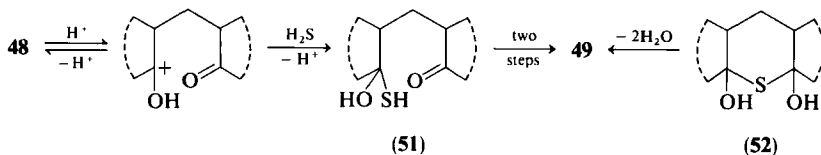
⁹⁶ S. K. Klimenko, M. N. Berethnaya, and V. G. Kharchenko, *Zh. Org. Khim.* **10**, 2425 (1974) [*CA* **82**, 86264 (1975)].



Similarly, condensed 4*H*-thiopyrans **21** having $n = 3$ or 4 and $R = \text{H}, \text{Ph}$, or 4-MeOC₆H₄ were prepared.^{93,96} The formation of tricyclic condensed products **49** was smoothly accomplished from the corresponding dienones **48**^{93,95,97} or their ketols **28**.^{60,98}



Transformations **48** $\rightarrow$ **49** were followed kinetically in the case of $R = \text{H}$.⁹⁷ Rates exhibit first-order kinetics with respect to substrate, agent, and catalyst; rate = $k[\text{48}][\text{H}_2\text{S}][\text{H}^+]$. They were interpreted by a reaction mechanism involving the rate determining step **50** $\rightarrow$ **51**.⁹⁷



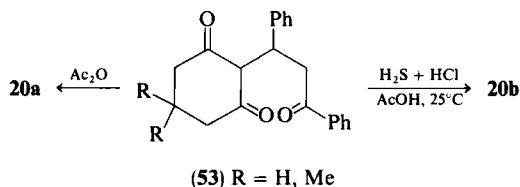
In some cases the formation of a 4*H*-thiopyran is accompanied by dehydrogenation⁹⁷ of the product. Hence the yield of thiopyrans may depend strongly on reaction conditions. Some other protic acids were found to be useful in place of the widely applied hydrogen chloride.^{93,97,98} The choice of solvent may also be of importance. Thus derivatives **19** having $n = 3$ were

⁹⁷ N. I. Marteni'yanova, M. I. Kuramskin, S. V. Dudun, and V. G. Kharchenko, *Zh. Org. Khim.* **13**, 1020 (1977) [*CA* **87**, 84058 (1977)].

⁹⁸ V. G. Kharchenko and A. F. Blinokhvatov, *Zh. Org. Khim.* **10**, 2462 (1974) [*CA* **83**, 125232 (1975)].

not isolated in the presence of methanol, probably due to their subsequent reactions with the solvent.⁹⁶

If a precursor contains more than two carbonyl groups, the reaction with H_2S involves those in 1,5-positions. Thus in the case of triketones **53**, products **20** ($\text{R} = \text{H}, \text{Me}$) were isolated in yields of 96 and 94%, respectively.^{61,99} 4*H*-Thiopyran **20a** ($\text{R} = \text{H}$) isomerizes under the reaction conditions.¹⁰⁰



The second approach to 4*H*-thiopyrans involves P_xS_y (usually P_4S_{10}) as cyclization agent. The reaction mechanism is unknown but may be related to that using a protic acid- H_2S system, at least in some steps.

A major preparative advantage of the P_xS_y method is the possibility of avoiding an acid medium in which some thiopyrans or starting 1,5-dicarbonyl compounds are unstable. On the other hand, a more elevated temperature is sometimes necessary to accomplish the cyclization with P_xS_y .

In comparison to the H_2S - HCl procedure,^{61,92,93} variable yields of 4*H*-thiopyrans **20**, **45** ($\text{R} = \text{Ph}$), **47**, and **49** ($n = 2$, $\text{R} = \text{H}, \text{Me}, \text{Et}, \text{Pr}$) were achieved if the starting 1,5-diketones **53**, **44**, **46**, and **48** reacted with P_4S_{10} in pyridine at 110 to 115°C.^{95,101-105} Tetrasubstituted^{101,105a} and pentasubstituted^{103,105} derivatives **47b**, **54**, and **55** were prepared similarly in variable yields up to 75%, whereas crude 1,1,3,3-propanetetracarbaldehyde, ob-

⁹⁹ L. T. Lelynh and V. G. Kharchenko, *Zh. Org. Khim.* **10**, 1547 (1974) [*CA* **81**, 120393 (1974)].

¹⁰⁰ S. K. Klimenko and V. G. Kharchenko, *Khim. Geterotsikl. Soedin. Sb.* **3**, 85 (1971) [*CA* **78**, 71851 (1973)].

¹⁰¹ V. G. Kharchenko, S. K. Klimenko, A. M. Plaksina, and A. R. Yakoreva, *Zh. Org. Khim.* **2**, 1122 (1966) [*CA* **65**, 15313 (1966)].

¹⁰² V. G. Kharchenko and T. I. Krupina, *Khim. Geterotsikl. Soedin.*, 468 (1967).

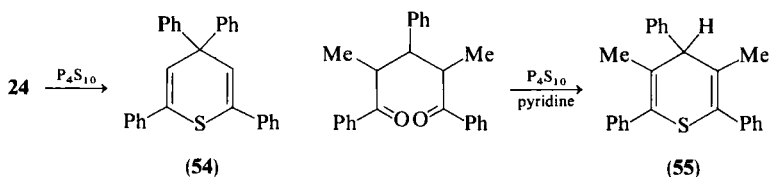
¹⁰³ V. G. Kharchenko, S. K. Klimenko, V. I. Kleimenova, N. M. Kupranets, and A. R. Yakoreva, *Khim. Geterotsikl. Soedin. Sb.* **3**, 73 (1972) [*CA* **78**, 71850 (1973)].

¹⁰⁴ V. G. Kharchenko, T. I. Krupina, and A. A. Rassudova, *Zh. Org. Khim.* **1**, 2245 (1965).

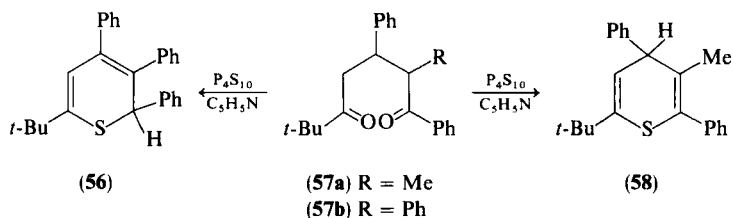
¹⁰⁵ V. G. Kharchenko, S. N. Chalaya, and L. G. Chichenkova, *Khim. Geterotsikl. Soedin.*, 79 (1971).

^{105a} V. G. Kharchenko, S. N. Chalaya, and L. G. Chichenkova, *Khim. Geterotsikl. Soedin.*, 762 (1981).

tained after norbornadiene ozonolysis, gave only 1 to 6% of 3,5-diformyl-4*H*-thiopyran (**38b**).⁸⁵



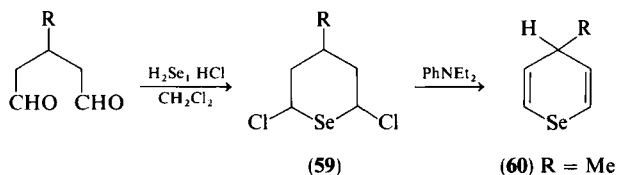
An exceptional cyclization was observed in the case of 2,3,4-triphenyl-1,5-diketone **57b**, giving 65% of 2*H*-thiopyran **56** in contrast to the expected behavior of the 3-methyl analog **57a**, which afforded 72% of 4*H*-thiopyran **58**.^{105a} The origin of **57** might be due to isomerization of a primary product.



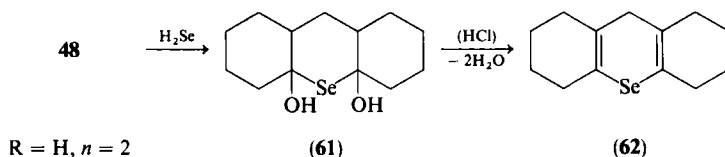
In special cases aromatizations of thiopyrans to thiopyrylium salts were observed when P_4S_{10} was used.¹⁰⁵ A report⁶ of the isolation of 2-methyl-4*H*-thiopyran (**3**) after heating disodium 3-methylglutarate with P_xS_y at 180 to 250°C should be checked by making a comparison of the reaction product with an authentic sample of **3** prepared by another procedure.⁷

C. SELENOPYRANS FROM 1,5-DICARBONYL COMPOUNDS

The cyclization of glutaric dialdehyde or its 3-methyl homolog with hydrogen selenide in the presence of HCl was found to be useful for the generation of simple 4*H*-selenopyrans **8** and **60**.^{7,90}



Bicyclic diketone **48** ($R = H$, $n = 2$) was recently cyclized to 65% of dihydroxy derivative **61**, which yielded 84% of **62** on treatment with catalytic traces of HCl.¹⁰⁶

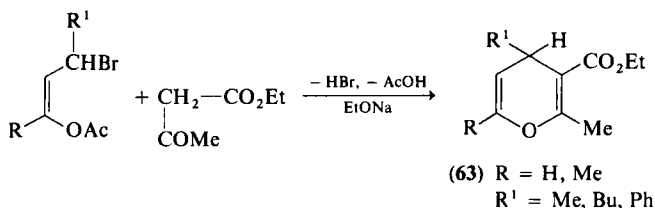


D. PYRANS FROM 1,3-DICARBONYL AND RELATED C-ACIDS

Two typical versions of the synthesis exist: two-component and three-component procedures. In many cases, 1,5-dicarbonyl intermediates may be formed (see Section III,A) but when not isolated they are transformed to pyran products.

The first and more frequently used approach consists of the cyclocondensation of one molecule of a β -diketone, a β -keto ester, or a malonic acid derivative with another molecule of an unsaturated component. It rarely gives a 2*H*-pyran but often yields a 4*H*-pyran.

In some cases halogen derivatives may serve as the second unsaturated component. Thus bromoenolacetates with ethyl acetoacetate were converted to 4*H*-pyrans **63** in 52 to 69% yields.¹⁰⁷



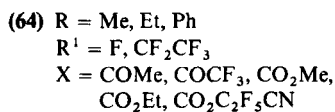
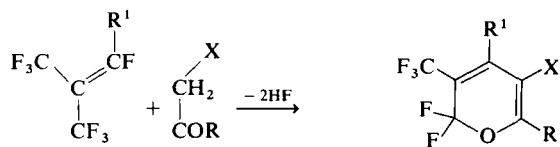
On the other hand, variable yields of fluorinated 2-alkoxy-2*H*-pyrans **64** were found^{108,109} in mixtures formed in the reaction of perfluoroalkenes with dialkyl malonates.

¹⁰⁶ A. F. Blinokhvatov, O. V. Markovceva, I. A. Shlaider, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, 640 (1981).

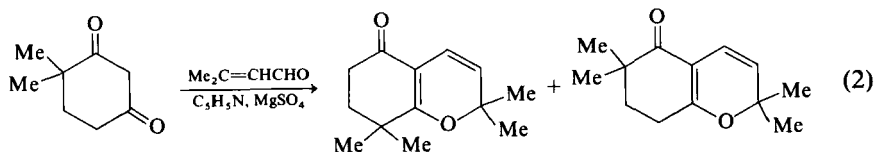
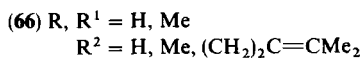
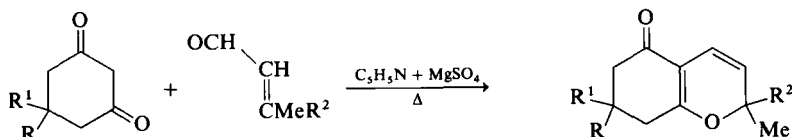
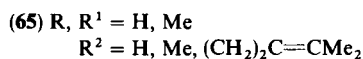
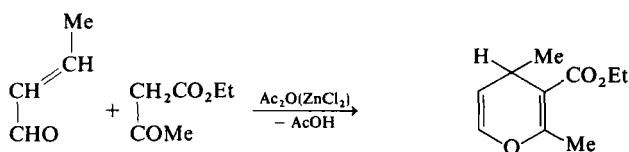
¹⁰⁷ I. V. Machinskaya and V. A. Barkhash, *Zh. Obshch. Khim.* **28**, 2873 (1958) [*CA* **53**, 9202 (1959)].

¹⁰⁸ L. A. Rozov, N. S. Mirzabekyants, Yu. F. Zeifman, Yu. A. Cheburkov, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1355 (1974).

¹⁰⁹ T. Kitazume, K. Chino, and N. Ishikawa, *J. Fluorine Chem.* **18**, 213 (1981).

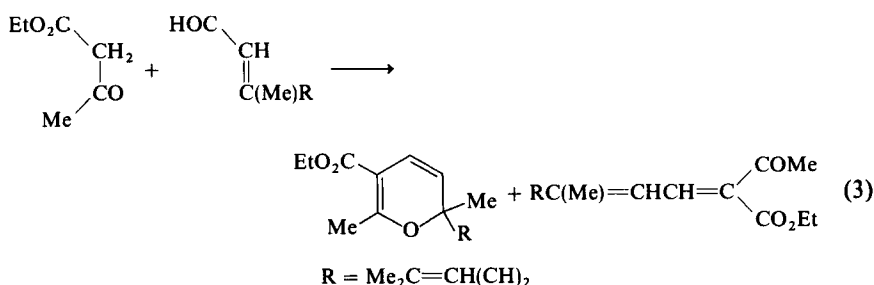


When the second component is an α,β -unsaturated aldehyde, somewhat different results are reported. Thus crotonaldehyde reacts with ethyl acetoacetate to give 4*H*-pyran **65**,⁸⁶ whereas 3-substituted crotonaldehydes with 1,3-cyclohexadiones afford 67 to 80% of the corresponding 2*H*-pyrans **66**.¹¹⁰ The reaction with 1,3-pentanedione proceeded also in the second way,¹¹⁰ but the former cyclization with ethyl benzoylacetate gave no pyran.⁸⁶ If asymmetrically substituted 1,3-cyclohexadienone components are used, the formation of mixtures of isomeric 2*H*-pyrans may be expected, as shown in Eq. (2).¹¹⁰

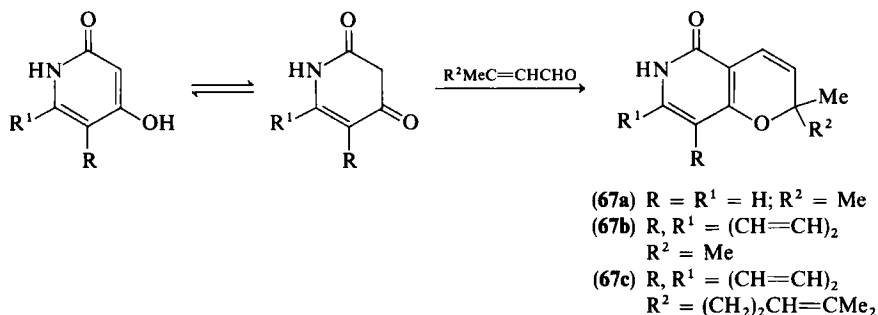


¹¹⁰ A. deGroot and B. J. M. Jansen, *Tetrahedron Lett.*, 3407 (1975).

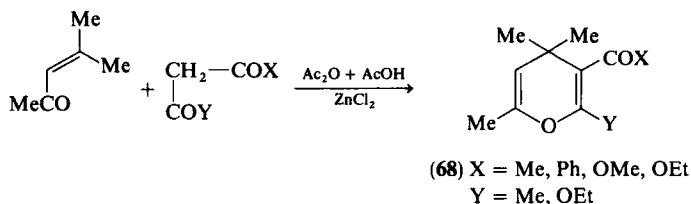
Citral exhibits similar behavior toward ethyl acetoacetate under the conditions of phase transfer catalysis with sodium carbonate and in the presence of $\text{PhCH}_2\text{NEt}_3^+\text{Cl}^-$ (Eq. 3).¹¹¹



The cyclization was further extended by the use of 4-hydroxy-2-quinolone and 4-hydroxy-2-pyridone, which yielded 85 to 89% of condensed 2H-pyrans **67a-c**.¹¹⁰



In an acidic medium several α, β -unsaturated ketones are converted to 4H-pyrans as demonstrated by the formation of **68**⁸⁶ (10 to 25%), **69**,^{112,113} and **70**^{114,115} (61 to 90%).



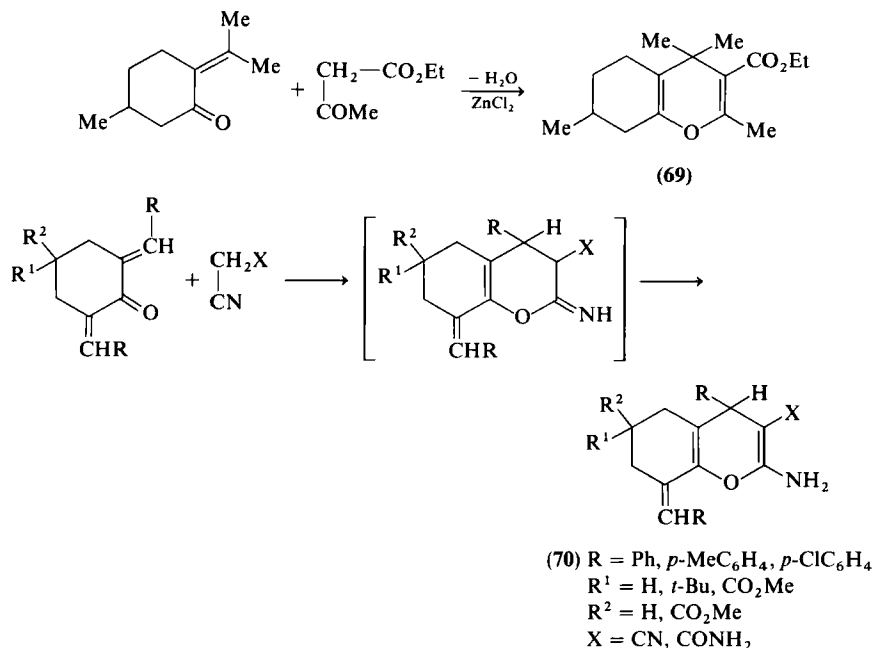
¹¹¹ G. V. Kryshyal, V. V. Kulganek, V. F. Kucherov, and L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2808 (1978) [*CA* **90**, 120973 (1979)].

¹¹² H. S. Hauer, *Diss. Abstr. Int. B* **30**, 1591 (1969).

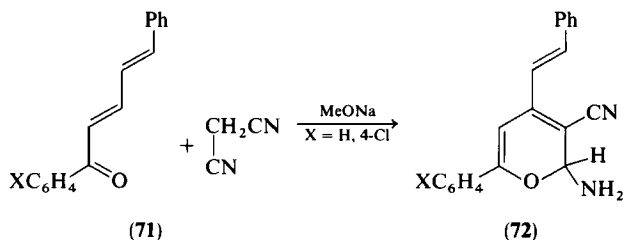
¹¹³ J. Wolinsky and H. S. Hauer, *J. Org. Chem.* **34**, 380 (1969).

¹¹⁴ H. H. Otto, *Arch. Pharm. (Weinheim, Ger.)* **307**, 367 (1974).

¹¹⁵ H. H. Otto, *Monatsh. Chem.* **109**, 681 (1978).



Unexpectedly, 2*H*-pyran structure **72** is reported for products prepared by adding dienones **71** to malonodinitrile.¹¹⁶



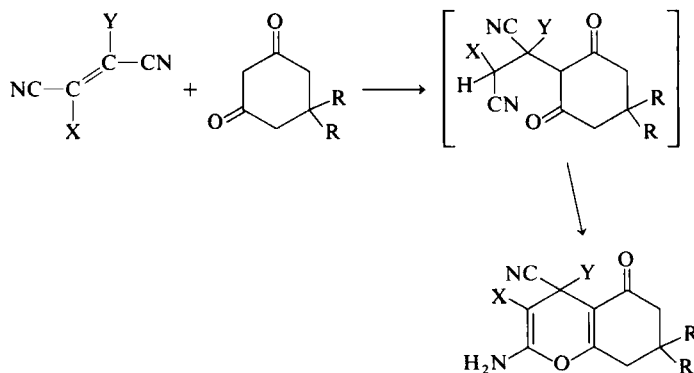
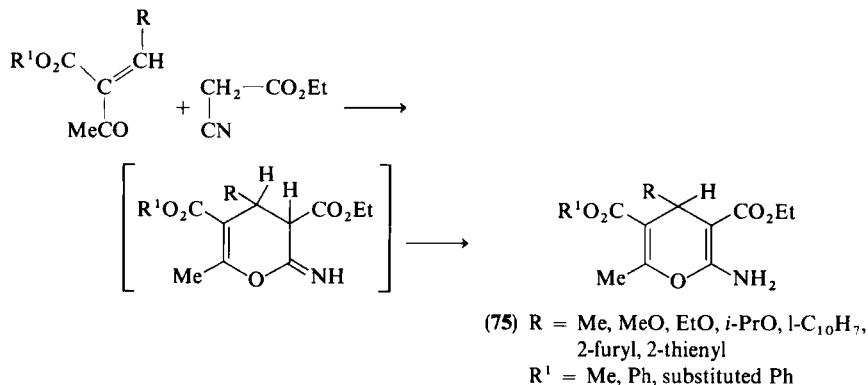
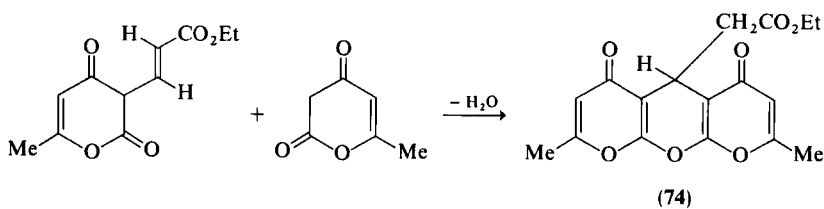
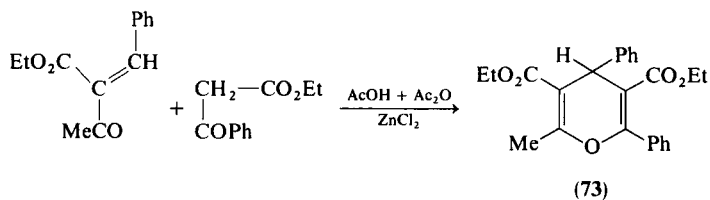
The formation of a 4*H*-pyrans appears to be less difficult when the components contain additional electron-withdrawing substituents, as illustrated by the following cyclizations to **73**⁸⁶ (yield 37%), **74**,¹¹⁷ **75**,¹¹⁸ **76a**,³⁶ and **76b**.¹¹⁹

¹¹⁶ A. Sammour, A. Raouf, M. Elkasaby, and M. A. Hassan, *Acta Chim. Acad. Sci. Hung.* **83**, 209 (1974).

¹¹⁷ S. F. Tan and T. H. Tjia, *J.C.S. Perkin I*, 2405 (1975).

¹¹⁸ H. Meyer, F. Bossert, W. Vater, and K. Stoepel, *Ger. Offen.* 2,235,406 (1974) [*CA* **80**, 120765 (1974)].

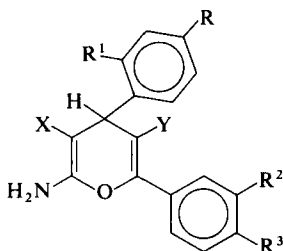
¹¹⁹ Yu. A. Sharanin, *Zh. Org. Khim.* **16**, 2188 (1980) [*CA* **94**, 156691 (1981)].



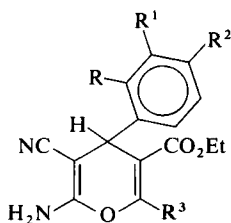
(76a) R = H, Me; Y = X = CN, CO₂Et

(76b) R = Me; X = CN; Y = 2-MeC₆H₄, 4-FC₆H₄, 2-ClC₆H₄, 4-ClC₆H₄, 2-furyl, 5-bromo-2,5-dihydro-2-furyl

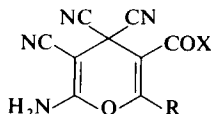
A large number of very stable 4*H*-pyran derivatives **77**^{41,120–121a} (yields 19 to 96%), **78**^{122,123} (yields 37 to 93%), **11**, **12**, and **79**^{35,36} were synthesized analogously.



(77) R = H, MeO, HO, Me, NO₂
 R¹ = H, MeO, Cl, NO₂
 R² = H, NO₂
 R³ = H, MeO, Me, Cl
 X = CN, CO₂Et
 Y = CN, COMe



(78) R = H, Cl, Me, MeO, NO₂
 R¹ = H, NO₂
 R² = H, F, Br, MeO, Me, *i*-Pr, NO₂
 R³ = Me, Ph, *p*-NO₂C₆H₄



(79) R = Me, Ph, *p*-NO₂C₆H₄
 X = Me, Ph, EtO

The primary adduct **81** prepared from 1,2-dicyanofumarate and 1,3-pentanedione undergoes a complex substitution with dimedone or 1,3-indanedione, leading to 4*H*-pyrans **82** and **83** (Scheme 2).³⁶

Alternative mechanisms for the additions of electrophilic olefins like TCE to 1,3-dicarbonyl C-acids have been discussed in detail.^{36,124}

2*H*-Pyran derivative **84** was synthesized from 1-chloro-2-benzoyl ethene and the thallium(I) salt of benzoylacetonitrile as shown in Eq. (4).¹²⁵

¹²⁰ M. Quintero, C. Seoane, and J. L. Soto, *An. Quim.* **74**, 678 (1978).

¹²¹ M. Quintero, C. Seoane, and J. L. Soto, *J. Heterocycl. Chem.* **15**, 57 (1978).

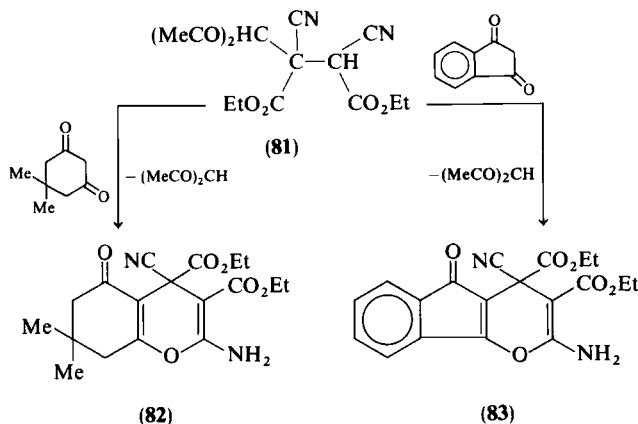
^{121a} M. A. E. Khalifa, G. H. Tammam, and E. M. Zayed, *Curr. Sci.* **50**, 441 (1981) [CA **95**, 150337 (1981)].

¹²² Yu. T. Abramenko, N. A. Borshchev, N. B. Vsevolozhskaya, A. V. Pashchenko, V. K. Promonenkov, and Yu. A. Sharanin, *Nov. Khim. Sredstva Zashch. Rast.*, 7 (1979) [CA **92**, 94181 (1980)].

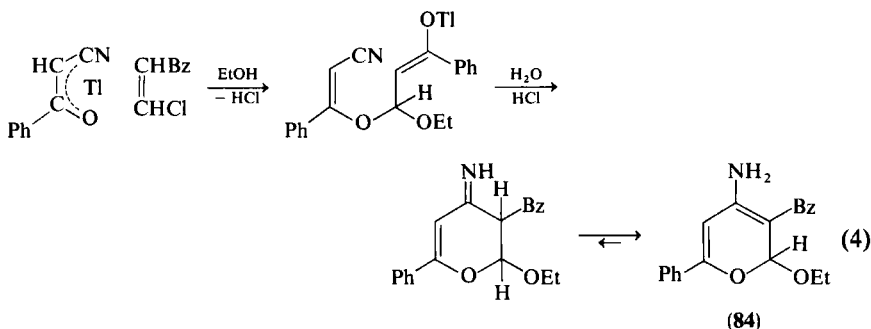
¹²³ M. Quintero, C. Seoane, and J. L. Soto, *Rev. Roum. Chim.* **24**, 859 (1979).

¹²⁴ J. W. Ducker and M. J. Gunter, *Aust. J. Chem.* **26**, 155 (1973).

¹²⁵ R. A. Abramovitch and I. Shinkai, *Pol. J. Chem.* **53**, 177 (1979).



SCHEME 2

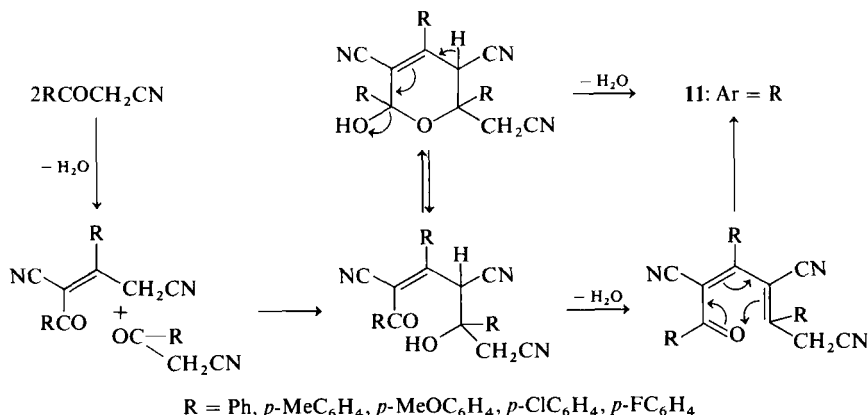


The second three-component pyran synthesis may involve the following combinations of precursors: three identical molecules, two identical and one different molecule, and three different molecules. Only the first two combinations have been described as yet.

The exceptional condensation of three identical molecules to a pyran was achieved in the case of aroyl acetonitriles RCOCH_2CN .^{35,126} It proceeds on melting, or more effectively by heating the starting compounds **84** in xylene in the presence of acetic acid and ammonium acetate. This "one-pot" procedure, leading to very stable 2H-pyrans **11**, involves the transformations shown in Scheme 3.¹²⁶

The more usual cyclocondensations of two identical molecules of 1,3-dicarbonyl or other C-acidic components with a third different oxo compound (mostly an aldehyde) afford exclusively 4H-pyrans and resemble the well-known Hantzsch synthesis of 1,4-dihydropyridines. It usually proceeds

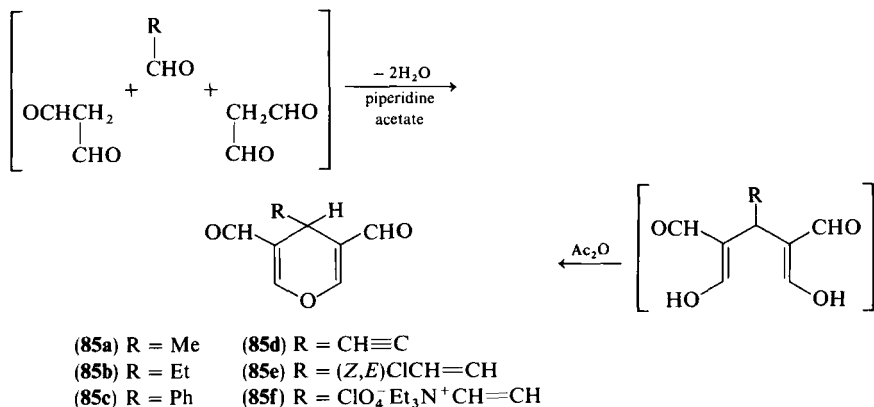
¹²⁶ J. Kuthan, J. Paleček, and J. Valířrach, *Collect. Czech. Chem. Commun.* **46**, 748 (1981).



SCHEME 3

on heating the reactants in acetic anhydride and is occasionally catalyzed with piperidine acetate or with ZnCl₂.

The simplest 1,3-dicarbonyl precursor for the synthesis of 4*H*-pyrans is malonic dialdehyde. Because of its instability¹²⁸ it must be generated *in situ* by hydration of propargyl aldehyde^{62,127} or 3-chloroacrolein,^{129,130} or by hydrolysis of 3-ethoxy-1,1,3-triethoxypropane.¹²⁷ It underwent^{62,127,131} cyclization with a simple aldehyde, giving 3,5-diformyl-4*H*-pyrans **85a-d** (40 to 90%). Lower yields were achieved in the preparation of **85e,f**.



¹²⁷ E. Winterfeldt, *Chem. Ber.* **97**, 1959 (1964).

¹²⁸ F. Wille and W. Schwab, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **32**, 733 (1877).

¹²⁹ A. P. Arendaruk, T. M. Goldzhello, V. N. Melyantseva, T. V. Protopopova, and A. P. Skoldinov, *Khim.-Farm. Zh.* **7**, 6 (1973) [*CA* **80**, 14505 (1974)].

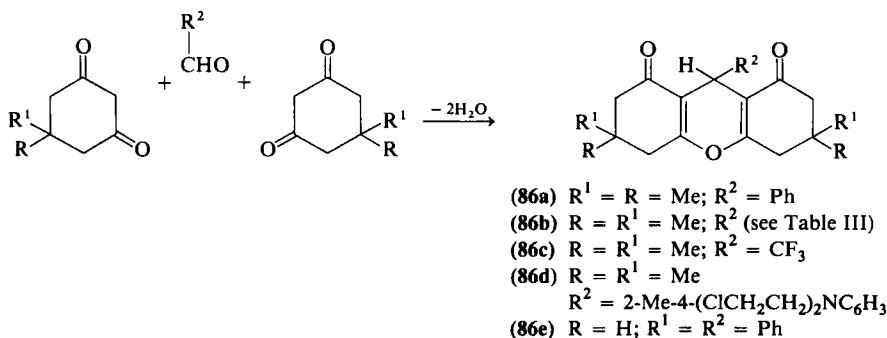
¹³⁰ A. P. Arendaruk, R. Ya. Popova, T. V. Protopopova, and A. P. Skoldinov, *Zh. Org. Khim.* **9**, 2621 (1973) [*CA* **80**, 59374 (1974)].

¹³¹ F. Wille, L. Saffer, and W. Weisskopf, *Justus Liebigs Ann. Chem.* **568**, 34 (1950).

TABLE III
MELTING POINTS OF 4*H*-PYRANS **86b** USED FOR IDENTIFICATION
OF ALDEHYDES ⁶³

Aldehyde	Mp (°C)	Aldehyde	Mp (°C)
AcH	176-177	<i>m</i> -O ₂ NC ₆ H ₄ CHO	222
CHOCHO	170	<i>m</i> -MeC ₆ H ₄ CHO	205
HCOCO ₂ H	245	PhCH ₂ CHO	125-126
CH ₂ =CHCHO	162	<i>p</i> -MeOC ₆ H ₄ CHO	241-243
EtCHO	141.5-143	<i>o</i> -MeOC ₆ H ₄ CHO	190-191
PrCHO	135-136	Piperonal	218-220
<i>i</i> -PrCHO	154-154.5	2,3-HO(MeO)C ₆ H ₄ CHO	226-228
<i>i</i> -BuCHO	172-173	2,3-(MeO) ₂ C ₆ H ₃ CHO	168-169
C ₆ H ₁₃ CHO	110.5-112	3,4-(MeO) ₂ C ₆ H ₃ CHO	184-185.5
Citronellal	170	<i>p</i> -Me ₂ NC ₆ H ₄ CHO	220-222
BzH	204,202 ⁶⁷	Acetylvaniline	148
<i>p</i> -HOC ₆ H ₄ CHO	246	Cuminaldehyde	172-173
<i>o</i> -HOC ₆ H ₄ CHO	209-210 ⁶⁷		

Cyclizations involving cyclic 1,3-diones are very effective. Thus 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and 5-phenyl-1,3-cyclohexanedione react with aldehydes R²CHO to give condensed 4*H*-pyrans **86a**,^{2,132} **86b**,^{63,133} **86d**,⁶⁵ and **86e**.²



Because cyclizations with aldehydes catalyzed by traces of piperidine provide crystalline products **86b** having well-defined melting points, the procedure has been used for identification (Table III).⁶³

The geminal disubstituted precursors CF₃CH(OH)₂ and PhCH(NHCOR)₂ were applied in place of trifluoroacetaldehyde¹³⁴ and benzaldehyde.¹³² The

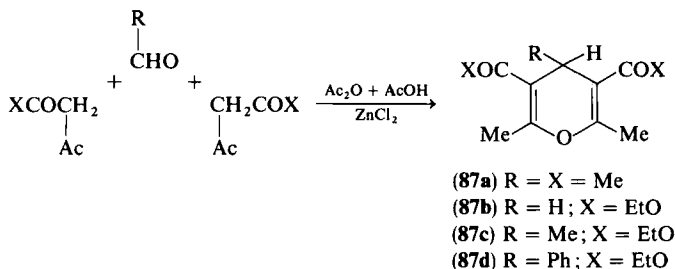
¹³² G. Swoboda and P. Schuster, *Monatsh. Chem.* **95**, 398 (1964).

¹³³ B. W. Benson, E. S. Olsen, and L. A. Smeltz, *J. Chem. Educ.* **47**, 220 (1970).

¹³⁴ H. Gourlaoven and P. Pastour, *C.R. Acad. Sci.* **256**, 3319 (1963).

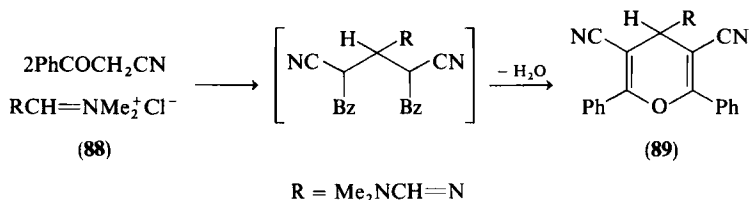
cyclocondensation to **86** was also accomplished by heating the reactants in toluene in the presence of *p*-toluenesulfonic acid.⁶⁵

The "oxygen" Hantzsch-like synthesis involving acyclic β -dicarbonyl compounds requires ZnCl_2 catalysis and yields 30 to 50% of 4*H*-pyrans **87a-d**, which exhibit somewhat lower stabilities in comparison to **86**.⁸⁶

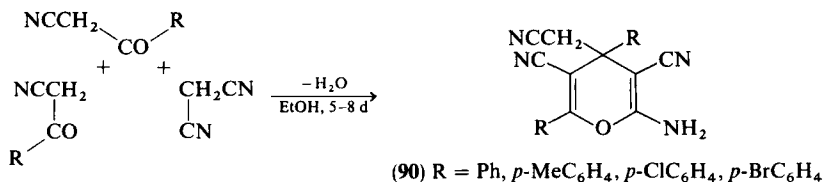


The 4-(1,2-dihydroxyethyl) derivative of **36** was prepared (50%) by an analogous cyclocondensation of 4-hydroxycoumarin with glyceraldehyde in dioxane.¹³⁵

Dimethyliminium salt $\text{Me}_2\text{NCH}=\text{NCH}=\text{NMe}_2^+\text{Cl}^-$ (**88**), generated from DMF and cyanuric chloride, reacts with PhCOCH_2CN to give stable 4*H*-pyran **89**.¹³⁶



Two molecules of aromatic β -ketonitriles RCOCH_2CN undergo a thermal cyclocondensation with one molecule of malonitrile to give 2-amino-3,5-dicyano-4*H*-pyrans (**90**, 12 to 52%).¹³⁷



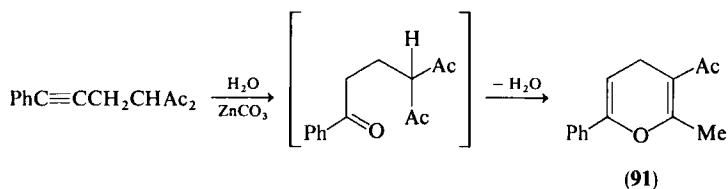
¹³⁵ M. Eckstein, and H. Pazdro, *Rocz. Chem.* **38**, 1115 (1964).

¹³⁶ S. Morimura, *Heterocycles* **14**, 1449 (1980).

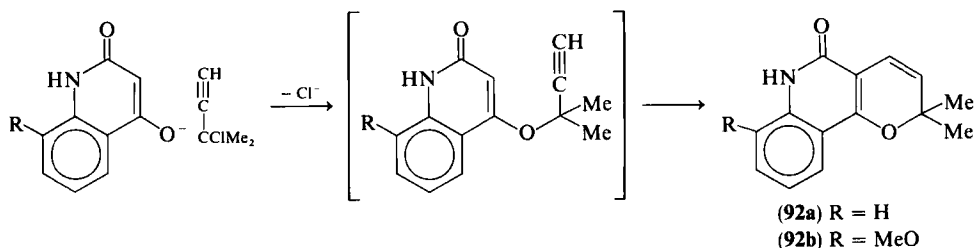
¹³⁷ J. L. Soto, C. Sedane, J. A. Valdes, N. Martin, and M. Quintero, *An. Quim.* **75**, 152 (1979).

E. PYRANS FROM ACETYLENES

Acetylenic compounds may in some cases be suitable sources of 1,3-dioxo precursors as shown for propynal in the synthesis of **85a-d**.^{62,127-131} Similarly, the preparation of probable 4*H*-pyran derivative **91** (61.7%) may be explained by a hydration catalyzed with Zn^{2+} ions, which leads to a 1,5-dicarbonyl intermediate.¹³⁸



The syntheses of findersine (**92a**) and its methoxy derivative **92b** (28 and 35%, respectively) starting from thallous salts of corresponding 2,4-dihydroxyquinolines and 3-chloro-3-methyl-1-propyne, on the other hand, did not apparently involve a hydration step.



All other cases of the pyran syntheses so far described involve one molecule of an ynamine as the acetylenic reactant. Simple $[4\pi + 2\pi]$ cycloaddition involving an ynamine and an α,β -unsaturated aldehyde or ketone constitutes a general approach to N,N-disubstituted 6-amino-4*H*-pyrans **93**; the stability and hence the yields depend on substituents R to R⁵ (Table IV).¹³⁹⁻¹⁴³

¹³⁸ K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm. (Weinheim, Ger.)* **295**, 627 (1962).

¹³⁹ J. Ficini and A. Krief, *Tetrahedron Lett.*, 1427 (1969).

¹⁴⁰ J. Ficini, J. Besseyre, J. D'Angelo, and C. Barbara, *C.R. Acad. Sci., Ser. C* **271**, 468 (1970).

¹⁴¹ L. L. Shchukovskaya, L. D. Budakova, and R. I. Palchik, *Zh. Obshch. Khim.* **43**, 1989 (1973) [*CA* **80**, 15001 (1974)].

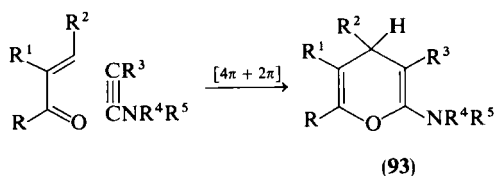
¹⁴² P. L. Myers and J. W. Lewis, *J. Heterocycl. Chem.* **10**, 165 (1973).

¹⁴³ J. Ficini, J. Besseyre, and A. Krief, *Bull. Soc. Chim. Fr.*, 987 (1976).

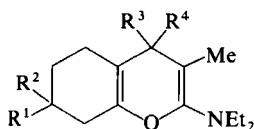
TABLE IV
SOME 4*H*-PYRANS (93) PREPARED FROM YNAMINES

R	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%)	References
H	H	H	Me	Et	Et	22	139, 143
H	H	H	Ph	Et	Et	24	139, 143
H	H	Ph	Me	Et	Et	10	139
H	Ph	H	Me	Et	Et	10	143
Me	H	H	Me	Et	Et	50	139, 143
Me	H	H	Ph	Et	Et	40; 41	139, 143
Me	H	H	Me	(CH ₂) ₂ O(CH ₂) ₂	Et	40	140, 143
Me	H	H	Me ₃ Si	Et	Et	20; 65	141, 143
Ph	H	Ph	Me	Et	Et	— ^a	142
Ph	Ph	Ph	Me	Et	Et	32	142
PhCH=CH	H	Ph	Me	Et	Et	— ^a	142

^a Not reported.

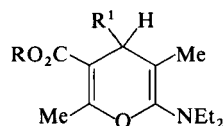


Condensed 2-diethylamino-4*H*-pyrans **94a**¹³⁹ and **94b**,¹⁴² obtained in 35 and 32% yields, respectively, were prepared using cyclic ketones as one component. Pharmaceutically interesting 6-diethylamino 3-esters **95** were prepared.¹¹⁸



(94a) R = R¹ = H; R² = R³ = R⁴ = Me

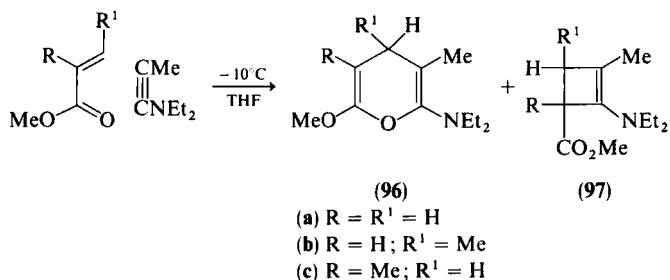
(94b) R, R¹ = PhCH; R² = R³ = H; R⁴ = Ph



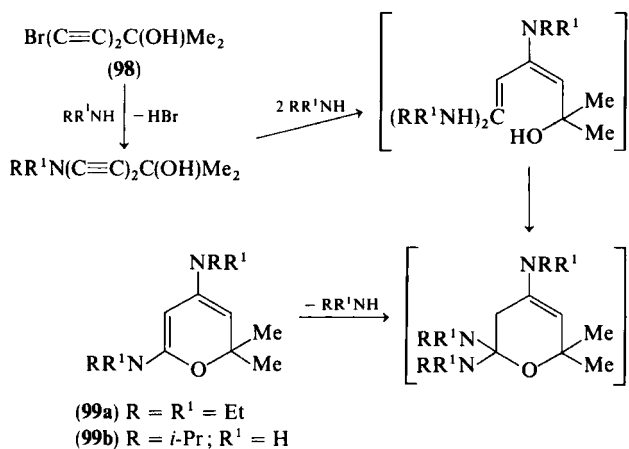
(95) R = Me, MeO, EtO, *i*-PrO; R¹ = Me, Ph, substituted Ph, 1-C₁₀H₇, 2-furyl, 2-thienyl

The extension of the method to methyl esters of simple α,β -unsaturated carboxylic acids leads to mixtures of $[4\pi + 2\pi]$ and $[2\pi + 2\pi]$ cycloadducts **96a-c** and **97a-c**.¹⁴⁴

¹⁴⁴ J. Ficini and A. Krief, *Tetrahedron Lett.*, 885 (1970).



A remarkable synthesis of 2*H*-pyran derivatives **99** was discovered in the reaction of diacetylene precursor **98** with amines RR^1NH .¹⁴⁵ The probable reaction path is shown in Scheme 4.



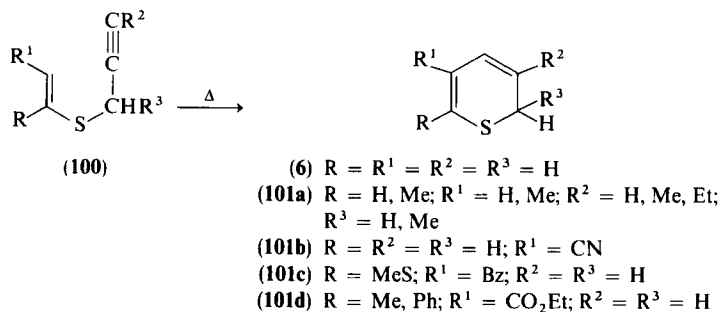
SCHEME 4

F. THIOPYRANS FROM ACETYLENES

The first approach to 2*H*-thiopyrans from acetylenes resembles the synthesis of oxa analogs **92a,b**. In contrast to the latter, intermediates like **100** have been directly used as starting compounds.

The same principle explored for the synthesis of 3,5-disubstituted 2*H*-pyran *S,S*-dioxides will be shown in Section V,G,3 (see Scheme 28).

¹⁴⁵ B. P. Gusev and V. F. Kucherov, *Dokl. Vses. Konf. Khim. Atsetilena*, 4th, 1972 Vol. 2, 456 [CA **82**, 170581 (1975)].



The cycloaddition was accomplished by heating **100** in HMPTA^{21,23,24} or in silicon oil,¹⁴⁶ or by treating with potassium *tert*-butoxide in DMF¹⁴⁷ as well as in triethylamine and/or pyridine.^{23,148} The cyclization **100** → **101** was found occasionally accompanied by the formation of isomeric thiophenes.²¹

The preparation of unsubstituted 2*H*-thiopyran (**6**, up to 82%) from 3-propynyl vinyl sulfide seems to be the simplest example.^{21,23} Similarly, homologs **101a**,²¹ cyanides **101b**,¹⁴⁶ ketones **101c**,¹⁴⁷ and ethyl esters **101d**¹⁴⁸ were prepared in satisfactory yields. The same approach was subsequently explored for the synthesis of **15** and similar condensed systems^{21,43,137} (see also *S,S*-dioxides in Section V,G,3).

The mechanism of the cycloaddition process was partly clarified on the basis of experiments with acetylenic dithio derivatives **102**, which were found to be thermally transformable to allenic isomers **103**.¹⁴⁹ The latter gave expected 2*H*-thiopyrans **104** in 41 to 78% yields under triethylamine catalysis, whereas isomeric thiophenes **105** were formed in the presence of protic acids (Scheme 5). The activation energies for some of the processes were also measured.¹⁴⁹

The key role of thio-Claisen rearrangements (of **102** → **103**) as well as the formation of thiophene byproducts were proved independently¹⁴⁸ during attempts to prepare **101d** esters.

Cycloadditions of dimethyl acetylenedicarboxylate (DMAD) to some thiacylmethylenethiazolines **107** were discovered to be the second approach to thiopyrans from acetylenic precursors.¹⁵⁰ The reaction was observed to

¹⁴⁶ R. A. Van der Welle and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **92**, 667 (1973).

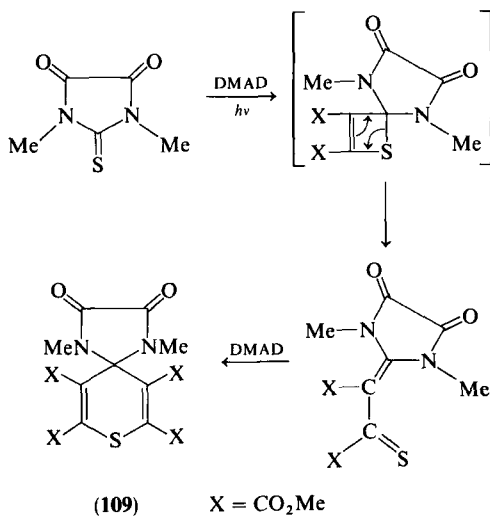
¹⁴⁷ F. C. V. Larison and S. O. Lawesson, *Tetrahedron* **28**, 5341 (1972).

¹⁴⁸ L. Dalgaard and S. O. Lawesson, *Tetrahedron* **28**, 2051 (1972).

¹⁴⁹ P. J. W. Schuijl, H. J. T. Bos, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **88**, 597 (1969).

¹⁵⁰ M. S. Chauhan, M. E. Hassan, and D. M. McKinnon, *Can. J. Chem.* **52**, 1738 (1974).

from reactions in benzene.^{150,151} On the other hand, 2*H*-thiopyrans **106b,c,f** or mixtures of both cycloadducts **106d,e** and **108d,e** were obtained from reactions in dioxane and when various ratios of components were used.¹⁵¹ Another photochemically induced cycloaddition reaction of DMAD, shown in Scheme 6, led to 4*H*-thiopyran derivative **109** (63%).¹⁵²



SCHEME 6

G. THIOPYRANS FROM ENAMINES

Diels-Alder cycloaddition reactions of enaminothiones¹⁵³⁻¹⁵⁵ or enamino thioesters^{154,156,157} as nucleophilic dienes with electrophilic dienophiles $R^4CH = CHX$ lead to appropriate 4-amino-2,3-dihydro-2*H*-thiopyran intermediates **110**, which easily eliminate amines R^2R^3NH to give the corresponding 2*H*-thiopyrans **111**.

¹⁵² H. Gotthardt and S. Nieberl, *Tetrahedron Lett.*, 3563 (1976).

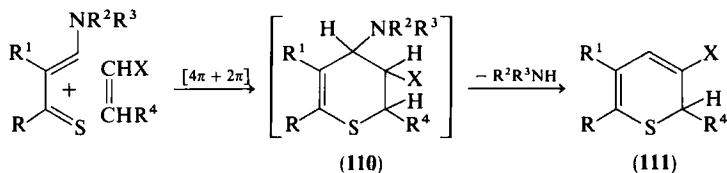
¹⁵³ J. P. Pradere and H. Quiniou, *C.R. Acad. Sci., Ser. C* **275**, 677 (1972).

¹⁵⁴ J. P. Pradere and H. Quiniou, *Ann. Chim. (Rome)* **63**, 563 (1973).

¹⁵⁵ J. P. Pradere, Y. T. N'Guessan, H. Quiniou, and F. Tonhard, *Tetrahedron* **31**, 3059 (1975).

¹⁵⁶ J. C. Meslin, J. P. Pradere, and H. Quiniou, *Bull. Soc. Chim. Fr.*, 1195 (1976).

¹⁵⁷ J. P. Pradere, H. Quiniou, C. Rabiller, and G. J. Martin, *Bull. Soc. Chim. Fr.*, 991 (1976).



X = CHO, Ac, CO₂Me, CO₂Et, CONH₂, CONMe₂, CN

R = Me, Ph, *p*-MeOC₆H₄, *p*-BrC₆H₄, MeS

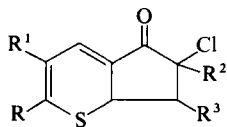
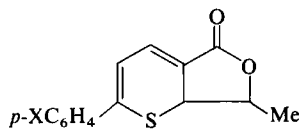
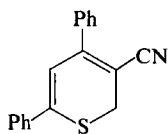
R¹ = H, Ph, Cl

R², R³ = Me, Me; Et, Et; (CH₂)₄; (CH₂)₂O(CH₂)₂

R⁴ = H, Me, Ph, EtO, EtS

Intermediates **110** were isolated and their conformations investigated by ¹H-NMR.¹⁵⁸

Further 2*H*-thiopyrans **112**,¹⁵⁸ **113**,¹⁵⁵ and **114**^{156,157} were prepared in the same way.



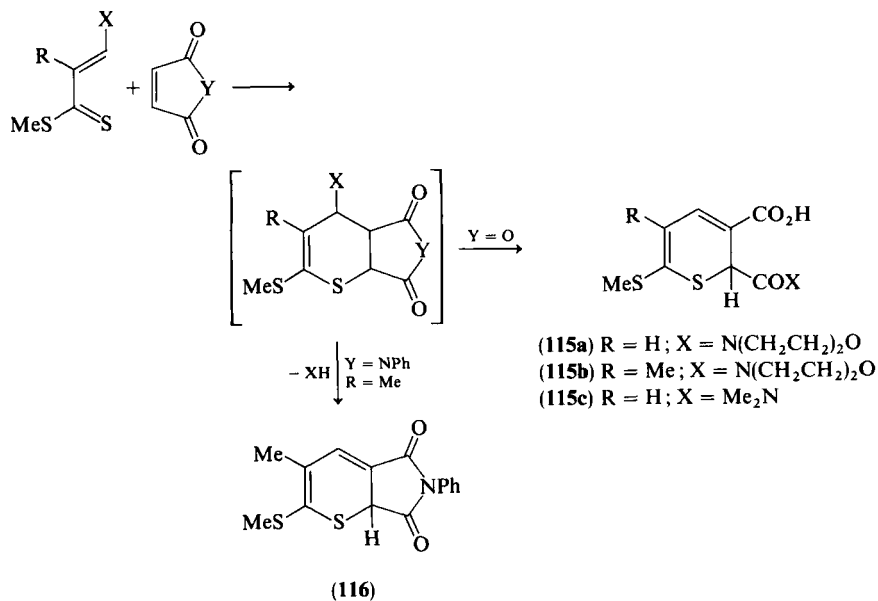
If maleic anhydride is used as the dienophile, aminolysis with XH was observed to accompany the 2*H*-thiopyran ring closure to give 69 to 91% of monocyclic products **115a-c**.⁵³ The use of *N*-phenylmaleimide gave 62% of expected bicyclic system **116**⁵³ (Scheme 7).

Probably a general approach to 2*H*-thiopyran dioxides **118** is the reaction of mesyl chloride with enamino ketone **117** (Scheme 8).¹⁵⁹

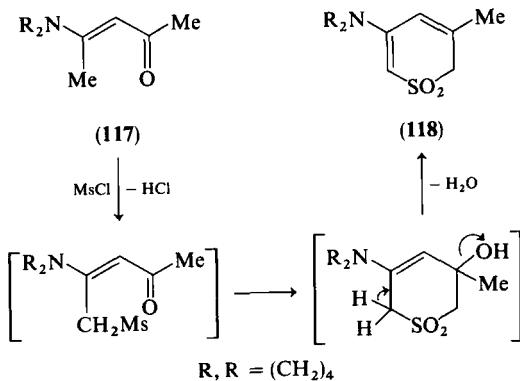
The preparation of pyrans from aminodienones is mentioned in the following section.

¹⁵⁸ J. P. Pradere and G. Hadjukovic, *C.R. Acad. Sci.* **286**, 553 (1978).

¹⁵⁹ M. Yoshimoto, T. Hiraoka, and Y. Kishida, *Chem. Pharm. Bull.* **18**, 2469 (1970).



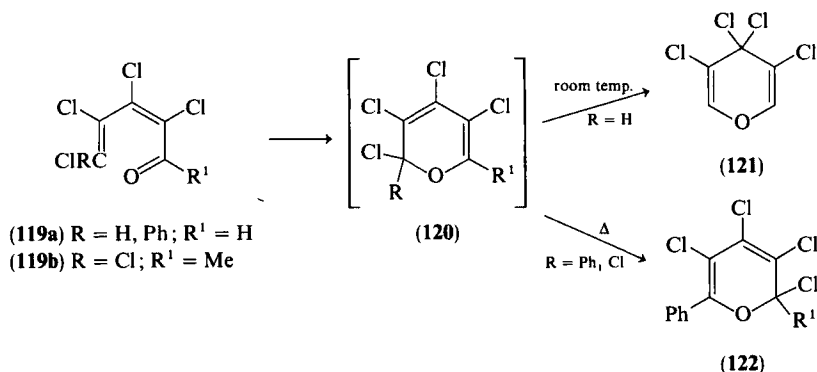
SCHEME 7



SCHEME 8

H. PYRANS FROM DIENALS AND DIENONES

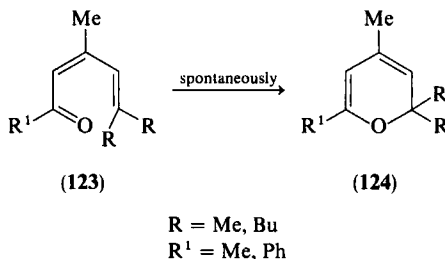
2*H*-Pyrans seem to be valence-bond isomers of the corresponding *cis* dienals or *cis* dienones with which they often form equilibrium mixtures (see Section V,E,1). Hence only such cases will be considered where a pyran is the isolable isomer.



SCHEME 9

The equilibrium mixtures of simple dienals and *2H*-pyrans consist, as a rule, of almost pure acyclic isomers. Exceptionally, some polychlorodienals **119a** or -one **119b** underwent the ring closure to primary *2H*-pyrans **120**, easily isomerizable to thermodynamically more stable secondary *4H*-pyran **121a**¹⁶⁰ or *2H*-pyran **122a**,¹⁶¹ and **122b**¹⁶² (Scheme 9).

Ring closure to *2H*-pyrans is more usual with unsaturated ketones. If suitable *cis* dienones are generated, their isomerization may proceed so rapidly that only the appropriate *2H*-pyrans are identified and/or isolated from the 2,2,4,6-tetrasubstituted species **123** and **124**.¹⁶³⁻¹⁶⁵ Other cases were not recognized.¹⁶⁶



The formation of a *2H*-pyran proceeds exceptionally smoothly if a condensed ring system arises. This is seen in attempts to prepare stereoisomeric β -

¹⁶⁰ A. Roedig, H. A. Renk, M. Schlosser, and Neukam, *Justus Liebigs Ann. Chem.*, 1206 (1974).

¹⁶¹ A. Roedig, H. A. Renk, V. Schaal, and D. Scheutzwow, *Chem. Ber.* **107**, 1136 (1974).

¹⁶² A. Roedig, J. Hilbert, and H. A. Renk, *Justus Liebigs Ann. Chem.*, 2251 (1975).

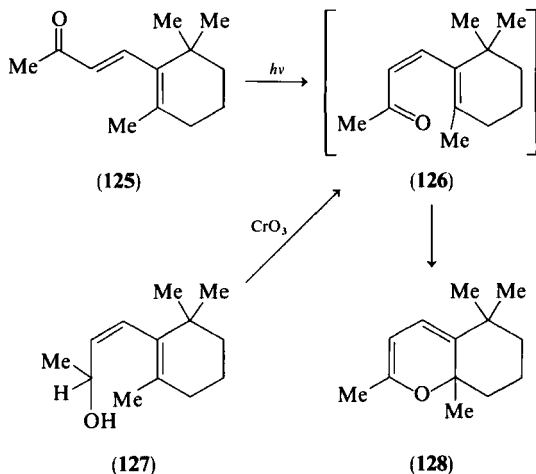
¹⁶³ J. P. Montillier and J. Dreux, *Bull. Soc. Chim. Fr.*, 3638 (1969).

¹⁶⁴ A. F. Kluge and C. P. Lillya, *J. Org. Chem.* **36**, 1977 (1971).

¹⁶⁵ E. N. Marvell, T. Chadwick, G. Caple, T. Gosink, and G. Zimmer, *J. Org. Chem.* **37**, 2992 (1972).

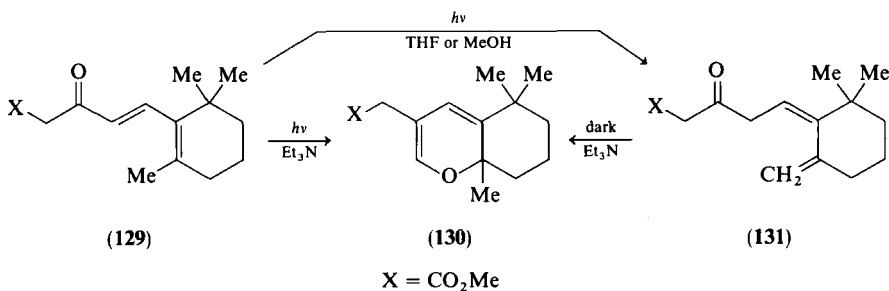
¹⁶⁶ A. Yamamoto and T. Ishimara, Japanese Patent 77/49,443 (1977) [*CA* **88**, 169600 (1978)].

ionone **126**. Although the trans isomer **125** is stable, great effort to isolate the cis form **126** by chemically¹⁶⁷ and photochemically^{165,167-172} induced isomerization of **125** or oxidation¹⁷³ of the corresponding alcohol **127** gives 2*H*-pyran derivative **128** in high yields (Scheme 10).



SCHEME 10

Catalysis by triethylamine in similar processes was recognized in the case of two regioisomeric dienones **129** and **131**, which isomerized to 2*H*-pyran **130**.¹⁷⁴



¹⁶⁷ G. Büchi and N. C. Yang, *J. Am. Chem. Soc.* **79**, 2318 (1957).

¹⁶⁸ G. Büchi and N. C. Yang, *Chem. Ind. (London)*, 357 (1955).

¹⁶⁹ G. Büchi and N. C. Yang, *Helv. Chim. Acta* **38**, 1338 (1955).

¹⁷⁰ P. de Mayo, J. B. Stothers, and R. W. Yip, *Can. J. Chem.* **39**, 2135 (1961).

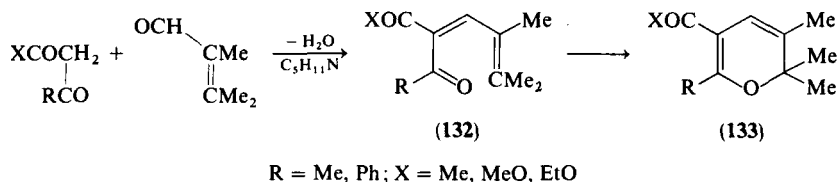
¹⁷¹ S. Kurata, Y. Inoue, and H. Kakisawa, *Tetrahedron Lett.*, 5153 (1973).

¹⁷² S. Kurata, T. Kusumi, Y. Inoue, and H. Kakisawa, *J.C.S. Perkin I*, 532 (1976).

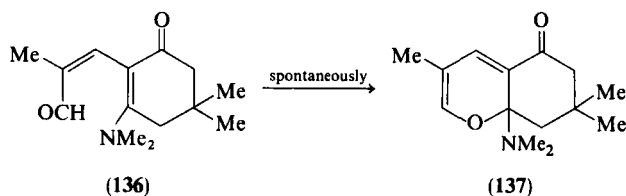
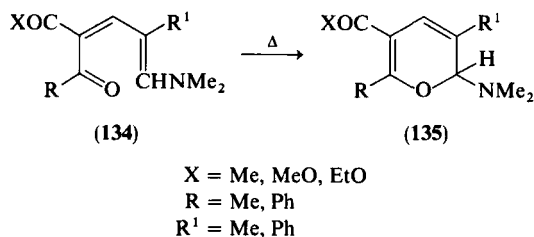
¹⁷³ B. R. von Wartburg and H. R. Wolf, *Helv. Chim. Acta* **57**, 916 (1974).

¹⁷⁴ J. D. White and R. W. Slean, *J. Am. Chem. Soc.* **100**, 6296 (1978).

2*H*-Pyrans **133** were obtained by spontaneous isomerization of dienones **132**, smoothly prepared by the Knoevenagel condensation of 2,3-dimethyl-2-butenal with 1,3-dicarbonyl compounds.^{175,176}



Ring closure of **132** → **133** is facilitated by low temperature¹⁷⁷ and especially by a methyl group at position 3.¹⁷⁵⁻¹⁷⁸ Analogous factors influence the cyclization of several *cis*-dimethylaminodienediones, **134** and **136** affording 2-dimethylamino-2*H*-pyrans **135**^{179,180} and **137**.¹⁷⁹



¹⁷⁵ Zh. A. Krasnaya, E. P. Prokofev, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 816 (1979).

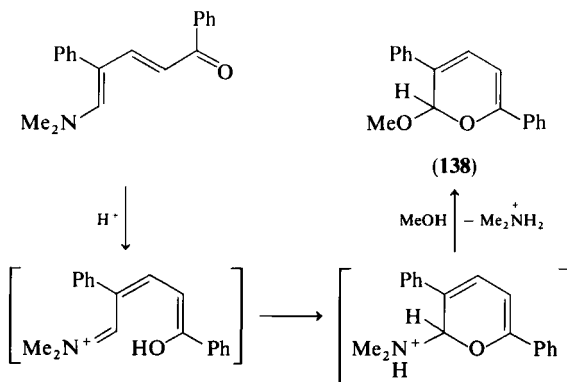
¹⁷⁶ E. P. Prokofev and Zh. A. Krasnaya, *Izv. Akad. Nauk SSSR, Ser. Khim.* **29**, 719 (1980).

¹⁷⁷ Zh. A. Krasnaya, E. P. Prokofev, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2318 (1970).

¹⁷⁸ Zh. A. Krasnaya, E. P. Prokofev, M. Sh. Zaripova, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2356 (1973).

¹⁷⁹ Zh. A. Krasnaya, E. P. Prokofev, I. P. Yakovlev, and E. A. Dubuzh, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2325 (1980).

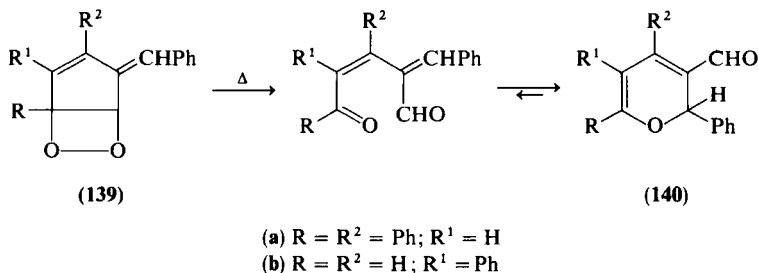
¹⁸⁰ E. P. Prokofev and Zh. A. Krasnaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2284 (1980).



SCHEME 11

A remarkable formation of *2H*-pyran **138** (99%) from *trans*-dimethylaminodienone (Scheme 11) and methanolic hydrochloric acid was evidently associated with *trans* → *cis* isomerization of the precursor.¹⁸¹

A less usual method for the generation of starting dienones is thermal rearrangement of fulvene-1,2-dioxetanes **139a,b**, leading to *2H*-pyrans (**140a,b**).¹⁸²



I. THIOPYRANS FROM DIENALS AND DIENONES

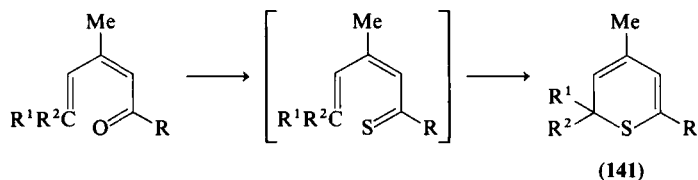
Conjugated dienals react readily with hydrogen sulfide or with P_4S_{10} to give the corresponding *2H*-thiopyrans **141a**¹⁸³ and **141b**.¹⁸⁴ The ring closure to heterocycles **141** may proceed via isomeric thioaldehydes or thioketones.

¹⁸¹ C. Jutz, R. M. Wagner, A. Kraatz, and M. G. Lobering, *Justus Liebigs Ann. Chem.*, 874 (1975).

¹⁸² J. P. Le Roux and C. Goasdoue, *Tetrahedron* **31**, 2761 (1975).

¹⁸³ A. J. Chechak, M. H. Stern, and C. D. Robeson, *J. Org. Chem.* **29**, 187 (1964).

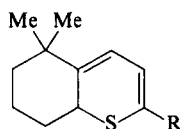
¹⁸⁴ C. Fournier, D. Paquer, and M. Vazeux, *Bull. Soc. Chim. Fr.*, 2753 (1975).



- (a) $R = R^1 = H$; $R^2 = \text{Ph}, \text{PhCH}=\text{CH}$,
2,6,6-trimethyl-1-cyclohexenyl
(b) $R = R^1 = R^2 = \text{Me}$

The cyclization was also successful with natural unsaturated aldehydes such as β -carotene, *cis*-retinal (95%), and *trans*-retinal (50%).^{183,184a} Compounds like **142** are potential intermediates in the syntheses of β -carotene derivatives and polymeric alkenes.^{184,185,186}

Using $\text{H}_2\text{S}-\text{HCl}$ or P_4S_{10} resulted in 50 to 60% yields of 2*H*-thiopyrans **142a,b** from the corresponding dienones.¹⁸⁴ In addition to **142** small amounts of ketolization products were formed.



- (142a) $R = \text{Me}$
(142b) $R = \text{Et}$

J. PYRANS FROM OTHER ACYCLIC PRECURSORS

The Williamson-type cyclization of chlorodienols **143a,b** with sodium was shown to be a useful approach to polychloropyrans **144a**¹⁸⁷ and **144b**.³² In the case of $R = \text{Cl}$, $R^1 = \text{H}$, and $R^2 = \text{Me}$, the initial product **144b** was labile and afforded a thermodynamically more stable isomer (**145**),³² whereas **144c** underwent spontaneous dehydrochlorination.¹⁸⁸

Occasionally pyrans result from an aldolization process. Thus 2,2,4,6-tetramethyl-2*H*-pyran (**124**) is a byproduct in the production of mesityl oxide and diacetone alcohol from acetone.^{189,190} Ketol **146** (readily accessible from

^{184a} A. J. Chechak, C. D. Robeson, and M. H. Stern, British Patent 945,882 (1964) [CA **66**, 2666 (1967)].

¹⁸⁵ A. J. Chechak and C. D. Robeson, U.S. Patent 3,125,571 (1964) [CA **61**, 5702 (1964)].

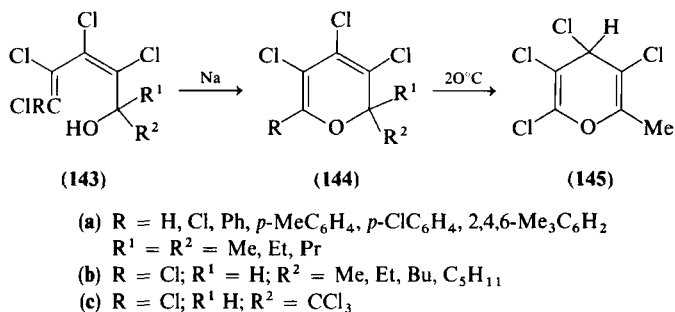
¹⁸⁶ A. J. Chechak and C. D. Robeson, U.S. Patent 3,184,516 (1965) [CA **63**, 5609 (1965)].

¹⁸⁷ A. Roedig and T. Neukam, *Chem. Ber.* **107**, 3463 (1974).

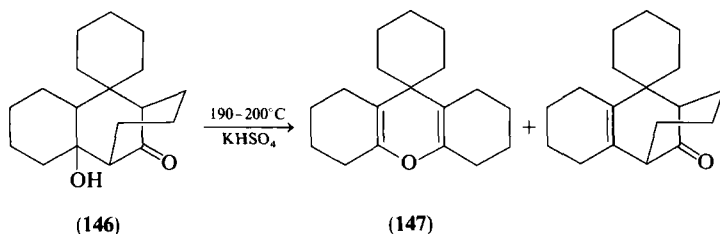
¹⁸⁸ A. Roedig and H. Goepfert, *Chem. Ber.* **113**, 806 (1980).

¹⁸⁹ A. Hinnen and J. Dreux, *Bull. Soc. Chim. Fr.*, 1492 (1964).

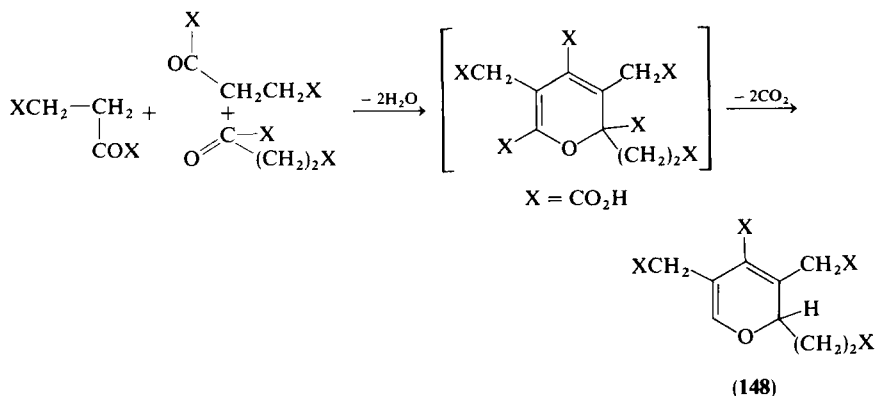
¹⁹⁰ A. Hinnen and J. Dreux, *C.R. Acad. Sci.* **255**, 1747 (1962).



cyclohexanone) with potassium hydrogen sulfate at elevated temperatures gave 4H-pyran **147** together with the expected dehydration product.¹⁹¹



Heating chloroacrolein yields 20% of 6-chloro-2-formyl-4H-pyran.¹⁹² The formation of pyrans by thermal decomposition of ethyl acetoacetate and its homologs on a copper powder catalyst is patented.¹⁹³ Surprisingly, 2H-pyran **148** (20%) was reported when 2-oxoglutaric acid reacted with lead(II) nitrate.¹⁹⁴



¹⁹¹ G. R. Pettit and E. G. Thomas, *Chem. Ind. (London)*, 1758 (1963).

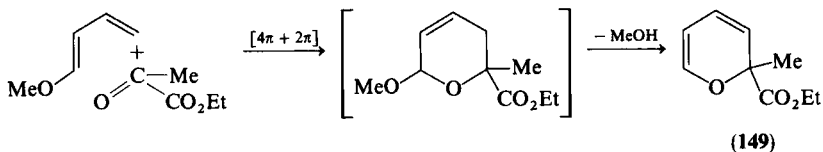
¹⁹² H. R. Guest and H. A. Stansbury, British Patent 778,899 (1957) [CA 52, 1208 (1958)].

¹⁹³ K. Rauscher, H. Opel, and W. Ardelt, *German (East) Patent* 13,889 (1957) [CA 53, 13179 (1959)].

¹⁹⁴ W. Anschütz and S. N. Datta, *Justus Liebigs Ann. Chem.*, 1971 (1975).

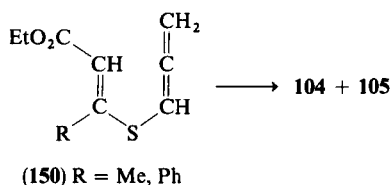
The reaction path at an early stage of the process might be similar to the cyclization of **84**, as in Eq. (4).¹⁹⁴

Diels-Alder cyclization of ethyl pyruvate with 1-methoxy-1,3-butadiene in the presence of AlCl_3 gave a 45% yield of 2*H*-pyran **149**, apparently via a dihydropyran intermediate.¹⁹⁵



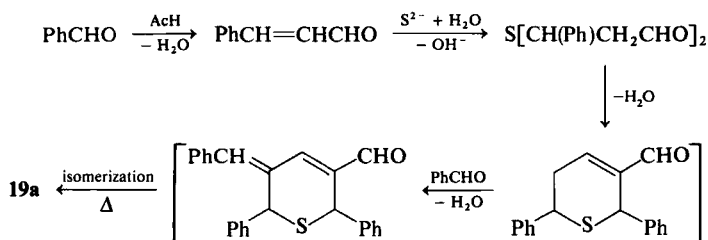
K. THIOPYRANS FROM OTHER ACYCLIC PRECURSORS

Allenic sulfides **150** provide 2*H*-thiopyrans **104** and isomeric thiophenes **105** on heating with quinoline, probably through the path $150 \rightarrow 102 \rightarrow 103 \rightarrow 104 + 105$.¹⁴⁸



2*H*-Thiopyran derivatives may be formed when a sulfide participates in an aldol transformation. An excellent example is the formation of 2*H*-thiopyran-5-carbaldehyde (**19a**) from benzaldehyde and acetaldehyde in the presence of sodium disulfide (Scheme 11A).¹⁹⁶

For the transformation of ketols **50** to 4*H*-thiopyrans **49** with hydrogen sulfide, see Section III,B.



SCHEME 11A

¹⁹⁵ K. Jankowski and R. Luce, *Tetrahedron Lett.*, 2069 (1974).

¹⁹⁶ K. A. Latif, M. A. Razzag, B. K. Adhikari, and M. M. Eunus, *J. Indian Chem. Soc.* **36**, 209 (1959).

IV. Syntheses from Cyclic Precursors

A. PYRANS FROM PYRYLIUM SALTS

In principle, pyrylium salts can be transformed to pyrans by the addition of an appropriate reagent to the 2-, 4-, or 6-position of the heterocycle. Although most transformations seem to be nucleophilic additions (because of the electrophilic character of the pyrylium substrates) some reactions, such as hydrogenation or one-electron reductions, are of a radical nature. Many nucleophilic additions to pyrylium salts proceeding via unstable pyran intermediates seem to be of general synthetic interest, especially in the fields of aromatic and other conjugated systems,^{11,197-200} but are of little interest in pyran chemistry.

The amount of a given isomer in reaction mixtures is affected by substitution patterns of the starting pyrylium ions and by the structure of a reagent, in accordance with quantum chemical interpretations using various LCAO-MO methods.^{201-202a} Almost all additions to 2,6-disubstituted pyrylium ions occur at position 4 to give 4*H*-pyrans. Unsubstituted or 2,4,6-trisubstituted substrates may be attacked, on the other hand, at α or γ positions providing 2*H*- and/or 4*H*-pyrans. Limited information on tetrasubstituted and pentasubstituted pyrylium ions leads to the conclusion that the former afford 4*H*-pyrans, whereas the latter tend to be attacked by nucleophiles only at positions 2 or 6.

A pyran generated under kinetic control may be transformed to a thermodynamically more stable isomer, or be in dynamic equilibrium with starting reactants.

1. Monomeric Pyrans by Reduction

The reduction of pyrylium salts to monomeric 2*H*- or 4*H*-pyrans has been accomplished by complex hydrides, hydrogen-transfer agents, electrochemically, and by catalytic hydrogenation.

¹⁹⁷ W. Schroth and G. Fischer, *Z. Chem.* **4**, 281 (1964).

¹⁹⁸ S. V. Krivun, O. F. Alferova, and S. V. Sayapina, *Usp. Khim.* **43**, 1739 (1964).

¹⁹⁹ T. Sugimoto, *J. Synth. Org. Chem.* **39**, 1 (1981).

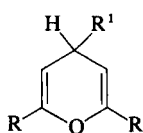
²⁰⁰ S. N. Baranov, A. I. Buryak, and S. V. Krivun, USSR patent 382,617 (1973) [*CA* **79**, 92008 (1973)].

²⁰¹ O. Chalvet, C. Decoret, J. Dreux, A. Saffiedine, and J. Royer, *Bull. Soc. Chim. Fr.*, 716 (1972).

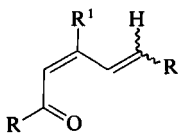
²⁰² M. H. Palmer, R. H. Findlay, W. Moyes, and A. J. Gaskell, *J.C.S. Perkin II*, 841 (1975).

^{202a} A. F. Pronin, V. G. Kharchenko, and A. A. Bagaturyanc, *Khim. Geterotsikl. Soedin.*, 1627 (1976).

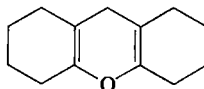
Sodium borohydride reduction of 2,6-disubstituted and 2,4,6-trisubstituted pyrylium salts provide 4*H*-pyrans **151a**²⁰³⁻²⁰⁵ and **151b**.^{203,206,207} Compounds **151b** are formed in mixtures with **152b** as artifacts from unstable 2*H*-isomers of **151b**. The dienone **152c** was prepared in the same way.²⁰⁸ Ratio **151b**/**152b** is sensitive to the size of substituents R and R'.²⁰⁶ Analogous lithium aluminum hydride reduction yielded 95% of **151a** (R = Ph)²⁰⁹ and 92% of **153**.²¹⁰



(151)



(152)



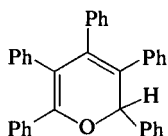
(153)

(a) R = Me, Ph; R' = H

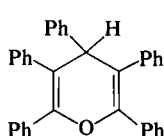
(b) R = Me, Et, *i*-Pr; R' = Me, Et

(c) R = R' = Ph

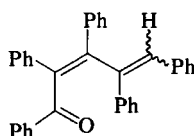
The reduction of pentaphenylpyrylium tetrafluoroborate with lithium borohydride in THF at -70°C gave, however, 60% of 2*H*-pyran **154** together with 10% of the 4*H* isomer and traces of dienone **156**.²¹¹



(154)



(155)



(156)

Similarly, 2,3,4,6-tetramethyl-2*H*-pyran is accessible from the corresponding pyrylium perchlorate.²¹²

Reductions of pyrylium salts with organic hydrogen-transfer agents, interesting as models of biological redox systems, exhibit regioselectivity

²⁰³ A. Saffieddine, J. Royer, and J. Dreux, *Bull. Soc. Chim. Fr.*, 2510 (1972).

²⁰⁴ H. W. Whitlock and N. A. Carlson, *Tetrahedron* **20**, 2101 (1964).

²⁰⁵ H. W. Whitlock and N. A. Carlson, *Tetrahedron* **20**, 2101 (1971).

²⁰⁶ A. T. Balaban, G. Mihai, and C. D. Nenitzescu, *Tetrahedron* **18**, 257 (1962).

²⁰⁷ E. N. Marvell and T. A. Gosink, *J. Org. Chem.* **37**, 3036 (1972).

²⁰⁸ T. A. Gosink, *Diss. Abstr.* **27**, 3852 (1967).

²⁰⁹ E. T. Østensen and M. M. Mishrikey, *Acta Chem. Scand., Ser. B.* **B30**, 635 (1976).

²¹⁰ V. G. Kharchenko, N. M. Yaireva, and N. I. Kozhevnikova, *Zh. Org. Khim.* **7**, 1551 (1971).

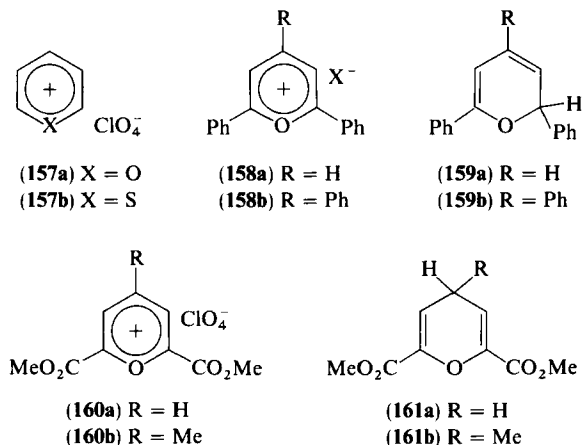
²¹¹ J. P. Le Roux, G. Letetire, P. L. Desbene, and J. J. Basselier, *Bull. Soc. Chim. Fr.*, 4059 (1971).

²¹² J. Royer and J. Dreux, *Tetrahedron Lett.*, 5589 (1968).

toward the substrates. Thus pyrylium perchlorate **157a** was readily reduced by 4*H*-thiopyran (**7**) to 4*H*-pyran (**5**) according to Eq. (5).²⁵



On the other hand, analogous reductions of **158a,b** with corresponding 4*H*-pyrans **151a** and **151c** at 80°C for 12 hours have led to dienones **152a,c**, apparently via unstable 2*H* isomers **159a,b**.²⁰⁹



Sodium formate was found to exhibit different regioselectivities toward cations **158a,b**.²⁰⁹ Although the reduction of 2,6-disubstituted substrate **158a** to 4*H*-pyran **151a** proceeded in acetonitrile at 20°C, the 2,4,6-trisubstituted cation **158b** reacted at all temperatures to give 60% of **152c**, evidently via 2*H*-pyran **159b**. The reactions of **158a** with dimethylaniline, diazomethane, or ethyl diazoacetate led to various mixtures of products containing 2,6-diphenyl-4*H*-pyran **151a**.^{205,212a}

The strongly electrophilic pyrylium perchlorate **160a** was readily reduced with cyclooctatriene,²¹³ toluene, anisole, dimethylaniline,²¹⁴ or diphenylmethanol²¹⁵ to 2,6-bis(methoxycarbonyl)-4*H*-pyran (**161a**). Other perchlorates like **160** exhibit similar behavior toward alcohols; equilibrium constants for the redox processes were estimated.²¹⁶

^{212a} S. V. Krivun, *Dokl. Akad. Nauk SSSR* **180**, 615 (1968).

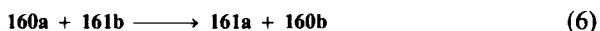
²¹³ E. T. Østensen and K. Undheim, *Acta Chem. Scand.* **27**, 2184 (1973).

²¹⁴ E. T. Østensen, *Acta Chem. Scand., Ser. B* **B28**, 1107 (1974).

²¹⁵ K. Undheim and E. T. Østensen, *Acta Chem. Scand.* **27**, 1385 (1973).

²¹⁶ K. Undheim and C. E. Carlberg, *Acta Chem. Scand., Ser. B* **B28**, 517 (1974).

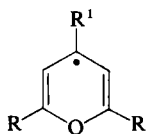
Compound **161a** was also generated in the reaction mixture by reduction with 4-methyl derivative **161b** according to Eq. (6).²¹³



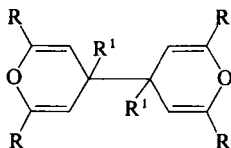
2,4,6-Triphenyl-4*H*-pyran **151c** or its 2*H* isomer was thought to be a product (mp 225°C) after partial hydrogenation on palladium of enedione **40** in acetic acid in equilibrium with 2,4,6-triphenylpyrylium acetate.²¹⁷

2. Reduction to Dimeric Pyrans

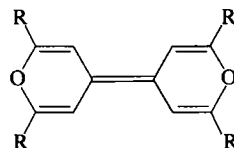
2,6-Disubstituted and 2,4,6-trisubstituted pyrylium cations of type **158a,b** are capable of a one-electron reduction to reactive 4-pyranyl radicals **162**, dimerizing easily to bis-4*H*-pyrans **163a**,^{218–220} **163b**,²²¹ **163c**,^{221,222} and **163d**^{223,224} in variable yields.



(162)



(163)



(164)

- (a) R = R¹ = Me
 (b) R = *t*-Bu; R¹ = H
 (c) R = Ph; R¹ = H
 (d) R = R¹ = Ph

- (164) R = Ph, *p*-MeC₆H₄,
p-MeOC₆H₄, 2-thienyl

Intermediates **162** may be generated electrochemically,^{224,225} with zinc,^{219,221,223} sodium, potassium, magnesium,²²¹ or organometallics.^{218,220} An electron-transfer mechanism for a reaction of perchlorate **158** with *tert*-butylmagnesium bromide was considered²²⁰ as follows (Eq. 7).

²¹⁷ W. Diltthey, G. Bauriedel, G. Geisselbrecht, A. Seeger, and J. Winkler, *J. Prakt. Chem.* **101**, 177 (1920).

²¹⁸ K. Conrow and P. C. Radlick, *J. Org. Chem.* **26**, 2260 (1961).

²¹⁹ A. T. Balaban, C. Bratu, and C. N. Rentea, *Tetrahedron* **20**, 265 (1964).

²²⁰ A. Safieddine, J. Royer, and J. Dreux, *Bull. Soc. Chim. Fr.*, 703 (1972).

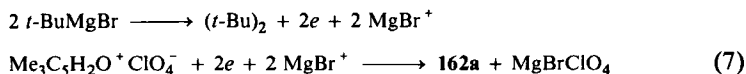
²²¹ L. A. Polyakova, K. A. Bilevich, G. N. Dorofeenko, O. Yu. Okhlobystin, and I. I. Bubnov, *Dokl. Akad. Nauk SSSR* **212**, 370 (1973).

²²² S. N. Baranov, M. A. Dumbai, and S. V. Krivun, *Khim. Geterotsykl. Soedin.*, 1313 (1972).

²²³ V. B. Panov, M. V. Nekhoroshev, and O. Yu. Okhlobystin, *Dokl. Akad. Nauk SSSR* **243**, 372 (1978).

²²⁴ F. Pragst, M. Janda, and I. Stibor, *Electrochim. Acta* **25**, 779 (1980).

²²⁵ F. Pragst and U. Seydewitz, *J. Prakt. Chem.* **319**, 952 (1977).

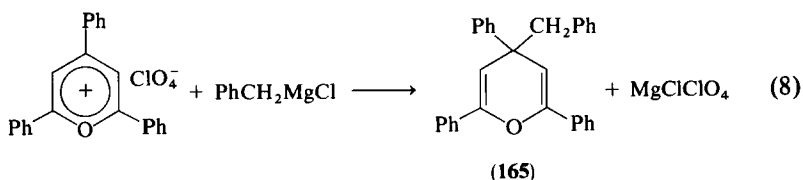


Primary radicals **162** were detected by voltammetric methods^{225–227} or by electroluminescence experiments with rubrene²²⁸ and identified by ESR.^{223,229–231} An extensive electrochemical investigation of the behavior of many pyrylium salts shows that the dimerization of **162** to **163** at position 4 proceeds more rapidly than at positions 2 or 6.²²⁷ The effect of variable 2-, 4-, and 6-substituents on the dimerization process was recognized, and some dimerization rate constants were also determined.²²⁷ In the generation of **162c** and some of its 2,6-diaryl analogs with zinc in acetonitrile, disproportionation of dimers **163** to dipyranylidenes **164** and corresponding 4*H*-pyrans like **151a** was observed.²³²

3. Reductive Alkylation and Arylation

The conversion of pyrylium salts to pyrans via reductive alkylation or arylation may be accomplished with organometallic compounds or electrochemically.

The reaction of pyrylium salts with Grignard reagents seems a generally applicable method for the preparation of substituted 2*H*- and 4*H*-pyrans. The syntheses of **165** according to Eq. (8) was the first in this field.^{233,234}



Only 2,6-disubstituted and highly substituted starting compounds have been explored, due to the lability of less substituted pyrans. The reactivities

²²⁶ E. Gird and A. T. Balaban, *J. Electroanal. Chem.* **4**, 48 (1962).

²²⁷ F. Pragst, R. Ziebig, U. Seydewitz, and G. Driesel, *Electrochim. Acta* **25**, 341 (1980).

²²⁸ F. Pragst, *Electrochim. Acta* **21**, 497 (1967).

²²⁹ V. A. Palchkov, Yu. A. Zhdanov, and G. N. Dorofeenko, *Zh. Org. Khim.* **1**, 1171 (1965).

²³⁰ I. Degani, L. Lunazzi, and G. F. Pedulli, *Mol. Phys.* **14**, 217 (1968).

²³¹ E. Krumbholz and F. W. Steuber, *Angew. Chem.* **87**, 588 (1975).

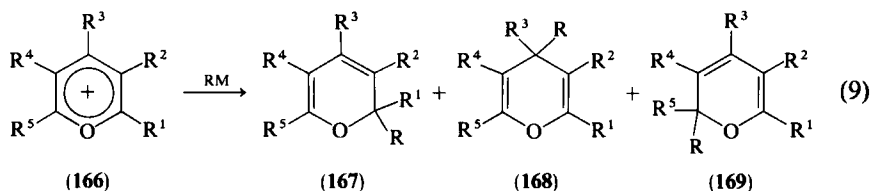
²³² C. Fabre, R. Fugnitti, and H. Strzelecka, *C.R. Acad. Sci.* **282**, 175 (1976).

²³³ K. Dimroth and G. Neubauer, *Chem. Ber.* **92**, 2042 (1959).

²³⁴ K. Dimroth and K. H. Wolf, *Angew. Chem.* **72**, 777 (1960).

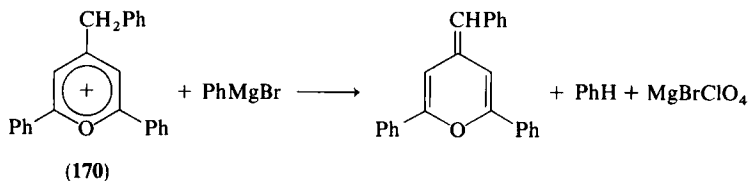
of the substrates with the Grignard agents were discussed quantum chemically by HMO and CNDO/2 methods,²⁰¹ but not all factors influencing the regioselectivity have as yet been recognized.

Two isomeric 2*H*-pyrans **167** and **169** together with a 4*H*-pyran **168** may be formed from substituted pyrylium ions **166** and organometallic reagent RM (Eq. 9).



As a rule, 4*H*-pyrans **168** are isolable, but their 2*H* isomers **167** or **169** undergo rapid valence isomerization to dienones $\text{R}^5\text{COCR}^4=\text{CR}^3-\text{CR}^2=\text{CRR}^1$ or $\text{RR}^5\text{C}=\text{CR}^4-\text{CR}^3=\text{CR}^2\text{COR}^1$.²³⁵⁻²³⁷ Other isomerizations of primary **167** and **169** to cyclic isomers possessing exocyclic double bonds were also observed.²³⁷ With excess Grignard reagent succeeding additions to **167** or **169** were sometimes found.^{212,238}

If a pyrylium ion possesses hydrogen atoms sufficiently active toward a given organometallic agent, elimination may occur instead of addition as was found in the case of **170**.²³⁶



No example of a simultaneous formation of three different products **167**, **168**, and **169** has been found so far. The following types of reaction mixtures from resulting Eq. (9) were reported: **167**, **167** + **169**, **167** + **168** and **168**.

2,6-Disubstituted ions **166** ($\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$) provide, as rule only, 4*H*-pyrans **168** independent of the nature of the organometallic reactant RM. The reactions of 2,6-di-*tert*-butylpyrylium perchlorate with *t*-BuMgCl or *t*-BuMgBr as well as of 2,6-diphenylpyrylium perchlorate or tetrafluoroborate with MeMgI, PhMgBr, PhCH_2MgCl , and $\text{PhC}\equiv\text{CLi}$ were thus explored for

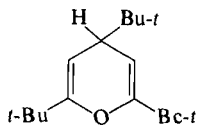
²³⁵ G. Köbrich and D. Wunder, *Justus Liebigs Ann. Chem.* **654**, 131 (1962).

²³⁶ K. Dimroth, K. Wolf, and H. Kroke, *Justus Liebigs Ann. Chem.* **678**, 183 (1964).

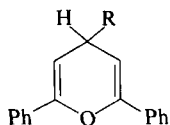
²³⁷ J. Royer and J. Dreux, *Bull. Soc. Chim. Fr.*, 707 (1972).

²³⁸ J. Royer and J. Dreux, *C.R. Acad. Sci.* **258**, 5895 (1964).

the preparation of **171**,^{239,240} **172a**,²³⁶ **172b**,^{236,241} and **172c**.²⁴² On the other hand, 2,6-dimethylpyrylium perchlorate with MeMgI yielded expected 4*H*-pyran **173** together with comparable amounts of stereoisomeric dienones and about 5% of unstable 2*H*-isomer.²³⁷



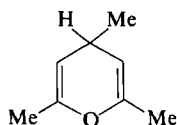
(171)



(172a) R = Me

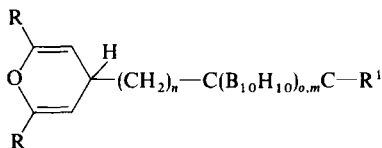
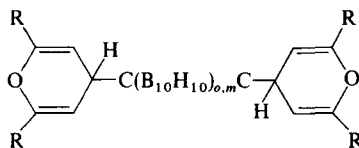
(172b) R = PhCH₂

(172c) R = PhC≡C



(173)

Variable carboranyl 4*H*-pyrans like **174a**,^{243,244} **174b**,²⁴⁵ and **175**²⁴⁵ were prepared, using the corresponding carboranyllithiums or carboranylmagnesium bromides.

(174a) R = *t*-Bu, Ph, *p*-MeOC₆H₄R' = Ph, *n* = 0(174b) R = *t*-Bu; R' = H, *n* = 1(175) R = *t*-Bu, Ph

The regioselectivity of the addition of organometallics to 2,4,6-trisubstituted pyrylium ions **166** (R² = R⁴ = H) is mainly determined by the structure of the entering group R. Thus 2,4,6-trimethylpyrylium perchlorate **177** was found to react with MeMgI, MeLi, or MeNa exclusively to give 2,2,4,6-tetramethyl-2*H*-pyran (**176**),^{212,220,237,238,246} whereas *i*-PrMgX, *i*-PrLi,

²³⁹ M. V. Nekhoroshev and O. Yu. Okhlobystin, *Zh. Org. Khim.* **13**, 1294 (1977).

²⁴⁰ J. Kuthan, S. Böhm, and R. Prantová, unpublished results.

²⁴¹ S. V. Krivun, *Dokl. Akad. Nauk SSSR* **182**, 347 (1968).

²⁴² G. N. Dorofeenko, A. V. Koblik, T. I. Polyakova, and B. A. Tertov, *Zh. Org. Khim.* **10**, 1998 (1974).

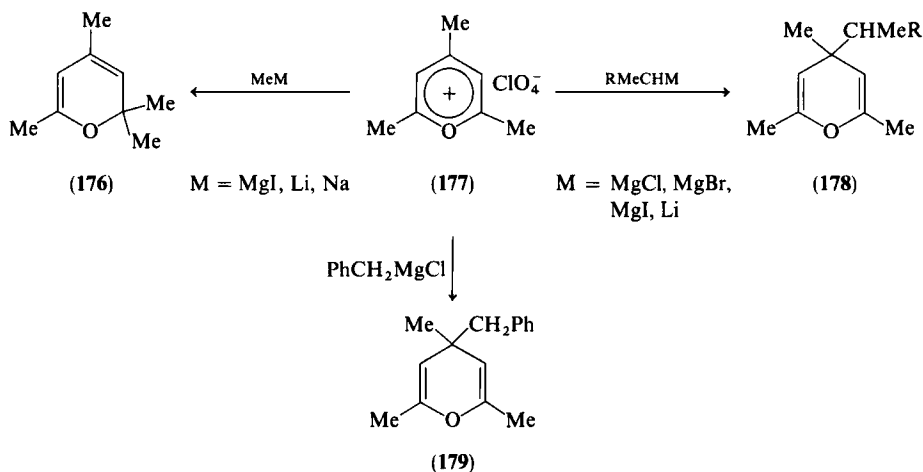
²⁴³ O. V. Drygina, G. N. Dorofeenko, and O. Yu. Okhlobystin, *Khim. Geterotsikl. Soedin.*, 1172 (1977).

²⁴⁴ O. V. Drygina, U. B. Panov, and O. Yu. Okhlobystin, *Khim. Geterotsikl. Soedin.*, 185 (1980).

²⁴⁵ O. V. Drygina, G. N. Dorofeenko, and O. Yu. Okhlobystin, *Khim. Geterotsikl. Soedin.*, 189 (1980).

²⁴⁶ J. Royer, A. Safieddine, and J. Dreux, *C.R. Acad. Sci., Ser. C* **274**, 1849 (1972).

s-BuMgX and PhCH₂MgCl yield only 4*H*-isomers **168**, e.g., **178**^{220,246} and **179**,²³⁶ as in Scheme 12.



SCHEME 12

Analogous reactions with EtMgX, *n*-PrMgX, CH₂=CHCH₂MgX, *i*-BuMgX, *t*-BuMgX, *n*-BuLi, and *n*-BuNa were less regioselective (Table V).^{220,246} In all cases both 2*H*- and 4*H*-pyrans are formed and, excluding the reactions with *n*-BuLi and *n*-BuNa, the 4-position in **177** appears to be more kinetically reactive if statistical factors are taken into account. Results^{220,236,237,246} cannot be interpreted in terms of simple electronic and/or steric effects before the detailed mechanism of the process is clarified. The different behavior of less regioselective *tert*-butylmagnesium halides (Table

TABLE V
ISOMERIC PYRANS FORMED FROM 2,4,6-TRIMETHYLPYRYLIUM ION BY REACTION (2)^a

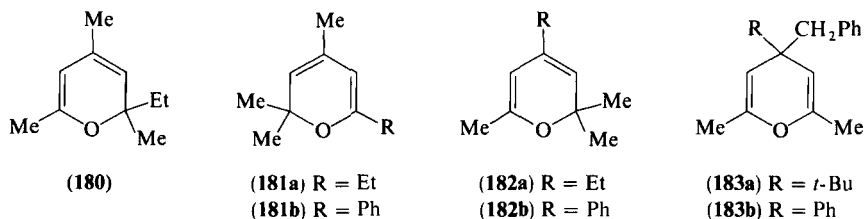
Agent RM	Products (relative %)		Agent RM	Products (relative %)	
	167 + 169	168		167 + 169	168
EtMgBr	60	40	<i>t</i> -BuMgCl	52	48
<i>n</i> -PrMgBr	57	43	<i>t</i> -BuMgBr	57	43
<i>n</i> -BuMgCl	45	53	<i>n</i> -BuLi	75	25
<i>n</i> -BuMgBr	50	50	<i>n</i> -BuNa	73	27
<i>n</i> -BuMgI	46	54	CH ₂ =CHCH ₂ MgI	65	35
<i>i</i> -BuMgBr	60	60	CH ₂ =CHCH ₂ Li	60	40

^a According to References 220 and 246.

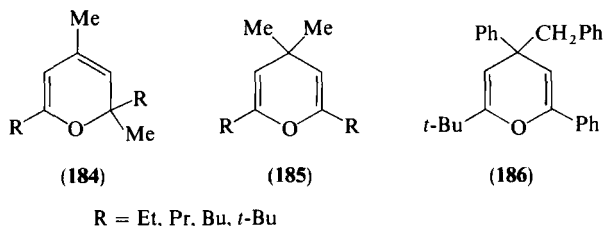
V) and analogous highly regioselective *sec*-alkyl reagents (Scheme 12) seems to be important.

Any change of individual substituents in 2,4,6-trisubstituted pyrylium salts results, as a rule, in negligible effects in comparison with the variations produced by the organometallic agents.

If one methyl group in **177** is replaced by another substituent, the ability of MeMgI to form 2*H*-pyrans and of PhCH₂MgCl to form 4*H*-pyrans, as shown in Scheme 12, is conserved. Thus 2-ethyl- or 2-phenyl-4,6-dimethylpyrylium salts with MeMgI gave a mixture of 2*H*-pyrans **180** and **181a** in the ratio 65:35 or unstable 2*H*-pyran **181b**, respectively.²³⁷ Similarly, 4-substituted 2,6-dimethylpyrylium salts with the same reagent afforded 2*H*-pyrans (**182a,b**)²³⁸ whereas PhCH₂MgCl attacked the substrates at position 4 to give 4*H*-pyrans **183a,b** in preparative yields of 61 and 79%, respectively.²³⁶



If both 2,6-methyl groups are replaced by other substituents, the reactivity of the appropriate substrates toward MeMgI is only slightly modified resulting mainly in 2*H*-pyrans **184**^{237,247} together with some secondary isomerizations.²⁴⁷ An enhancement of the size of 2,6-substituents leads to an increase in the population of the minor 4*H*-isomer **185**; the resulting mixture exhibits the ratios **184**:**185** as follows: 100:0 (R = Et), 94:6 (R = Pr), 91:9 (R = Bu), and 88:12 (R = *t*-Bu). Surprisingly, 2,6-diphenyl-4-methylpyrylium ion gave no pyrans.²³⁷ Other 2,4,4,6-tetrasubstituted 4*H*-pyrans were successfully prepared by analogous reactions of 2,4,6-trisubstituted pyrylium perchlorates or tetrafluoroborates with various Grignard reagents, including **165** and asymmetrically substituted 4*H*-pyran **186** (Table VI).²³⁶



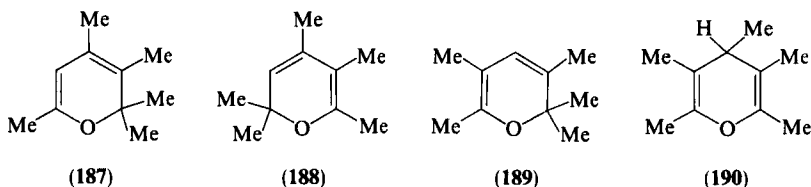
R = Et, Pr, Bu, *t*-Bu

²⁴⁷ J. Royer and J. Dreux, *C.R. Acad. Sci., Ser. C* **262**, 927 (1966).

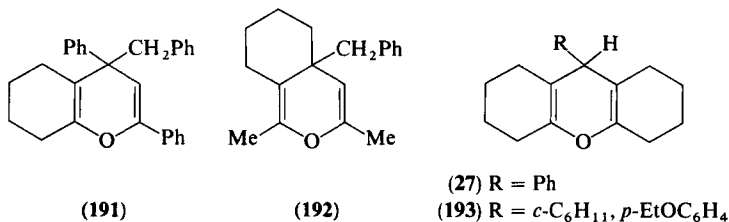
TABLE VI
SOME 4*H*-PYRANS FORMED BY REACTION (2) FROM 2,4,6-TRISUBSTITUTED
PYRYLIUM IONS²³⁶

R	X ⁻	R ¹ R ¹	R ³	R ⁵	Yield (%)
PhCH ₂	ClO ₄ ⁻	Ph	Ph	Ph	71
PhCH ₂	BF ₄ ⁻	<i>t</i> -Bu	Ph	Ph	52.5
PhCH ₂	BF ₄ ⁻	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -MeOC ₆ H ₄	51.5
<i>p</i> -MeOC ₆ H ₄	ClO ₄ ⁻	Ph	Ph	Ph	72
1-naphthyl	ClO ₄ ⁻	Ph	Ph	Ph	57
3-thionaphthyl	ClO ₄ ⁻	Ph	Ph	Ph	68

The regioselectivity in the Grignard reactions of tetrasubstituted pyrylium salts is the consequence of simultaneous effects of substitution patterns in both the substrate and the reagent. Thus the reaction of MeMgI with 2,3,4,6- or 2,3,5,6-tetramethylpyrylium ions provide mixtures of isomeric 2*H*-pyrans **187** and **188** in the ratio 91:9 or of 2*H*-pyran **189** and 4*H*-pyran **190** in the ratio 48:52, respectively.²³⁷

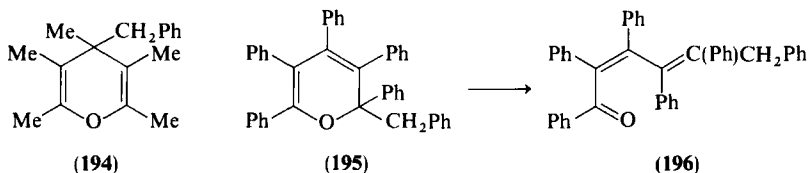


However, if a tetrasubstituted pyrylium ion possessed one or two condensed six-membered carbocyclic rings, then only 4*H*-pyrans **191**, **192**, **27**, and **193** are isolable (35 to 92%) after reaction with PhCH₂MgCl²³⁶ or with other Grignard reagents RMgX.²¹⁰

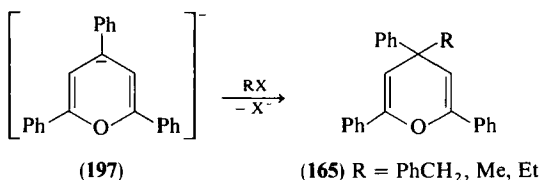


With pentasubstituted pyrylium salts **166** the regioselectivity of the Grignard reactions is controlled mainly by the substitution patterns of the substrate. Pentamethylpyrylium perchlorate with PhCH₂MgCl gave exclusively 4*H*-pyran **194** (72%) while pentaphenylpyrylium perchlorate with

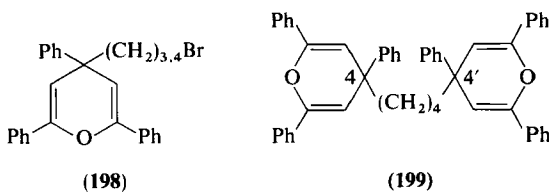
the same reagent yielded only dienone **196**.²³⁶ The latter transformation resembles the borohydride reduction of the same salt to **156** and proceeds via the labile *2H*-pyran **195**.



An alternative general approach to *4H*-pyrans has been found recently in cathodic alkylation of 2,4,6-triphenylpyrylium perchlorate²²⁴ and might be useful, especially where the Grignard reaction (Eq. 9) fails. The salt is electrolyzed (mercury electrode) in the presence of a reactive alkyl halide: two-electron reduction generates pyranyl anion **197**, which is alkylated with RX to *4H*-pyrans **165** (11 to 36%).



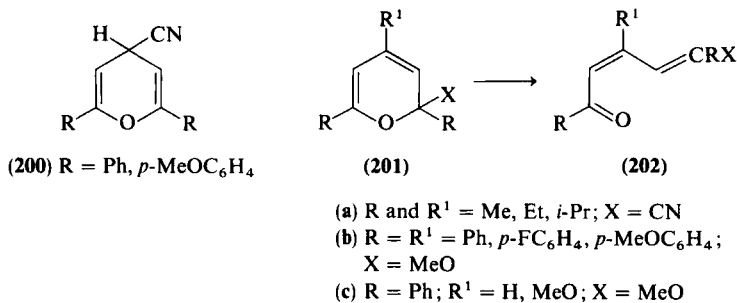
Using dibromides $Br(CH_2)_{3,4}Br$ in place of RX gives 12 to 28% of simple *4H*-pyrans **198** and 6 to 15% of 4,4'-bis-*4H*-pyrans **199**. The rate constants for the alkylation were determined.²²⁴



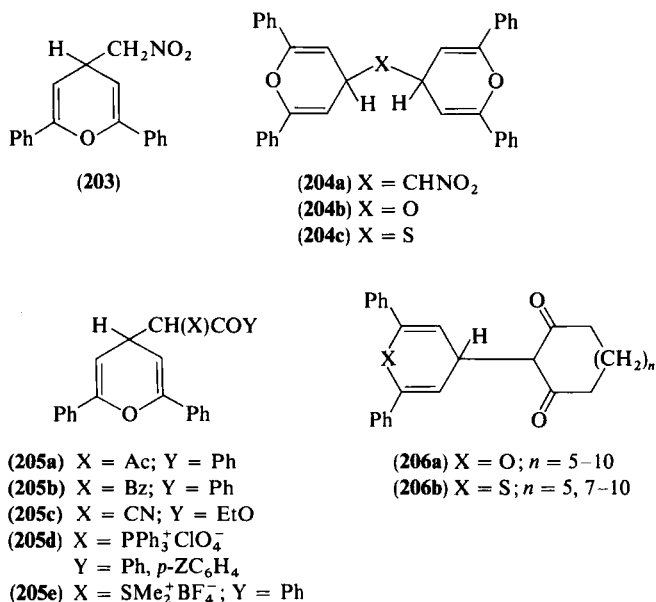
4. Reactions with Anions of C-Acids

2,6-Diarylpyrylium perchlorates with sodium cyanide yields quantitatively 4-cyano-*4H*-pyrans (**200**),²²² whereas 2,4,6-trisubstituted substrates give only dienones **202** via unstable *2H*-pyrans (**201a**).²⁴⁸

²⁴⁸ A. T. Balaban and C. D. Nenitzescu, *J. Chem. Soc.*, 3566 (1961).



2,6-Diphenylpyrylium perchlorate underwent with some carbon acids, in the presence of bases such as methanolic sodium hydroxide, trimethylamine, or pyridine, a number of additions to form 4*H*-pyrans.²⁴⁹ Thus nitromethane gave 96% of **203** or 85% of **204a**, depending on the reactant ratios. Similarly, Ac_2CH_2 , Bz_2CH_2 , and ethyl cyanoacetate provided the corresponding 4*H*-pyrans **205a–c** (59, 90, and 91%, respectively). 1,3-Cycloalkanediones yielded analogous products **206a** in the presence of sodium ethanolate.²⁵⁰ Phosphoranes $p\text{-XC}_6\text{H}_4\text{CO}^-\text{CH}^+\text{PH}_3$ and the sulfurane $\text{PhCO}^-\text{CHS}^+\text{Me}_2$

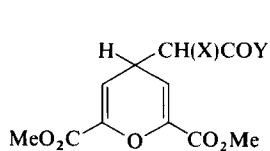


²⁴⁹ F. Kröhnke and K. Dickoré, *Chem. Ber.* **92**, 46 (1959).

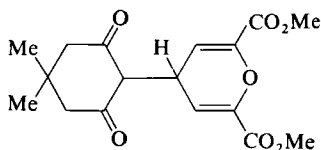
²⁵⁰ B. Eistert, A. Schmitt, and T. J. Arackal, *Chem. Ber.* **109**, 1549 (1976).

can replace C-anions for the preparation of 4*H*-pyranil salts **205d**²⁵¹ and **205e**.²⁵²

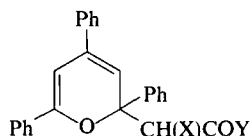
Strongly electrophilic bis-2,6-methoxycarbonylpyrylium perchlorate (**160a**) spontaneously undergoes addition of acetone, acetophenone, Ac_2CH_2 , Bz_2CH_2 , or dimesone in liquid SO_2 at -30°C to give 4*H*-pyrans **207** and **208** (57 to 90%).²¹³ 2,4,6-Triphenylpyrylium tetrafluoroborate adds to diethyl 1,3-acetonedicarboxylate in the presence of *t*-BuOK to give 58% 2*H*-pyran **209a**.⁹ 2*H*-Pyrans **209b** (yields 80 to 87%) were obtained similarly using active methylene compounds XCH_2COY with 1-substituted 2,6-diphenylpyrylium perchlorates under phase-transfer conditions.²⁵³



(207) X = H, Ac, Bz



(208)



(209a) R = Ph; X = CO_2Et

Y = $\text{CH}_2\text{CO}_2\text{Et}$

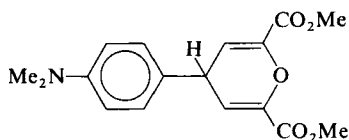
(209b) R = Ph, 2-thienyl

X = COMe, CO_2Et

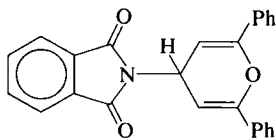
Y = Me, EtO

5. Reactions with Amines and Anions of *N*-Acids

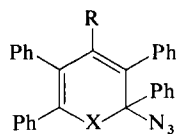
The addition of ammonia or primary and secondary amines to pyrylium salts is usually accompanied by a rapid ring opening without detection of the expected 2*H*-pyran intermediates. The exceptional behavior of the salt **160a** was observed in its reaction with *N,N*-dimethylaniline, affording 85% of 4*H*-pyran **210**, whereas analogous addition products from toluene and methoxybenzene were too unstable to be isolated.²¹⁴



(210)



(211)



(212a) X = O; R = H, Ph

(212b) X = S; R = H, Ph

²⁵¹ V. I. Boev and A. V. Dombrovskii, *Zh. Obshch. Khim.* **50**, 1473 (1980).

²⁵² Y. Suzuki, T. Todda, and T. Mukai, *Heterocycles* **4**, 739 (1976).

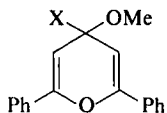
²⁵³ G. N. Dorofeenko, A. V. Koblik, and K. F. Suzdalev, *Zh. Org. Khim.* **17**, 1050 (1981).

2,6-Diphenylpyrylium perchlorate with phthalimide ion gives **4H**-pyran **211** (79%).²²²

Analogously, **2H**-pyrans **212a** were prepared from sodium azide in acetonitrile and the corresponding pentasubstituted pyrylium salts at -35°C .²⁵⁴

6. Reactions with Hydroxide, Alkoxide, and Sulfide Ions.

An earlier report²⁵⁵ of the isolation of **4H**-pyran ether **204b** by reaction of water with two 2,6-diphenylpyrylium ions in DMF was later found to be erroneous.^{256,257} The formation of intermediated **2H**-pyrans **201b** was proved by ^{13}C - and ^{19}F -NMR spectroscopy.²⁵⁸ Similarly, the reactions of 2,6-diphenyl- and 4-methoxy-2,6-diphenylpyrylium ions **158** ($\text{R} = \text{H}$ or MeO) lead to **4H**-pyrans **213** and to **2H** isomers **201c**, which in case of $\text{R}^1 = \text{H}$ easily isomerized to the corresponding dienone **202c** ($\text{R}^1 = \text{H}$).^{258a} Compounds **213** were first formed under kinetic control whereas the formation of **201c** or **202** was thermodynamically controlled. The equilibrium and rate constants for the process were determined at 25°C in the $\text{Et}_3\text{N}/\text{Et}_3\text{NH}^+$ buffer system.²⁵⁹



(213) $\text{X} = \text{H}, \text{MeO}$

Hydroxide ion adds to 2,4,6-Triphenylpyrylium ion in the presence of sodium acetate^{260,261} or in aqueous solution at pH 14 to give **2H**-pyran **40**, which isomerizes to the corresponding dienone at lower pH.⁸⁸ The same reaction was discovered for 2,6-dimethyl-4-(*p*-methoxyphenyl)pyrylium ion.^{261a}

²⁵⁴ J. P. Le Roux, J. C. Cherton, and P. L. Desbene, *C.R. Acad. Sci., Ser. C* **280**, 37 (1975) [*CA* **83**, 78194 (1975)].

²⁵⁵ S. V. Krivun, USSR Patent 225,212 (1968) [*CA* **70**, 19935 (1969)].

²⁵⁶ N. G. Bokii and Yu. T. Struchkov, *Cryst. Struct. Commun.* **6**, 317 (1977).

²⁵⁷ A. I. Pyshchev, N. G. Bokii, and Yu. T. Struchkov, *Tetrahedron* **34**, 2131 (1978).

²⁵⁸ A. R. Katritzky, R. T. C. Brownlee, and G. Musunarra, *Heterocycles* **12**, 775 (1979).

^{258a} S. Bersani, G. Doddi, S. Fornarini, and F. Stegel, *J. Org. Chem.* **43**, 4112 (1978).

²⁵⁹ G. Doddi, S. Fornarini, G. Illuminati, and F. Stegel, *J. Org. Chem.* **44**, 4496 (1979).

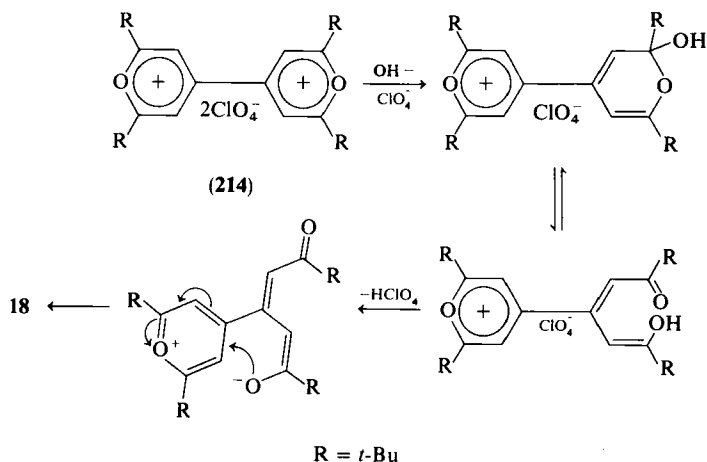
²⁶⁰ W. Diltthey, *J. Prakt. Chem.* **94**, 53 (1916).

^{260a} C. Gastaldi, *Gazz. Chim. Ital.* **51**, (II), 289 (1921).

²⁶¹ D. Iwanow and T. Iwanow, *Chem. Ber.* **77**, 180 (1944).

^{261a} W. Diltthey and R. Taucher, *Chem. Ber.* **53**, 252 (1920).

The formation of the spirocyclic 4*H*-pyran **18** from 4,4'-bis-(2,2',6,6'-tetra-*tert*-butyl)pyrylium diperchlorate (**214**) by heating with aqueous KOH or AcOH–AcONa is explained by the mechanism shown in Scheme 13.⁵²

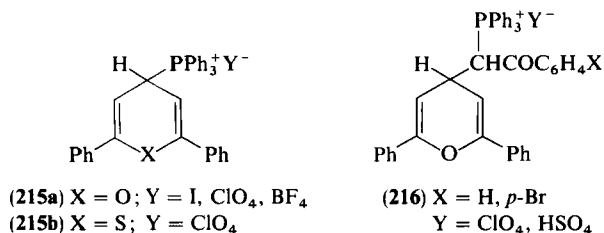


SCHEME 13

2,6-Diphenylpyrylium perchlorate reacted smoothly with sodium sulfide to give S-bridged 4,4'-bis-4*H*-pyran **204c** in 77% yield.²²²

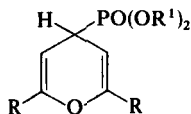
7. Reactions with Phosphines and Anions of P-Acids

Triphenylphosphine adds smoothly to 2,6-diphenylpyrylium iodide, perchlorate, or tetrafluoroborate to provide 4*H*-pyranyltriphenylphosphonium salts **215a** (80 to 99%).^{241,262,262a} The analogous addition of phosphoranes $\text{XC}_6\text{H}_4\text{COCHPPh}_3$ to the pyrylium perchlorate or hydrogen sulfate led to salts **216**.²⁵¹

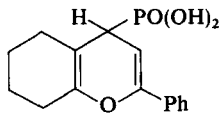


²⁶² Yu. A. Zhdanov, S. V. Krivun, and V. A. Polenov, *Khim. Geterotsikl. Soedin.*, 368 (1969).

^{262a} G. A. Reynolds and C. H. Chen, *J. Org. Chem.* **45**, 2458 (1980).



(217) R = *t*-Bu, Ph, *p*-BrC₆H₄,
p-MeOC₆H₄, 2,4-(MeO)₂C₆H₃
 R¹ = Me, Et, Bu

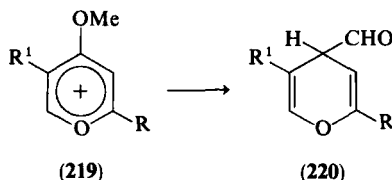


(218)

2,6-Disubstituted pyrylium salts reacted with $\text{NaOP(OR}^1)_2$ to give 4*H*-pyranylphosphonates (**217**),^{263–265} which are hydrolyzed to the corresponding phosphoric acids **217** ($\text{R}^1 = \text{H}$).^{263–265} The condensed acid **218** was prepared in the same way.²⁵⁹ If a mixture of P(Obu)_3 and BuI is used in place of NaOP(Obu)_2 , the Arbuzov rearrangement gives the same products.^{264a}

8. Miscellaneous Reactions

The cited^{160,161} formation of polychloropyrans **120** → **121** and **120** → **122** may be regarded as proceeding via 2-phenyl-3,4,5-trichloro- or 3,4,5-trichloropyrylium chlorides, which are attacked by a chloride ion. The transformation of pyrylium salts **219** to 4-formyl-4*H*-pyrans **220** with hippuric acid, acetic anhydride, and sodium acetate^{265a} is discussed in Section IV, J.


$$R = R^1 = H, Ph$$

B. THIOPYRANS FROM THIOPYRYLIUM SALTS

Thiopyrylium salts are, in general, capable of accepting nucleophiles by addition at positions 2, 4, or 6 to give the corresponding 2*H*- and/or 4*H*-

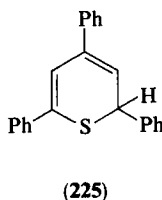
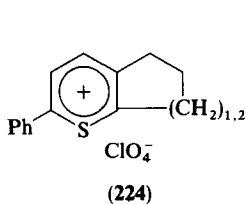
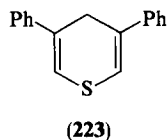
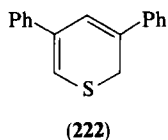
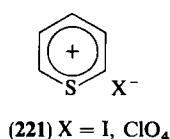
- ²⁶³ S. V. Krivun, V. I. Dulenko, O. F. Voziyanova, N. S. Semenov, and S. N. Baranov, *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol. Geofiz., Khim. Biol.* **33**, 823 (1971) [CA **75**, 151874 (1971)].
- ^{263a} S. V. Krivun, O. F. Voziyanova, and S. N. Baranov, *Dopov. Akad. Nauk Ukr. SSR, Ser. B: Geol. Geofiz., Khim. Biol.* **34**, 529 (1972) [CA **77**, 101765 (1972)].
- ²⁶⁴ S. V. Krivun, O. F. Voziyanova, and S. N. Baranov, *Zh. Obshch. Khim.* **42**, 58 (1972).
- ^{264a} V. I. Boev and A. V. Dombrovskii, *Zh. Obshch. Khim.* **50**, 467 (1980).
- ²⁶⁵ C. H. Chen and G. A. Reynolds, *J. Org. Chem.* **45**, 2449 (1980).
- ^{265a} S. V. Krivun, USSR Patent 463,665 (1975) [CA **83**, 9787 (1975)].

thiopyran derivatives in agreement with HMO reactivity indices.^{265b} The behavior of the starting substrates thus resembles the formation of pyrans from pyrylium salts (see Section IV,A) with two differences, namely, (i) the ability of electron lone pairs on sulfur atoms to coordinate with a reagent, leading to stable intermediates, and (ii) in a lack of secondary valence-bond isomerizations, leading to an enhanced stability of the initially formed 2*H*-thiopyrans. Factor (i) may partly modify the effects of substitution patterns in a thiopyrylium salt as well as in a reagent molecule on relative amounts and structures of products.

1. Reduction

The widely used reduction of thiopyrylium salts to thiopyrans has been accomplished with complex hydrides. Alternative reductions with ethanolamine mixtures or with trichlorosilane are rarely used.

The reduction of unsubstituted thiopyrylium perchlorate or iodide **221** with LiAlH_4 leads to mixtures of 2*H*-thiopyran (**6**) and 4*H*-thiopyran (**7**), in which **6** prevails.^{20,266} 3,5-Diphenylthiopyrylium ion gives an equimolar ratio of both 2*H* and 4*H* isomers **222** and **223**.²⁶⁷ Condensed perchlorates **224** were analogously converted to 4*H*-thiopyrans **21** ($\text{R} = \text{H}$) (88 to 90%). 2,4,6-Triphenylthiopyrylium salts afforded 54% of 4*H*-thiopyrans **45** ($\text{R} = \text{Ph}$) with the same reagent.³⁹ Mixtures of **45** and 2*H* isomer **225** in the ratio 1:1 or their 4- and 2-deutero derivatives were formed if NaBH_4 or NaBD_4 were used.²⁶⁸



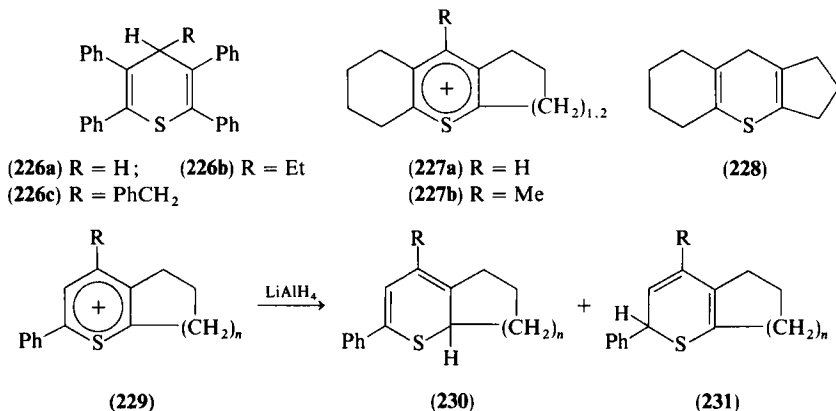
^{265b} J. Koutecký, *Collect. Czech. Chem. Commun.* **24**, 1608 (1959).

²⁶⁶ I. Degani, R. Fochi, and C. Vincenzi, *Gazz. Chim. Ital.* **97**, 397 (1967).

²⁶⁷ A. G. Hortmann, R. L. Harris, and J. A. Miles, *J. Am. Chem. Soc.* **96**, 6119 (1974).

²⁶⁸ E. T. Østensen, A. A. Abdallah, S. H. Skaare, and M. M. Mishrikey, *Acta Chem. Scand., Ser. B* **B31**, 496 (1977).

Tetrasubstituted thiopyrylium salts also provide a variety of products. Thus symmetrically substituted 2,3,5,6-tetraphenylthiopyrylium ion with LiAlH_4 or the condensed tricyclic salt with NaBH_4 gave exclusively 4*H*-thiopyrans **226a**⁴⁰ or **49** and **228**.^{269,270} Dithieno-4*H*-thiopyran **16** was obtained similarly from the appropriate thiopyrylium pentachlorostannate.¹³⁰ On the other hand, asymmetrically substituted substrates **229** with LiAlH_4 afforded 2*H*-thiopyran **230** in yields of 60 to 73% accompanied by 13 to 14% of isomers **231** for the 4-phenyl derivatives.²⁷¹



Pentasubstituted tricyclic 4*H*-thiopyran **48** ($n = 2$, $R = \text{Me}$) was also prepared by the reduction of the corresponding thiopyrylium salt **227b** with LiAlH_4 .²⁶⁹ The reduction with zinc proceeds via a dimeric 4*H*-thiopyran intermediate.²⁷² Ion **229** ($R = \text{Ph}$, $n = 2$) was reduced with zinc in hydrochloric acid to a mixture of 2*H*-thiopyran **230** ($R = \text{Ph}$, $n = 2$), 4*H*-thiopyran **232**, and the corresponding perhydrothiopyran.¹⁰⁰

4,6-Diphenyl-2*H*-thiopyran **233** is one of the products (12 to 72%) formed by ethanolic methylamine, ethylamine, benzylamine or triethylamine with 2,4-diphenylthiopyrylium perchlorate.²⁷³ Trichlorosilane was found to demethylate thiabenzene sulfoxide **234** reductively to mixtures of isomeric thiopyrans **222** and **223**.^{267,274}

²⁶⁹ V. G. Kharchenko, N. M. Yartseva, and A. A. Rassudova, *Zh. Org. Khim.* **6**, 1513 (1970).

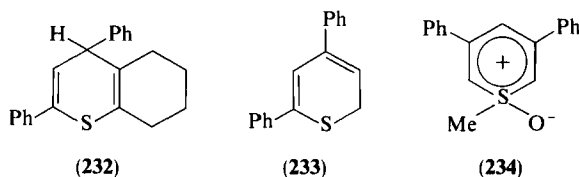
²⁷⁰ V. G. Kharchenko, N. I. Martemyanova, N. D. Zaitseva, and M. I. Kuramshin, *Zh. Org. Khim.* **12**, 1802 (1976).

²⁷¹ S. K. Klimenko, M. N. Berezhnaya, T. V. Stolbova, I. Ya. Evtushenko, and V. G. Kharchenko, *Zh. Org. Khim.* **11**, 2173 (1975).

²⁷² Z. Yoshida, S. Yoneda, T. Sugimoto, and O. Kikukawa, *Tetrahedron Lett.*, 3999 (1971).

²⁷³ B. J. Graphakos, A. R. Katritzky, G. Lhomme, and K. Reynolds, *J.C.S. Perkin I*, 1345 (1980).

²⁷⁴ A. C. Hortman and R. L. Harris, *J. Am. Chem. Soc.* **92**, 1803 (1970).



2. Reductive Alkylation and Arylation

The approach to thiopyrans involving reductive alkylation and arylation consists of the reaction of organolithium compounds or Grignard reagents with the corresponding thiopyrylium salts.

a. Reactions with Organolithium Reagents. Reactions of thiopyrylium salts **235** with reagents RLi can be formulated as shown in Eq. (10). The primary nucleophilic attack occurs at sulfur to give colored unstable thiabenzene intermediate **236**, which undergoes intramolecular rearrangement to colorless thiopyrans **237** and/or **238**.^{38,39,275-279} The rearrangement of intermediates **236** is more rapid if R is an alkyl, alkenyl, or alkynyl group than if it is an aryl group.^{39,275,277,280} Although electron-donating substituents in the migrating aryl group decrease the rate of rearrangement,²⁸¹ the same type of substituents in analogous aryl groups R¹ and R³ increase it.^{280,282} As expected, electron-withdrawing groups exert the opposite effect.²⁸³ In addition, involvement of the bulky groups R², e.g., the replacement of a hydrogen atom by methyl, also increases the rate of rearrangement.²⁷⁷ Rate constants of some transformations **236** → **238** and **236** → **237** + **238** were determined,²⁸⁴ and crossover experiments with substrates **235** having variable substituents R, R¹, and R³ have proved the process (Eq. 10) to be an intramolecular 1,2 and 1,4 migration of the aryl group.²⁸⁴ Rearrangements may be induced photochemically.^{281,282}

²⁷⁵ G. Suld and C. C. Price, *J. Am. Chem. Soc.* **84**, 2094 (1962).

²⁷⁶ U. Eisner, unpublished work.

²⁷⁷ B. E. Maryanoff, J. Stackhouse, G. H. Senkler, and K. Mislow, *J. Am. Chem. Soc.* **97**, 2718 (1975).

²⁷⁸ F. Ogura, W. D. Hounshell, C. A. Maryanoff, W. J. Richter, and K. Mislow, *J. Am. Chem. Soc.* **98**, 3615 (1976).

²⁷⁹ C. A. Maryanoff, K. S. Hayes, and K. Mislow, *J. Am. Chem. Soc.* **99**, 4412 (1977).

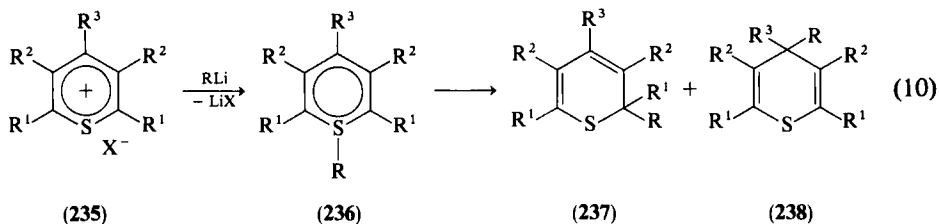
²⁸⁰ C. C. Price, J. Follweiler, H. Pirelahi, and M. Siskin, *J. Org. Chem.* **36**, 791 (1971).

²⁸¹ C. C. Price and H. Pirelahi, *J. Org. Chem.* **37**, 1718 (1972).

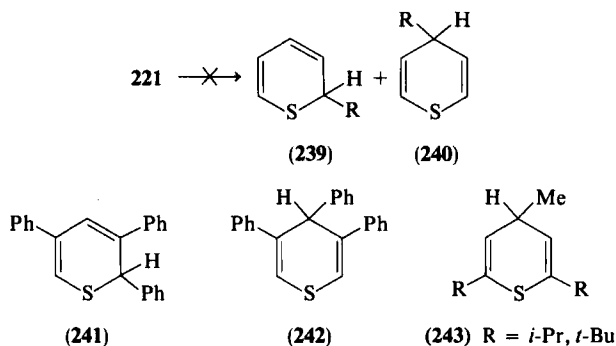
²⁸² H. Pirelahi, Y. Abdoh, F. Hadjmirsadeghi, and H. Sagherichi, *J. Heterocycl. Chem.* **13**, 237 (1976).

²⁸³ H. Pirelahi, Y. Abdoh, and M. Tavassoli, *J. Heterocycl. Chem.* **14**, 199 (1977).

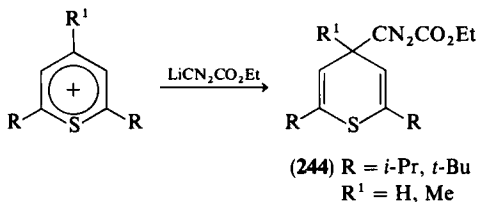
²⁸⁴ H. Pirelahi, and H. Highhooii, *J. Heterocycl. Chem.* **16**, 917 (1979).



The reaction of phenyllithium with unsubstituted thiopyrylium perchlorate (**221**) did not give thiopyrans **239** and **240** according to Eq. (10), but products were not identified.²⁷⁷ On the other hand, 3,5-diphenylthiopyrylium tetrafluoroborate with phenyllithium gave a mixture of expected *2H*- and *4H*-thiopyrans **241** and **242**,²⁶⁷ whereas methyllithium with analogous 2,6-diisopropyl- and 2,6-di-*tert*-butylthiopyrylium salts provided exclusively the *4H* isomers **243**.^{285,286}



If R, R¹, and R³ are all alkyl, the reactions shown in Eq. (10) proceed rapidly at room temperature unselectively. However, *4H*-thiopyran derivatives **244** were isolated in 90 to 94% yields from the reaction of ethyl lithio-



²⁸⁵ S. Yano, K. Nishino, K. Nakasuji, and I. Murata, *Chem. Lett.*, 723 (1978).

²⁸⁶ K. Nishino, S. Yano, Y. Kohashi, K. Yamamoto, and I. Murata, *J. Am. Chem. Soc.* **101**, 5059 (1979).

TABLE VII
REACTION TIMES FOR THE PREPARATION OF 2,4,6-TRISUBSTITUTED
4*H*-THIOPYRANS (238) ACCORDING TO EQ. (3)

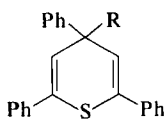
R	R ¹ = R ³	Time ^a	Yield (%)	References
PhC≡C	Ph	Not detected	70	280
Ph	Ph	20 d	25	38
4-MeC ₆ H ₄	Ph	27 d	35	280
4-CF ₃ C ₆ H ₄	Ph	10 h	61	283
4-CF ₃ C ₆ H ₄	4-MeOC ₆ H ₄	3 h	56	283
4-CF ₃ C ₆ H ₄	4-Me ₂ NC ₆ H ₄	10 min	31	283

^a Of 236 decomposition at room temperature (~25°C).

diazoacetate with the corresponding thiopyrylium salts in a THF-Et₂O solution at -120°C.^{285,286}

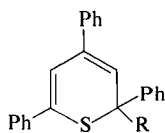
2,4,6-Trisubstituted thiopyrylium salts 235 (R² = H) have been investigated extensively and have been observed to react less rapidly, according to Eq. (10). The reaction time takes into account the rearrangement of intermediate 236 (Table VII).^{38,280,283}

Only 4-substituted 2,4,6-triphenyl-4*H*-thiopyrans 245a-d were isolated from the reaction of butyllithium or corresponding aryllithium reagents with 2,4,6-triphenylthiopyrylium salts.^{38,39,280,283} The same procedure was explored for the preparation of 4*H*-thiopyrans 247a,²⁸⁰ 247b,²⁷⁷ and 248.²⁸³ The use of more reactive agents (CH=CH)₂CHLi or PhC≡CLi led to 2*H*-thiopyran 246f³⁹ or to a mixture of both isomers 245g and 246g.²⁸⁰ The exceptional formation of 2*H* and 4*H* isomers 245e and 246e in the case of 4-MeOC₆H₄Li during the photochemically induced rearrangement of intermediate 249 might be associated with an isomerization like 245e → 246e.²⁸²



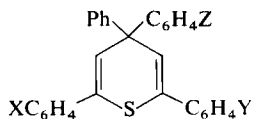
(245)

- (a) R = Bu
(b) R = Ph
(c) R = 4-MeC₆H₄
(d) R = 4-CF₃C₆H₄
(e) R = 4-MeOC₆H₄
(f) R = (CH=CH)₂CH

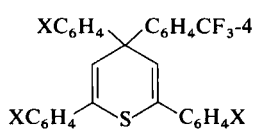
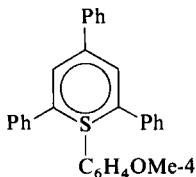


(246)

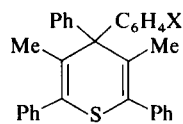
- (g) R = PhC≡C
(i) R = Me
(j) R = Et
(k) R = 4-Me₂NC₆H₄
(l) R = PhCH₂



- (247a) X = 4-Me
Y = Z = H
(247b) X = Y = 2-*i*-Pr
Z = H

(248) X = MeO, 4-Me₂N

(249)

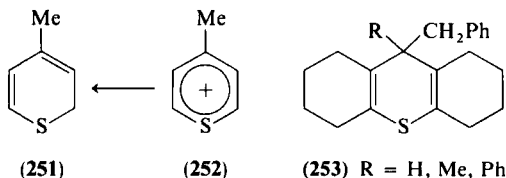


(250) X = H, 4-Me

Hexasubstituted 4*H*-thiopyrans **250** were easily prepared from 3,5-dimethyl-2,4,6-triphenylthiopyrylium tetrafluoroborate with phenyl- and *p*-tolyllithium via thermal decomposition of corresponding thiabenzene intermediates.²⁷⁷

b. *Reactions with Grignard Reagents.* Contrary to the reaction with organolithium compounds shown in Eq. (10), no unambiguous evidence concerning the formation of thiabenzene intermediates like **236** is available where organomagnesium halides were used. Hence only thiopyrans have usually been isolated and/or detected.

Unsubstituted thiopyrylium iodide (**221**) was found to afford with MeMgI a complex reaction mixture of expected 2*H*- and 4*H*-thiopyrans **239** and **240** (R = Me) in the ratio 1:2 together with unsubstituted thiopyrans **6** and **7** in the ratio 1:3 in addition to 4-methyl-2*H*-thiopyran (**251**).²⁶⁶ The formation of unexpected **6**, **7**, and **251** might be explained by side redox transformations like **240** + **221** → **6** + **7** + **252** and **252** + **7** → **251** + **221**.



(251)

(252)

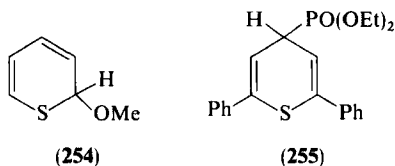
(253) R = H, Me, Ph

2,4,6-Triphenylthiopyrylium salts exhibit different regioselectivities toward Grignard reagents. Thus the reaction with BuMgBr gave exclusively 4*H* isomer **245a**, whereas MeMgI and EtMgBr afforded 1:3 and 3:1 mixtures of 2*H*- and 4*H*-thiopyrans **245i** and **246i** or **245j** and **246j**; respectively.³⁹ Similarly, the use of 4-Me₂NC₆H₄MgBr or PhCH₂MgCl yielded 70% of both isomers **245k** and **246k**²⁸¹ or 56% of **245l** and **246l**,²³⁶ respectively.

2,3,5,6-Tetraphenylthiopyrylium chloride or perchlorate was converted to 4*H*-thiopyrans **226b,c** with the appropriate Grignard reagents.⁴⁰ An analogous conversion with PhCH₂MgCl was explored for the preparation of condensed 4*H*-thiopyrans **253** from corresponding thiopyrylium species.²⁶⁹

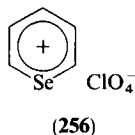
3. Reaction with Other Nucleophiles

Thiopyrans were obtained after the addition of anions of C-, O-, N-, and P-acids or triphenylphosphine to a suitable thiopyrylium salt. Thus unsubstituted thiopyrylium (**221**) reacted with sodium hydrogen carbonate to form 2-methoxy-2*H*-thiopyran (**254**).^{20,266} The addition of water to **221** was followed spectrophotometrically and interpreted in terms of calculated π -electron energy differences.²⁸⁷ 2,6-Diphenylthiopyrylium perchlorate gave the following 4*H*-thiopyrans: **206b** with corresponding 1,3-cycloalkanediones and sodium ethanolate,²⁵⁰ **215** with triphenylphosphine,^{262a} and **255** (yield 32%) with NaOP(OEt)₂ in THF at -78°C .²⁸⁸ On the other hand, only 2*H*-thiopyrans **212b** were obtained from sodium azide and the corresponding thiopyrylium salts.²⁵⁴



C. SELENOPYRANS FROM SELENOPYRYLIUM SALTS

4*H*-Selenopyran (**8**) was formed by hydrogen transfer from 4*H*-thiopyran (**7**) to perchlorate **256** according to Eq. (11).²⁵



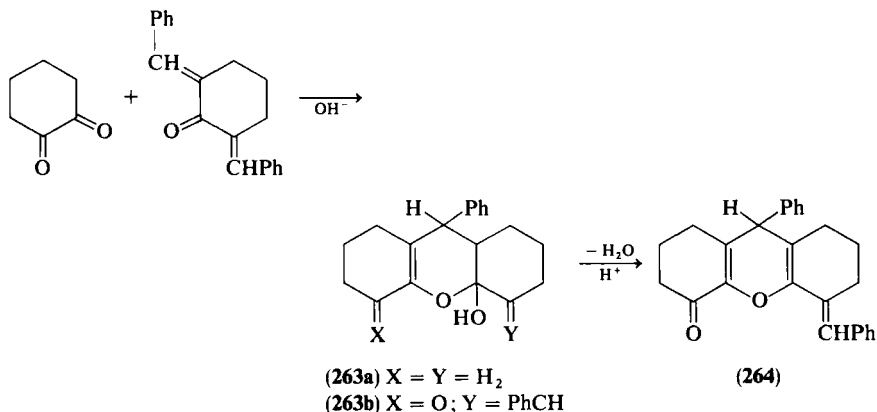
D. PYRANS FROM DIHYDROPYRANS AND TETRAHYDROPYRANS

Dihydro- and tetrahydropyrans are usual although rarely isolated intermediates of many ring-closure reactions leading to pyrans (see Section III). This approach always involves certain elimination reaction steps as has already been demonstrated in the preparation of pyrans **5**, **27**, and **99**.

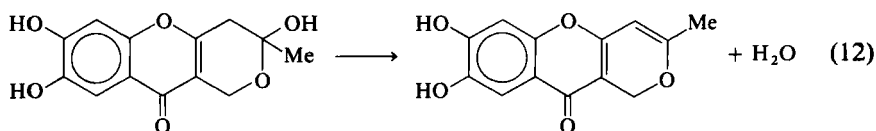
²⁸⁷ R. G. Turnbo, D. L. Sullivan, and R. Pettit, *J. Am. Chem. Soc.* **86**, 5630 (1964).

²⁸⁸ C. H. Chen and G. A. Reynolds, *J. Org. Chem.* **45**, 2453 (1980).

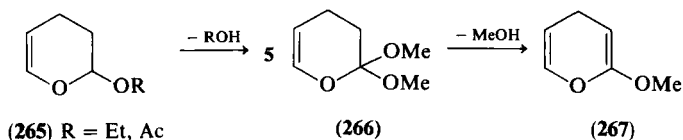
²⁹¹ A. Banaszek, B. Szechner, J. Mieckowski, and A. Zamojski, *Rocz. Chem.* **50**, 105 (1976) [*CA* **84**, 165150 (1976)].



A similar dehydration affording *2H*-pyrans is the case of fulvic acid, a yellow acidic metabolite that is transformed to anhydrofulvic acid,²⁹² as shown in Eq. (12).



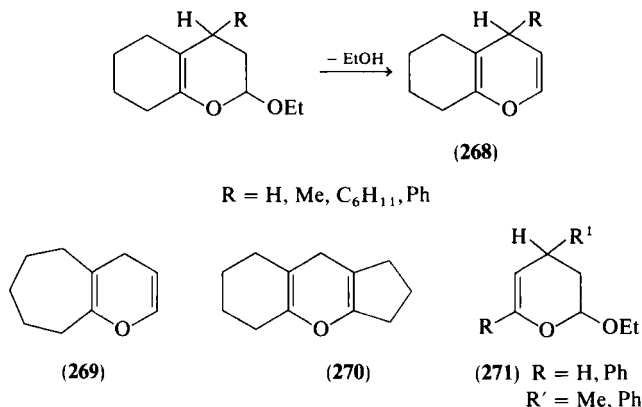
The elimination of methanol, ethanol, or acetic acid is useful for the preparation of *4H*-pyrans, provided that the products exhibit sufficient stability. Thus the thermolyses of 2-ethoxy- and 2-acetoxy-2,3-dihydro-*4H*-pyrans **265** undoubtedly led to unsubstituted *4H*-pyran (**5**),^{18,293} but only when R = Ac was it possible to separate the unstable product **5** from reaction mixtures by GLC in 15 to 30% yields.¹⁸ Analogously, 25% of air-sensitive 2-methoxy-*2H*-pyran (**267**) was obtained on heating **266** with aluminum tri-butoxide under a nitrogen atmosphere at 155°C.³³ A general technique for the preparation of condensed *4H*-pyrans from their 2-ethoxy-2,3-dihydro derivatives is based on the elimination of ethanol in the presence of *p*-toluenesulfonic acid or polyphosphoric acid at decreased pressures²⁹³ to give



²⁹² F. M. Dean, R. A. Eade, R. A. Moubasher, and A. Robertson, *Nature (London)* **179**, 366 (1957).

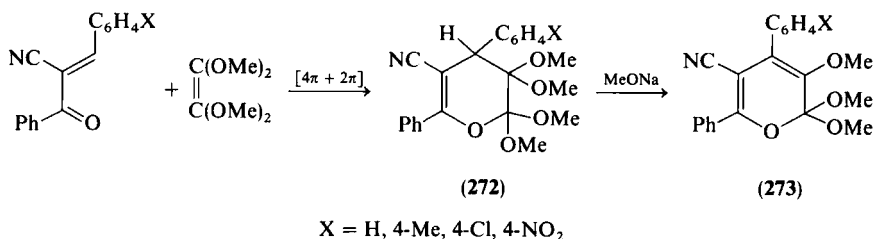
²⁹³ V. M. Thuy, C. Normant-Chefnay, P. Maitee, and H. Petit, *Bull. Soc. Chim. Fr.*, 241 (1975).

condensed *4H*-pyrans in the following yields: **268** (45 to 65%), **269** (29%), **270** (58%), and **153** (60%). The method failed for the decomposition of non-condensed starting compounds **271** due to the polymerization of the products.²⁹³



A dihydropyran may be an unstable intermediate and may be rapidly transformed to a pyran. Thus when 1-methoxy-1,3-butadiene underwent cycloaddition to ethyl pyruvate, a 45% yield of *2H*-pyran **258b** was isolated; dihydro **257b**¹⁹⁵ was an intermediate.

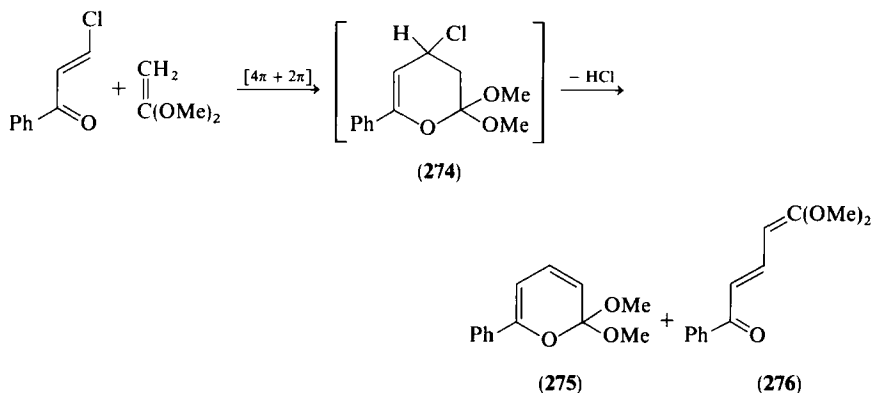
Similarly, complex *2H*-pyran derivatives **273** were formed in 73 to 92% yields by elimination of methanol from 2,2,3,3-tetramethoxy intermediates **272** with sodium methanolate.²⁹⁴



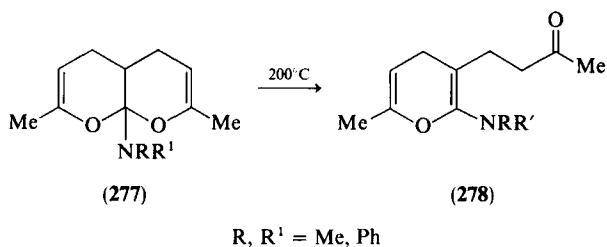
2,2-Dimethoxy-3,4-dihydro-*2H*-pyran **274** was formed by the cycloaddition of chloromethyleneacetophenone to 1,1-dimethoxyethene followed by a spontaneous dehydrochlorination to *2H*-pyran **275** together with isomeric dienone **276** on heating at 95°C.²⁹⁵

²⁹⁴ P. H. J. Ooms, L. P. C. Delbressine, H. W. Scheeren, and R. J. F. Nivard, *J.C.S. Perkin I*, 1533 (1976).

²⁹⁵ A. Bélanger and P. Brassard, *Can. J. Chem.* **53**, 201 (1975).

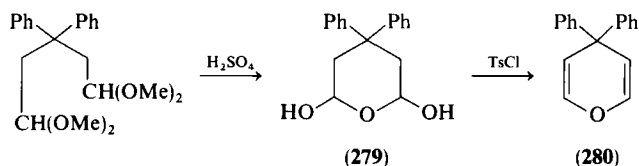


An interesting ring-opening elimination reaction of bicyclic derivative **277** to monocyclic *4H*-pyran **278** takes place on thermolysis.¹⁴⁰



2. Elimination Reactions of Tetrahydropyrans

The double dehydrochlorination of 2,6-dichloro-1-oxacyclohexanes to *4H*-pyran (**5**) and its 4-methyl homolog^{7,9,19,57} has been mentioned in Section III,A. Another double dehydration occurs in the synthesis of 4,4-diphenyl-*4H*-pyran **280** in 80% yield by the action of tosyl chloride on 2,6-dihydroxytetrahydropyran **279** in pyridine.²⁹⁶ Another diphenyl derivative (mp 56°C) was reported to be isolable from a mixture after the reaction of cellulose with benzene in sulfuric acid.²⁹⁷



²⁹⁶ D. Gravel, C. Leboeuf, and S. Caron, *Can. J. Chem.* **55**, 2373 (1977).

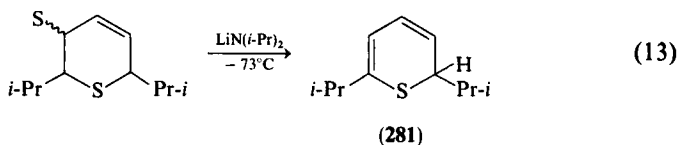
²⁹⁷ A. A. Nikolskii, *J. Gen. Chem. USSR (Engl. Transl.)* **6**, 1151 (1936) [*CA* **31**, 1027 (1937)].

3,5-Dihydro-2-hydroxymethyl-4*H*-pyran and/or its tautomeric forms are among the pyrolysis products of cellulose.²⁹⁸

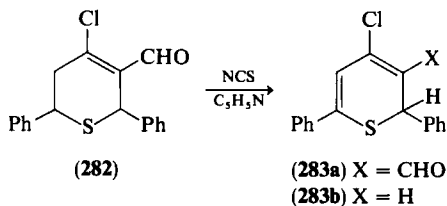
E. THIOPYRANS FROM DIHYDROTHIOPYRANS AND TETRAHYDROTHIOPYRANS

The preparation of thiopyrans from dihydro- and tetrahydrothiopyrans, based on elimination reactions, appears to be effective especially for the preparation of different 2*H*-thiopyrans and corresponding *S,S*-dioxides.

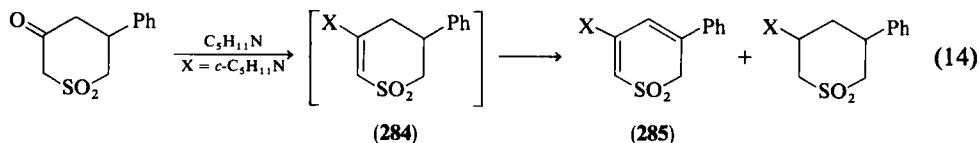
The standard elimination procedure for mesylates was successfully applied to the synthesis of 2,6-diisopropyl-2*H*-thiopyran (**281**), prepared in 82% yield according to Eq. (13).²⁸⁵



A dehydrogenation accompanied by decarbonylation occurred when *N*-chlorosuccinimide was allowed to react with dihydrothiopyran aldehyde **282** in pyridine, and hence a mixture of 2*H*-thiopyrans **283a** and **283b** was formed.²⁹⁹



Dihydrothiopyran dioxide **284** disproportionates to a mixture of 2*H*-thiopyran **285** and its tetrahydro derivative **286** in the presence of piperidine,³⁰⁰ as shown in Eq. (14).

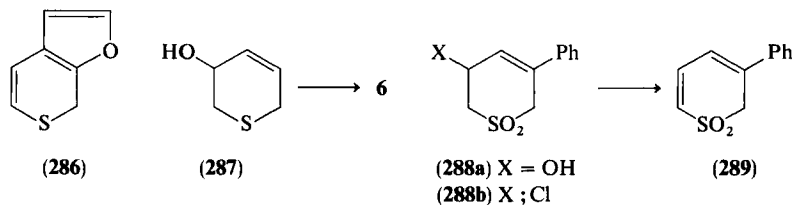


²⁹⁸ F. Shafizadeh, R. H. Turneaux, T. J. Stevenson, and T. G. Cochran, *Carbohydrate Res.* **67**, 433 (1978).

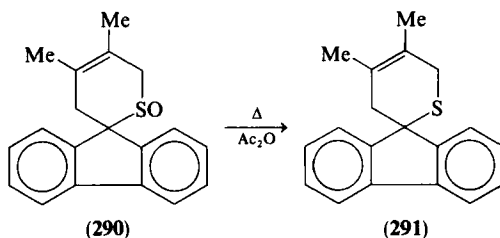
²⁹⁹ C. H. Chen and G. A. Reynolds, *J. Org. Chem.* **44**, 3144 (1979).

³⁰⁰ G. Pagani, *Gazz. Chim. Ital.* **97**, 1518 (1967).

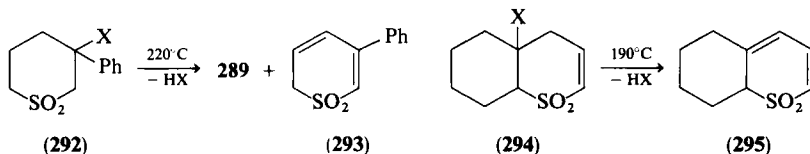
Dehydration procedures have led to 2*H*-thiopyrans. Thus unsubstituted parent heterocycle **6** was prepared by the dehydration of hydroxy derivative **287** with potassium hydrogen sulfate.²⁰ The same procedure applied to a mixture of isomeric hydroxy 2-methyl-5,6-dihydro-2*H*-thiopyrans and 3,5-dihydroxy-2,4,5,6-tetrahydrothiopyran gives all the corresponding thiopyrans.⁹¹ 3-Phenylthiopyran dioxide **289** was obtained after the dehydration of hydroxy derivative **288a** with phosphoric acid at elevated temperatures.^{300,301} The same approach was explored for the preparation of furano-2*H*-thiopyran **14**.⁴²



An unusual dehydration reaction was observed in the case of sulfoxide **290**, which yielded 99% of 2*H*-thiopyran **291** on heating with acetic anhydride.³⁰²



A very fruitful approach to 2*H*-thiopyrans such as **111** was shown to be the deamination of 4-amino-2,3-dihydro-4*H*-thiopyrans such as **110**,^{53,153-155,157,159} (see Section III,G). The reaction may be extended to thiopyran dioxides as illustrated by the rapid vacuum thermolysis of *N*-morpholinyl derivatives **292** and **294**, affording 74% of a 7:3 mixture of **289** and **293** or 84% of **295**.³⁰³

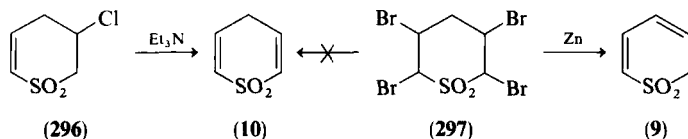


³⁰¹ S. Rossi and G. Pagani, *Tetrahedron Lett.*, 2129 (1966).

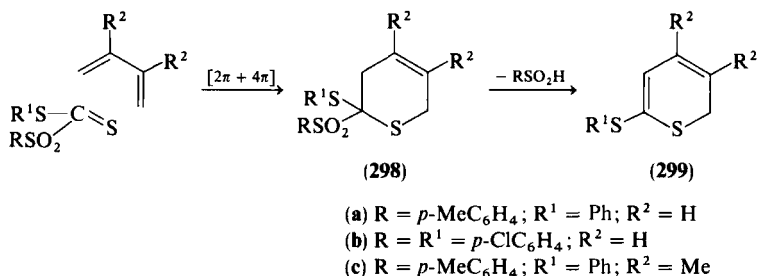
³⁰² K. Praefcke and C. Weichsel, *Tetrahedron Lett.*, 2229 (1976).

³⁰³ S. Bradamante, S. Maiorana, and G. Pagani, *J.C.S. Perkin I*, 282 (1972).

Dehydrochlorination with diethylaniline was explored for the preparation of 4*H*-thiopyran (7) and its 3-methyl and 4-isopropyl derivatives from 2,6-dichloro-1-thiacyclohexanes^{7,19,24,303a} (see Section III,B). Chlorosulfone **288b** undergoes dehydrochlorination to **289**.³⁰⁰ Chloro derivative **296** was similarly dehydrochlorinated with triethylamine to 4*H*-thiopyran sulfoxide (10).²⁷ On the other hand, debromination of 2,3,5,6-tetrabromo derivative **297** with zinc surprisingly gives 2*H*-dioxide **9** instead of expected **10**,⁴⁶ probably due to an isomerization of **10** with ZnBr₂.



The elimination of the RSO₂ group may also be used in the synthesis of 6-arylthio-2*H*-thiopyrans **299a-c** via intermediates **298a-c**; elimination takes place by means of bases.³⁰⁴



F. SELENOPYRANS FROM TETRAHYDROSELENOPYRANS

As mentioned in Section III,C, 4*H*-selenopyran (**8**) and its 4-methyl derivative **60** were prepared by the dehydrochlorination of 2,6-dichloro-1-selenacyclohexanes **59** with triethylaniline.^{7,90}

G. PYRANS FROM PYRONES, PYRANTHIONES, AND DIHYDROPYRONES

The approach consists of electrophilic or nucleophilic addition of suitable reagents to the title heterocycles. The formation of mainly 2*H*-pyrans has been observed after the additions to 2- as well as to 4-pyrones. In general,

^{303a} I. Degani and C. Vincenzi, *Boll. Sci. Fac. Chim. Ind. Bologna* **25**, 77 (1967) [*CA* **68**, 114369 (1968)].

³⁰⁴ J. A. Boerma, N. H. Nilsson, and A. Senning, *Tetrahedron* **30**, 2735 (1974).

pyrones usually react with one or two equivalents of a reagent, whereas dihydropyrones react with only one.

An electrophilic attack of an alkylating agent usually occurs on negatively charged endocyclic oxygen atoms, whereas nucleophiles attack the substrates at positively charged positions of the heterocycle, e.g., predominantly on carbons of the carbonyl group. The mechanism of the multistep processes is best understood in the reaction of pyrones and dihydropyrones with Grignard reagents.^{305,306} The use of pyrones for the preparation of pyrans is limited by the stability of the products; only pyrones with favorable substitution patterns are of interest. In some cases the formation of 2*H*-pyrans is accompanied by byproducts.

1. Reactions of 2-Pyrones with Nucleophiles

Except in one case, all reactions of 2-pyrones with nucleophiles use alkyl or aryl magnesium halides.

The reaction of 2-pyrones with Grignard reagents is complex³⁰⁵⁻³¹⁰; the mechanism may be rationalized as in Scheme 14 and includes a knowledge of valence-bond isomerism of 2*H*-pyrans (see Section V,E).

Support for the mechanism comes from various sources including NMR spectroscopy using ¹³C labeled MeMgI,³⁰⁹ methylation of primary MeMgI adducts with methyl iodide,³⁰⁶ isolation of intermediates of type **301** and **304**^{163,305,308,309,311-313} or of type **303** and **306**,^{163,305,308,309,314,315} respectively, as well as identification of both expected 2*H*-pyrans like **302** and **305**.^{312,313} Earlier reports^{311,316} ignoring the possibility of the first reaction path **300** → **302** have been later found to assign incorrect structures to products³¹² or have led to irreproducible results.¹⁹⁰

The many-step character of the process shown in Scheme 14 limits the achievement of preparatively useful yields of 2*H*-pyrans **302** and **305**; as a rule, the formation of ketols **303** and **306** and/or dihydropyranols **301** and **304** occurs. The negative effect of the competition of the two reaction paths,

³⁰⁵ M. Trollet, R. Longeray, and J. Dreux, *Tetrahedron* **30**, 163 (1974).

³⁰⁶ P. Lhoste, M. Moreau, J. C. Duplan, and J. Dreux, *C.R. Acad. Sci.* **286**, 269 (1978).

³⁰⁷ G. Köbrich and D. Wunder, *Justus Liebigs Ann. Chem.* **654**, 131 (1962).

³⁰⁸ J. P. Montillier and J. Dreux, *C.R. Acad. Sci.* **264**, 891 (1967).

³⁰⁹ J. P. Shirmann and J. Dreux, *Bull. Soc. Chim. Fr.*, 3896 (1967).

³¹⁰ P. Lhoste, M. Moreau, and J. Dreux, *C.R. Acad. Sci., Ser. C* **279**, 801 (1974).

³¹¹ R. Gompper and O. Christmann, *Chem. Ber.* **94**, 1784 (1961).

³¹² P. Rouillier and J. Dreux, *C.R. Acad. Sci.* **258**, 5228 (1964).

³¹³ P. Rouillier, D. Gagnaire, and J. Dreux, *Bull. Soc. Chim. Fr.*, 689 (1966).

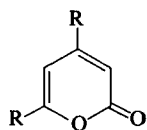
³¹⁴ J. P. Shirmann and J. Dreux, *C.R. Acad. Sci., Ser. C* **262**, 652 (1966).

³¹⁵ M. Trollet, J. Royer, R. Longeray, and J. Dreux, *Tetrahedron* **30**, 173 (1974).

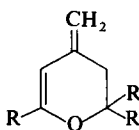
³¹⁶ R. Gompper and O. Christmann, *Angew. Chem.* **71**, 32 (1959).

300 → **302** and **300** → **305**, on the yields of the products may be, however, eliminated for substrates **300** ($R^2 = R^4$) if the group R in a reagent is the same as R^1 .

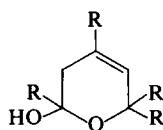
The best results were achieved for 2,4-disubstituted **300** ($R^2 = R^4 = H$) because of the general stability of 2,2,4,6-tetrasubstituted 2*H*-pyrans and the favorable cyclization of the corresponding ketols, e.g., **303** → **301** and **306** → **304**, respectively. Thus, 2,4-dimethyl-2-pyrone **307a** reacted with MeMgI via intermediate **309a**^{312,313} to give 2,2,4,6-tetramethyl-2*H*-pyran (**176**)^{190,309-314,316} accompanied by its isomer **308a**,^{190,310,312} whereas the reaction with PhMgBr led to less clear results.³⁰⁷ Similarly, 2,2,4,6-tetraphenyl-2*H*-pyran **310a** was obtained from **307b** and PhMgBr by dehydration of intermediates **309b**, whereas the use of MeMgI resulted in a mixture 75% dihydropyranol **312** and 25% 2*H*-pyran **310b**.^{163,308} The structure of analogously prepared **310c**^{311,316} should be checked, however.³¹²



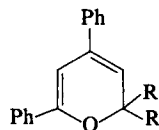
(**307a**) R = Me
(**307b**) R = Ph



(**308a**) R = Me
(**308b**) R = Et

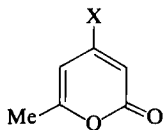


(**309a**) R = Me
(**309b**) R = Ph

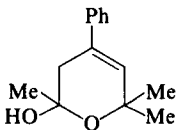


(**310a**) R = Ph
(**310b**) R = Me
(**310c**) R = Pr, Bc

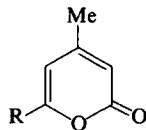
An additional nucleophilic substitution of 4-chloro and 4-methoxy groups with MeMgI affording **176** and **308a** occurred when 2-pyrones **311** were used instead of **307**.³⁰⁹ As expected, 2-substituted 4-methyl-2-pyrones **313** gave with reagents RMgX 2*H*-pyrans **314a**³⁰⁹ and **314b**,^{163,308} and eventually their mixture with **308b**.³⁰⁹



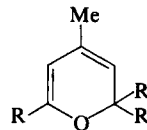
(**311**) X = MeO, Cl



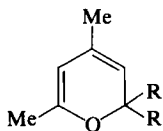
(**312**)



(**313**) R = Et, Ph

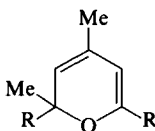


(**314a**) R = Et
(**314b**) R = Ph

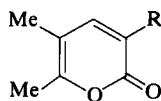


(**315a**) R = Et

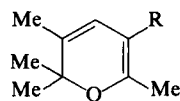
(**315b**) R = Pr, Bu, *n*-C₈H₁₇,
o-, *p*-tolyl, *i*-PrC₆H₅



(**316**)
(**184**) R = Et



(**317**) R = Me, Ph

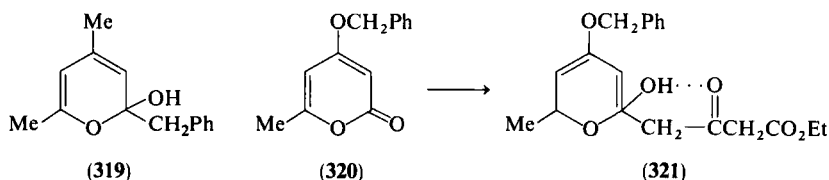


(**318**) R = Me, Ph

Two isomeric 2*H*-pyrans of type **302** and **305** could arise by the reaction of **307a** with RMgX where R $\neq$ Me. In fact, only in the case of **307a** and EtMgBr were both isomers **184** (R = Et) and **315** isolated.^{312,313} The use of PhMgBr resulted in the formation of isomer **316** only.^{312,313} In this connection a reinvestigation of the earlier report^{311,316} on the preparation of 2*H*-pyrans **315b** from **307b** and corresponding Grignard reagents would be desirable.

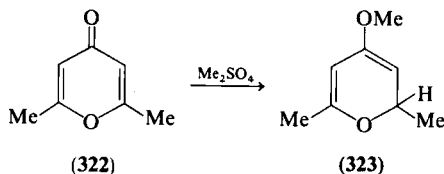
The reactions of 3,5,6-trisubstituted 2-pyrones **317** with MeMgI lead to mixtures containing about 13% 2*H*-pyrans **318**.³⁰⁵

The products of the addition of one molecule of a nucleophile to a 2-pyrone sometimes were trapped. Thus the reaction of **307a** with PhCH₂MgBr was reported to give hemiacetal **319** after hydrolysis of the reaction mixture.³¹¹ Similarly, a nucleophilic reagent obtained from ethyl acetoacetate by the successive action of sodium hydride in THF and BuLi in hexane reacts with **320** to afford hemiacetal **321** in 20% yield.³¹⁷



2. Reactions of 4-Pyrones with Alkylating Agents

2,6-Dimethyl-4-pyrone (**322**) was reported to react with dimethyl sulfate at 50°C to provide up to 85% of syrupy 2,6-dimethyl-4-methoxy-2*H*-pyran (**323**),^{318,319} but proof for structure **323** is lacking.



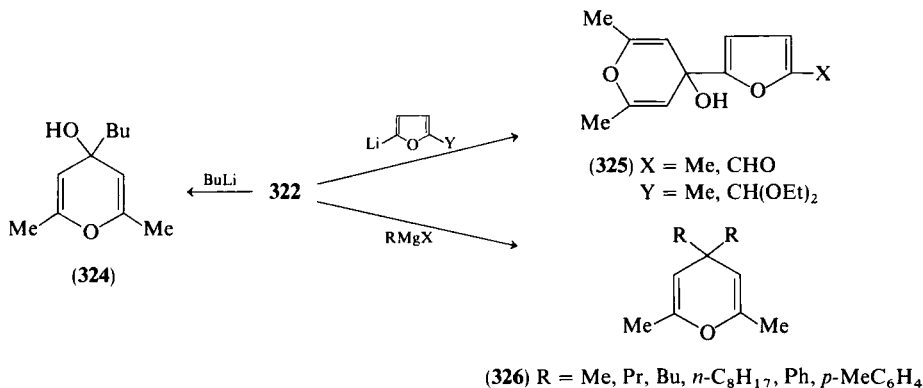
³¹⁷ H. Stockinger and U. Schidt, *Justus Liebigs Ann. Chem.*, 1617 (1976).

³¹⁸ A. Baeyer, *Ber. Dtsch. Chem. Ges.* **43**, 2337 (1910).

³¹⁹ F. Benington, R. D. Morin, and R. J. Bradley, *J. Heterocycl. Chem.* **13**, 749 (1976).

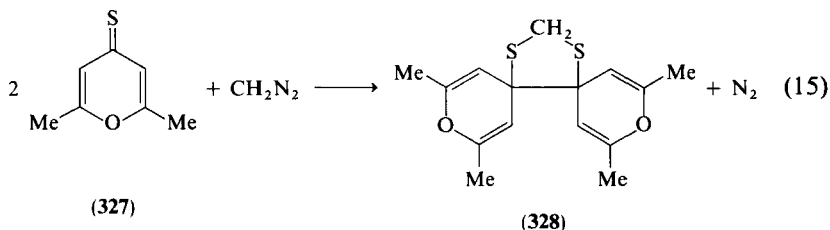
3. Reactions of 4-Pyrones and 4-Pyranthiones with Nucleophiles

As shown in Scheme 15, 4-substituted 4-hydroxy-2,6-dimethyl-4*H*-pyrans **324** and **325** were obtained by reaction of 4-pyrone **322** with BuLi³²⁰ or substituted furyllithium reagents,³²¹ respectively. 4,4-Disubstituted 2,6-dimethyl-4*H*-pyrans **326** were prepared by the reaction of a threefold excess of the corresponding Grignard reagents RMgX with 4-pyrone **322**.^{311,316}



SCHEME 15

Ultraviolet spectroscopic evidence was reported for the 4,4'-dimeric 4*H*-pyran adduct **328** from 2,6-diphenyl-4-pyranthione (**327**),³²² as shown in Eq. (15).



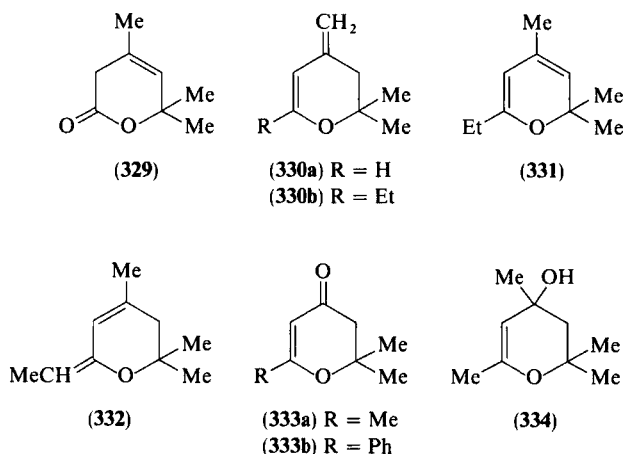
³²⁰ M. Yamamoto and N. Sugiyama, *Bull. Chem. Soc. Jpn.* **48**, 508 (1975).

³²¹ A. V. Koblik, T. I. Polyakova, B. A. Tertov, B. V. Mezhev, and G. N. Dorofeenko, *Zh. Org. Khim.* **10**, 2153 (1975).

³²² A. Schönberg, M. Elkaschef, M. Nosseir, and M. M. Sidky, *J. Am. Chem. Soc.* **80**, 6312 (1958).

4. Reactions of Dihydropyrones with Nucleophiles

Dihydropyrones may react with lithium aluminum hydride or with Grignard reagents to provide 2*H*-pyrans via corresponding dihydropyransols. Thus 4,6,6-trimethyl-3,6-dihydro-2-pyrone (**329**) was reduced with LiAlH_4 to hemiacetal **259**, which was dehydrated to 2,2,4-trimethyl-2*H*-pyran (**260**)²⁸⁹ or to a 1:1 mixture of **260** and **330**.³²³ Similarly, **329** with MeMgI gave via dihydropyranol **309a** a 1:1 mixture of 2,2,4,6-tetramethyl-2*H*-pyran (**176**) and its isomer **308a** with diol $\text{Me}_2\text{C}(\text{OH})\text{CH}=\text{C}(\text{Me})\text{CH}_2\text{CMe}_2\text{OH}$, depending on the amount of MeMgI used in excess.^{289,323} A more complex mixture containing 45% of 2*H*-pyran **331**, 16% of **330b**, 21% of **332**, and 18% of diol $\text{Me}_2(\text{OH})\text{CH}=\text{C}(\text{Me})\text{CH}_2\text{C}(\text{Et})_2\text{OH}$ resulted when EtMgBr was used instead of MeMgI .²⁸⁹ The individual components were separable by means of GLC.



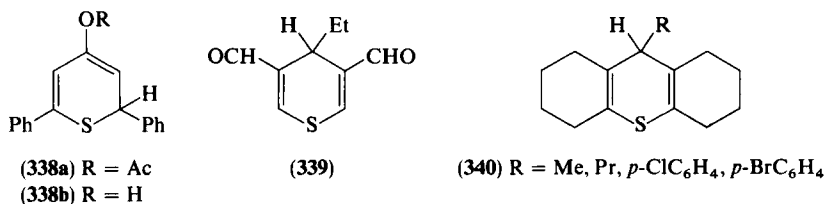
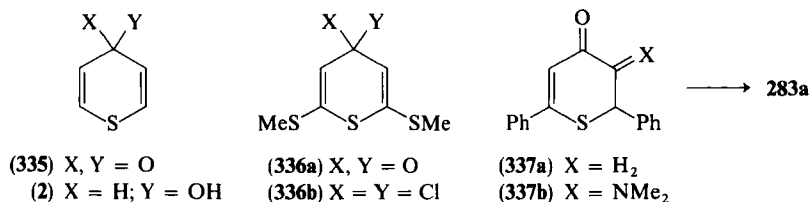
An alternative approach to 2,2,4,6-tetrasubstituted 2*H*-pyrans is the Grignard reaction of 2,3-dihydro-4-pyrones.³²⁴ Thus a mixture of **176** and **308a** was obtained by heating 4-hydroxy intermediate **334**, prepared by the reaction of 2,2,6-trimethyl-2,3-dihydro-4-pyrone (**333a**) with MeMgI .³²⁴ Analogously, both 4-pyrones **333a,b** with PhMgBr afforded 2,2,6-trimethyl-4-phenyl-2*H*-pyran (**182b**) and 2,2-dimethyl-4,6-diphenyl-2*H*-pyran (**310b**) in mixtures with the corresponding ketols $\text{Me}_2\text{C}=\text{CHCOCH}_2\text{C}(\text{OH})\text{Ph}(\text{Me})$ and $\text{Me}_2\text{C}=\text{CHCOCH}_2\text{CPh}_2\text{OH}$, respectively.

³²³ A. Duperrier and J. Dreux, *C.R. Acad. Sci., Ser. C* **269**, 34 (1969).

³²⁴ A. Duperrier, M. Moreau, S. Gelin, and J. Dreux, *Bull. Soc. Chim. Fr.*, 2207 (1974).

H. THIOPYRANS FROM THIOPYRONES

Only rare reports of the conversion of thiopyrones to thiopyrans are available. Unsubstituted 4-thiopyrone (**335**) was reduced with aluminum hydride to the corresponding 4-thiopyranol (**2**).^{5,90} A precipitate formed during the reaction of thiopyrone **336a** with thionyl chloride was regarded to be a 4*H*-thiopyran derivative (**336b**).³²⁵



I. THIOPYRANS FROM PYRANS

The conversion of pyrans to thiopyrans can be accomplished only in the 4*H* series by the reaction of a 4*H*-pyran with hydrogen sulfide or P₄S₁₀. The first procedure was successfully used for the preparation of 4*H*-thiopyrans **22**,³²⁶ **45**,³²⁷ **47**,³²⁷ **49** ($n = 2$),^{60,326} **55**,³²⁷ and **339**.^{60,326} The second approach applied to 4*H*-pyran **85b** provided 20% of 4*H*-thiopyran 3,5-dicarboxaldehyde **340**.⁸⁵

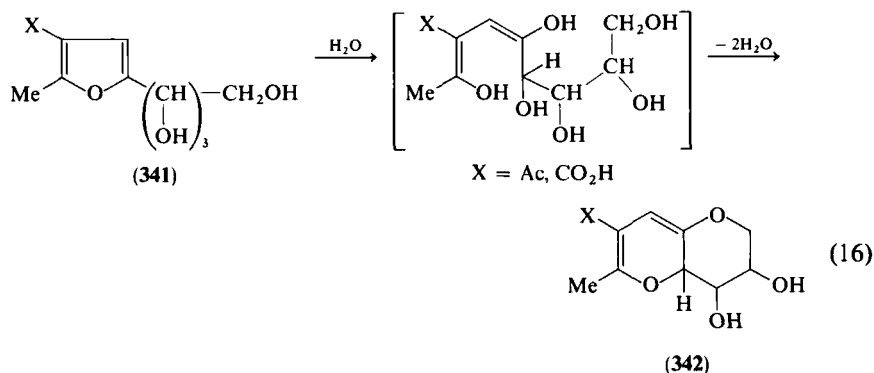
³²⁵ B. Eistert and T. J. Arackal, *Chem. Ber.* **108**, 2397 (1975).

³²⁶ V. G. Kharchenko, N. M. Yartseva, N. I. Kozhevnikova, and A. A. Rassudova, *Zh. Org. Khim.* **10**, 99 (1974).

³²⁷ V. G. Kharchenko and S. N. Chalaya, *Zh. Org. Khim.* **11**, 1540 (1975).

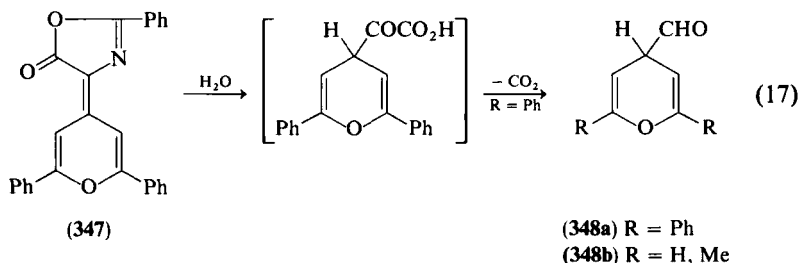
J. PYRANS FROM OTHER HETEROCYCLES

2*H*-Pyrans **342** were prepared from furan derivatives **241**, readily accessible by the reaction of glucose with β -dicarbonyl compounds.³²⁸ The reaction was accomplished under acidic conditions and probably proceeds according to Eq. (16).



Some 4*H*-pyrans may also be prepared by addition reactions of appropriate 2- or 4-pyranylidene compounds. Thus butyl-, methyl-, or phenyllithium were found to add to monosubstituted 1,2-benzoxalenes **343** to give adducts **344**, which were alkylated, acylated, or hydrolyzed to 4*H*-pyrans **345** or **346**, respectively.^{329,330} (Scheme 16).

4-Pyranylidene oxazolone **347** gives 95% of 2,6-diphenyl-4-formyl-4*H*-pyran (**348a**) by successive hydrolysis with sodium hydroxide and hydrochloric acid, as shown in Eq. (17).^{331,332} The already mentioned, trans-



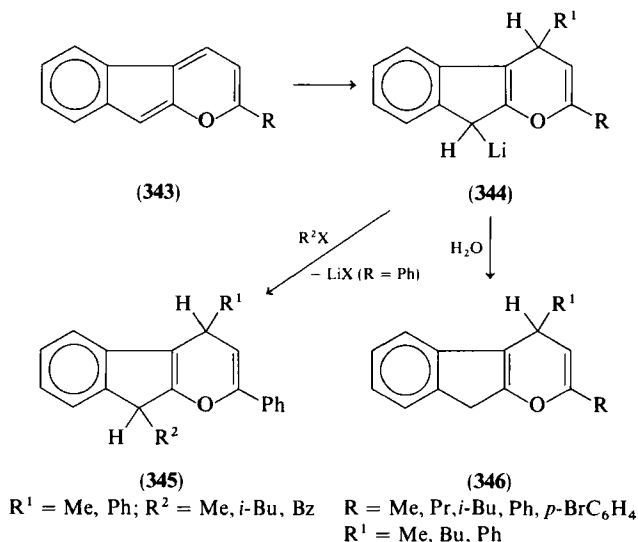
³²⁸ J. K. N. Jones, *J. Chem. Soc.*, 116 (1945).

³²⁹ W. Schroth and G. Fischer, *Z. Chem.* **4**, 27 (1964).

³³⁰ G. W. Fischer and W. Schroth, *Tetrahedron* **32**, 2225 (1976).

³³¹ S. V. Krivun, *Izv. Akad. Nauk SSSR, Ser. B* **36**, 717 (1974).

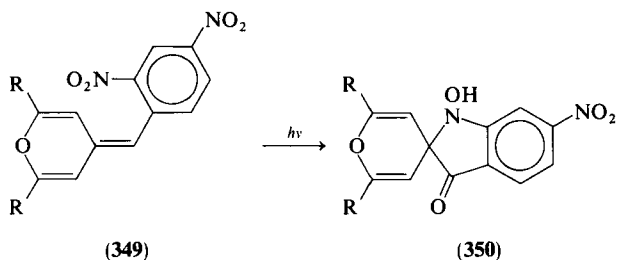
³³² S. V. Krivun, *Khim. Geterotsikl. Soedin.*, 757 (1976).



SCHEME 16

formation of pyrylium salts **219** to 4*H*-pyran-4-carboxaldehydes **220** with hippuric acid also involved oxazolone intermediates like **347**.^{265a}

2,4-Dinitrobenzylidene derivatives **349** are converted quantitatively to spirocyclic 4*H*-pyrans **350** by UV irradiation.³³³



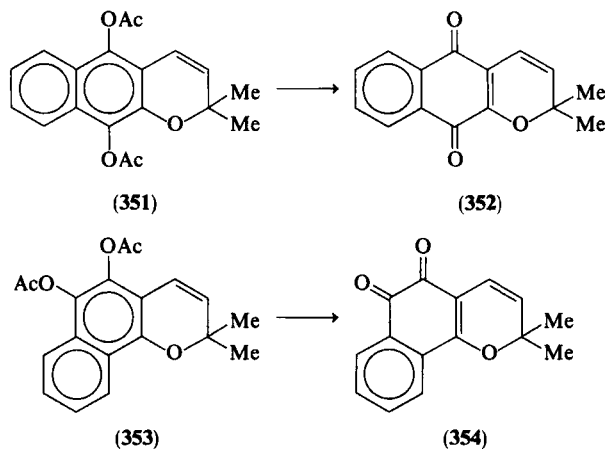
Tricyclic 2*H*-pyrans **352** and **354** were prepared using the reactions of naphthopyrans **351** and **353** with ethylmagnesium bromide followed by hydrolysis and oxidation.^{334,335}

Compound **352** was also obtained by dehydrogenation of an appropriate dihydro derivative with dichlorodicyanobenzoquinone.³³⁵

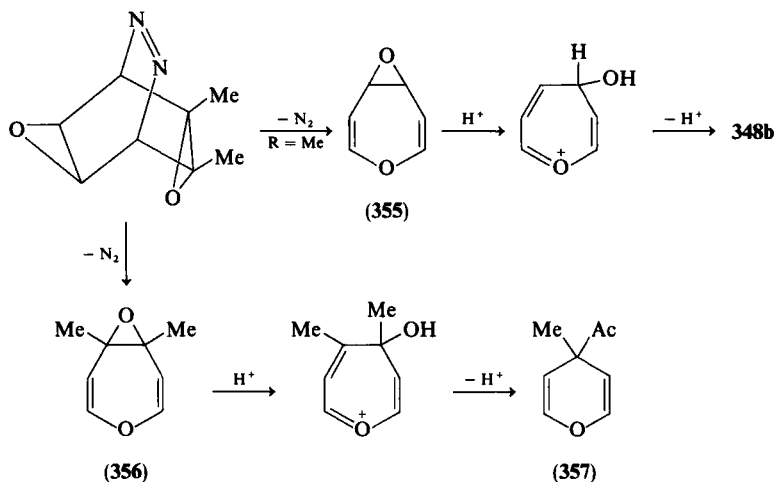
³³³ J. A. Van Allan, S. Farid, G. A. Reynolds, and S. C. Chang, *J. Org. Chem.* **38**, 2834 (1973).

³³⁴ S. C. Hooker, *J. Am. Chem. Soc.* **58**, 1190 (1936).

³³⁵ A. R. Burnet and R. H. Thompson, *J. Chem. Soc. C*, 1261 (1967).



sym-Oxepine oxides **355** and **356** generated in various ways isomerize with methanesulfonic acid to give 4*H*-pyran derivatives **248b** and **357**, as shown in Scheme 17.^{336–339}



SCHEME 17

Pyridine derivative **358** underwent a hydrolysis with sulfuric acid to the condensed 4*H*-pyran **86** ($R = R^1 = H$, $R^2 = 4-NO_2C_6H_4$).⁶⁴ The similar 4*H*-

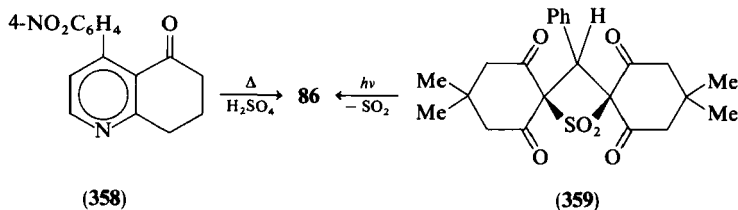
³³⁶ H. Klein and W. Grimme, *Angew. Chem.* **86**, 742 (1974).

³³⁷ W. H. Rastetter, *J. Am. Chem. Soc.* **97**, 210 (1975).

³³⁸ W. H. Rastetter, *J. Am. Chem. Soc.* **98**, 6350 (1976).

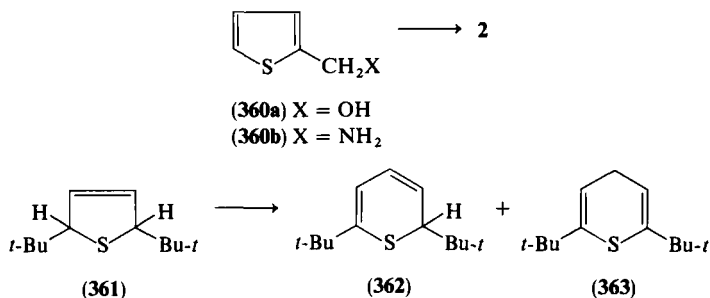
³³⁹ W. H. Rastetter and T. J. Richard, *Tetrahedron Lett.*, 2995 (1978).

pyran **86** ($R = R^1 = \text{Me}$, $R^2 = \text{Ph}$) was obtained by the photochemically induced extrusion of SO_2 from spirocyclic thietane dioxide **359**.³⁴⁰



K. THIOPYRANS FROM OTHER HETEROCYCLES

2-Thienylmethanol (**360a**) underwent allylic rearrangement to 4-hydroxy-2*H*-pyran (**2**) with oxalic acid at 20°C for 6 days.³⁴¹ 2-Thienylmethylamine (**360b**) with nitrous acid (Demyanov reaction) gave a mixture of **360a** and **2**.³ An 86% yield of a mixture of 2,6-di-*tert*-butyl-2*H*- and 4*H*-thiopyrans **362** and **363** was obtained when 2,5-dihydrothiophene ketone **361** (readily accessible by Birch reduction of 2-pivaloyl-5-*tert*-butylthiophene) was reduced with zinc and sodium hydroxide in the presence of trimethylsilyl chloride.²⁸⁶



As mentioned in Section IV,B,2, thiabenzene can rearrange to 4*H*-thiopyrans^{275,277,280,342} or mixtures of both 2*H* and 4*H* isomers^{39,277,280-282} thermally,^{275,277,280,281,342} with acids,²⁸¹ or photochemically.^{281,282} A detailed discussion concerning the changes in the structure of the starting thiabenzene during their interaction with phenyllithium is available.³⁴³

The rearrangement of dihydropyran sulfoxide **290** to 2*H*-thiopyran derivative **291**³⁰² was mentioned in Section IV,E. An unusual dehydrochlorination of 3-thiabicyclo[3.1.0]hexane *S,S*-dioxides **364** affording 2*H*-

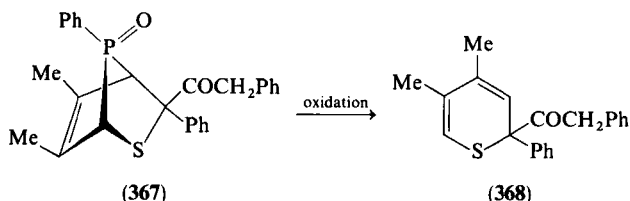
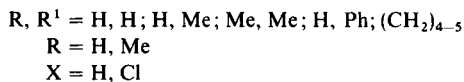
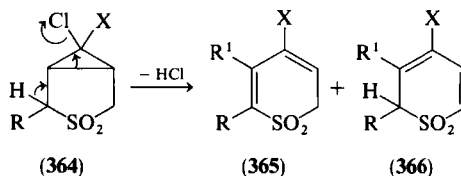
³⁴⁰ S. Ito and J. Mori, *Bull. Chem. Soc. Jpn.* **51**, 3403 (1978).

³⁴¹ V. S. Egorova, *Zh. Obshch. Khim.* **30**, 107 (1960).

³⁴² C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Am. Chem. Soc.* **85**, 2278 (1963).

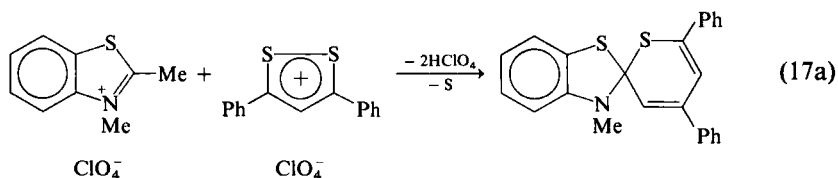
³⁴³ C. C. Price and J. Follweiler, *Heterocycles* **11**, 219 (1978).

thiopyran dioxides **365** and/or **366** was observed to proceed with heat or, more effectively, with lithium diisopropylamide.³⁴⁴



The oxidation of 8-phospha-2-thiabicyclo[3.2.1]octane *P*-oxide **367** with *m*-chloroperbenzoic acid yielded 47% of 2*H*-pyran derivative **368**.³⁴⁵

Self-condensation of some dithiolyl perchlorates in the presence of base proceeds via spirothiopyrans.^{345a} Similarly, the reaction of 2,3-dimethylbenzothiazolium and 3,5-diphenyl-1,2-dithiolium perchlorates led to 90% of a 2*H*-thiopyran product, as shown in Eq. (17a).



L. PYRANS FROM OTHER CYCLIC PRECURSORS

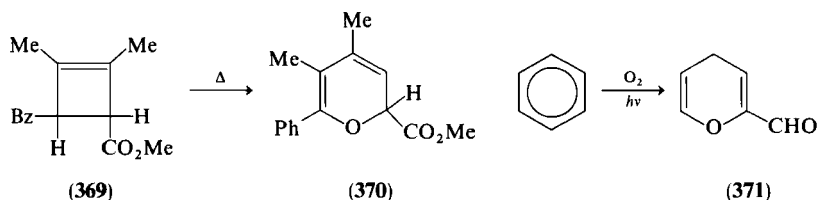
Heating cyclobutenes **369** in toluene led to equilibrium mixtures of 2*H*-pyran **370** and stereoisomeric keto esters $\text{MeO}_2\text{CCH}=\text{C}(\text{Me})-\text{C}(\text{Me})=\text{CHBz}$.³⁴⁶

³⁴⁴ Y. Gaoni, *J. Org. Chem.* **46**, 4502 (1981).

³⁴⁵ Y. Kashman and O. Awerbouch, *Tetrahedron* **31**, 53 (1975).

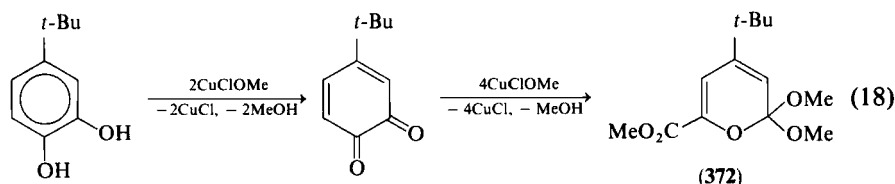
^{345a} E. I. Brown, D. Leaver, and D. M. McKinnon, *J.C.S. Perkin Trans. I*, 1511 (1977).

³⁴⁶ G. Maier and M. Wiessler, *Tetrahedron Lett.*, 4987 (1969).



Oxidation of benzene in its first excited singlet state gave labile 2-formyl-4H-pyran (371).^{347,348} The mechanism of the process was studied in detail,^{347,349} and a high degree of conversion was demonstrated.³⁴⁹

An interesting oxidative transformation of 4-*tert*-butylcatechol or of 4-*tert*-butyl-1,2-benzoquinone with copper(II) complex $(C_5H_5N)_nCuClOMe$ to 2H-pyran 372, shown in Eq. (18), was discovered in connection with the investigation of the nonenzymatic oxidation of aromatics.³⁵⁰



V. Reactions

A. OXIDATION

Pyrans and thiopyrans with oxidizing agents in acidic medium, as a rule, lead to aromatization to the corresponding pyrylium and thiopyrylium salts. Oxidations proceeding in a neutral or basic medium tend to form alkylidene-pyrans and thiopyrans or products of ring rearrangements. In addition, thiopyrans typically give their *S*-oxides with hydrogen peroxide.

Equilibrium aromatizations of 4H-pyran (5), 4H-thiopyran (7), and 4H-selenopyran (8) with appropriate pyrylium ions were explored for the estimation of relative stabilities of the latter.³⁵¹

³⁴⁷ G. Farenhorst, *Tetrahedron Lett.*, 4835 (1968).

³⁴⁸ M. Luria and G. Stein, *J. Phys. Chem.* **76**, 165 (1972).

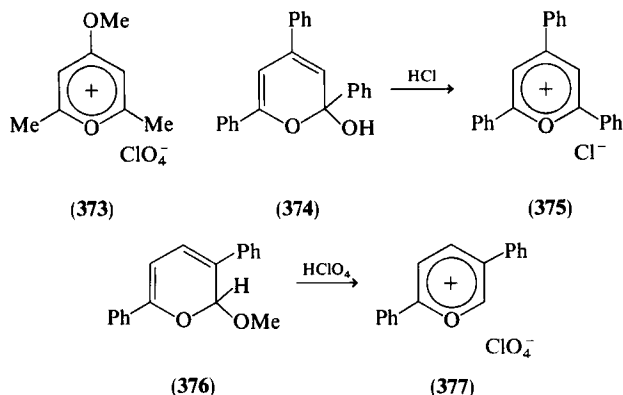
³⁴⁹ M. Luria and G. Stein, *Chem. Commun.*, 1651 (1970).

³⁵⁰ M. M. Rogic and T. R. Demmin, *J. Am. Chem. Soc.* **100**, 5472 (1978).

³⁵¹ J. Degani, R. Fochi, and C. Vincenzi, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 21 (1965) [*CA* **63**, 8137 (1965)].

1. Aromatization of Pyrans to Pirylium Salts

In contrast to *4H*-pyrans, the *2H*-pyrans have been rarely reported to be aromatized to pyrylium salts. 2,6-Dimethyl-4-methoxy-*2H*-pyran (**323**) was easily converted to the corresponding perchlorate **373** with perchloric acid.^{318,319} A similar oxidation was reported for 2,4,6-triphenyl-*2H*-pyran.²¹⁷ The formation of pyrylium salts **375** and **377** from **374** and hydrogen chloride^{261a} or from **376** and perchloric acid¹⁸¹ are not oxidations.



The aromatization of *4H*-pyrans with oxidizing agents is a more general approach to pyrylium salts. The reagents used are listed in Table VIII.

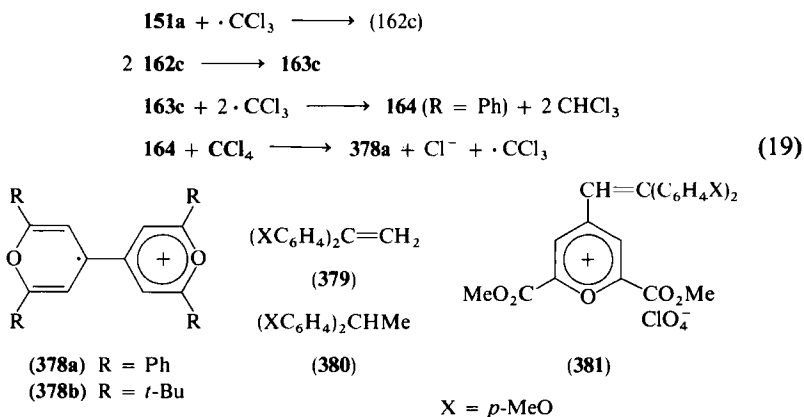
Unsubstituted *4H*-pyran (**5**) as well as its 4-methyl derivative react with trityl perchlorate or with PCl_5 to give pyrylium salts of the **157a** type.^{7,90} The reaction of **5** with hydrogen sulfide in the presence of hydrogen chloride gave

TABLE VIII
AGENTS USED FOR AROMATIZATION OF *4H*-PYRANS TO PYRYLIUM SALTS

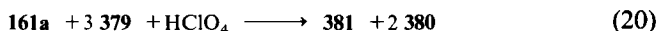
Agent	References	Agent	References
O_2	356	$[\text{2,4-(MeO)}_2\text{C}_6\text{H}_3]_2\text{N}^+ \text{ClO}_4^-$	244
$\text{CCl}_3\cdot$	353	$(p\text{-BrC}_6\text{H}_4)^+ \text{NSnCl}_4^-$	245
HClO_4	52, 215, 234, 244, 251	MeNO_2	355
$\text{Ac}^+ \text{ClO}_4^-$	239, 242, 245	PCl_5	90
$\text{Ph}_3\text{C}^+ \text{ClO}_4^-$	7, 90, 221, 222, 263a, 264, 358	$2,6\text{-(}t\text{-Bu)}_2\text{C}_6\text{H}_3\text{O}\cdot$	357
$\text{CH}_2 = \text{CAR}_2 + \text{H}^+$	354	384	239
$\text{XC}_6\text{H}_4\text{N}_2^+\text{BF}_4^-$	356	$(\text{NC})_2\text{C}(\text{CH} = \text{CH})_2\text{C}(\text{CN})_2$	357
		388	359
		Anodic oxidation	243, 357

analogously thiopyrylium chloride of the **157b** type,³⁵² but the participation of the disproportionation process (see Section V,B) may not be excluded in this case.

2,6-Diphenyl-4*H*-pyran (**151a**: R = Ph) undergoes a free-radical chain process with trichloromethyl radicals generated from carbon tetrachloride, affording pyrylium radical cation **378a**³⁵³ (see Eq. 19).



Another complex transformation of bis-2,6-methoxycarbonyl-4*H*-pyran (**161a**) with 1,1-diarylethenes **379** in the presence of strong acids provides 4-substituted pyrylium salts **381** (Eq. 20).³⁵⁴



The steps of the process have been discussed in detail.³⁵⁴ Bis-2,6-methoxycarbonyl-4*H*-pyrans **161a,b** were converted to the corresponding pyrylium perchlorates **160a,b** by perchloric acid as the oxidizing agent.²¹⁵

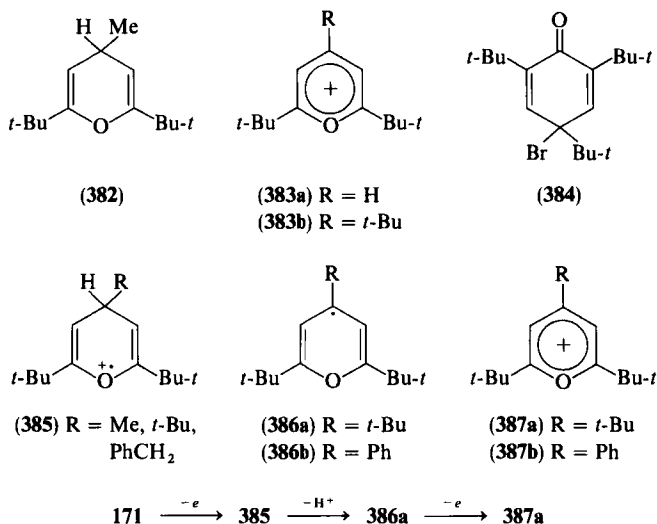
The reaction of 2,4,6-tri-*tert*-butyl-4*H*-pyran (**171**) as well as its 4-methyl analog **382** react with acetyl perchlorate by elimination of the 4-substituent to 2,6-di-*tert*-butylpyrylium (**383a**).²³⁹ Similar eliminations of 4-substituents were observed after the reaction of 4-benzyl-2,4,6-triphenyl-4*H*-pyran (**165**) with perchloric acid as well as of 4-substituted 2,6-diphenyl-4*H*-pyrans **203** and **205a** with hydrogen chloride, affording the perchlorate of **158a**²³⁴ or hydrochloride of **158b**,²³⁶ respectively. Contrary to the unusual behavior, **171** was aromatized to the expected 2,4,6-trisubstituted pyrylium **383b** with

³⁵² V. G. Kharchenko, N. M. Yartseva, M. E. Stankevich, and M. N. Berezhnaya, USSR Patent 400,590 (1973) [CA **80**, 47847 (1974)].

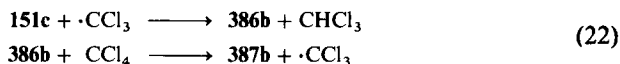
³⁵³ V. B. Panov, M. V. Nekhoroshev, and O. Yu. Okhlobystin, Dokl. Akad. Nauk SSSR **249**, 622 (1979).

³⁵⁴ E. T. Østensen, Acta Chem. Scand., Ser. B **29**, 927 (1975).

bromo derivative **384**²³⁹ or with a nitromethane–aluminum chloride mixture.³⁵⁵ The one-electron mechanism of the reactions given in Eq. (21) was proved on the basis of EPR evidence of **385** and **386**.³⁵⁵



Similar mechanisms were proposed for the aromatization of 2,4,6-triphenyl-4*H*-pyran (**151c**) to **387b** with aryldiazonium tetrafluoroborates,³⁵⁶ with 2,6-di-*tert*-butylphenoxide radical, and tetracyanoquinone dimethide³⁵⁷ on the basis of kinetic and electrochemical experiments. Another free radical chain pathway for the reaction of **151c** with trichloromethyl radical and tetrachloromethane was also postulated³⁵³ (Eq. 22).



Further examples of preparative aromatization of 4*H*-pyrans are the syntheses of 2,4,6-trisubstituted pyrylium salts: **172c** → **388**,²⁴² **389** → **390**,²⁵¹ **391a** → **392a**,^{222,358} **391b** → **392b**,^{263a} and **391c** → **392c**.²⁶⁴

³⁵⁵ O. Yu. Okhlobystin, V. A. Samarskii, M. V. Nekhoroshev, and V. D. Pokhodenko, *Zh. Org. Khim.* **15**, 1110 (1979).

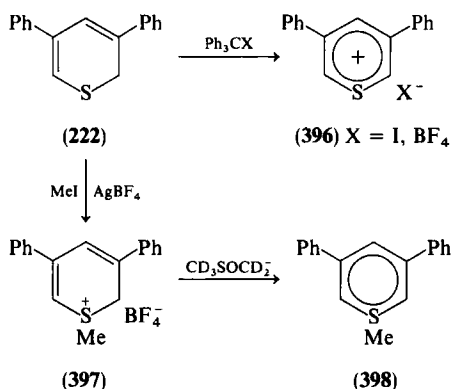
³⁵⁶ A. F. Levit, L. A. Kiprianova, V. I. Bogillo, M. V. Nekhoroshev, V. B. Panov, I. P. Gragerov, and O. Yu. Okhlobystin, *Zh. Org. Khim.* **15**, 1344 (1979).

³⁵⁷ N. T. Berberova, A. A. Bumber, M. V. Nekhoroshev, V. B. Panov, and O. Yu. Okhlobystin, *Dokl. Akad. Nauk SSSR* **246**, 108 (1979).

³⁵⁸ S. N. Baranov, M. A. Lazovskaya, and S. V. Krivun, USSR Patent 351,846 (1972) [CA **78**, 58242 (1973)].

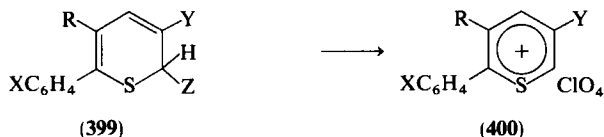
2. Aromatizations of Thiopyrans to Thiopyrylium Salts

The agents used for oxidative aromatization of *2H*-thiopyrans were trityl perchlorate,^{42,155,156} tetrafluoroborate,²⁶⁷ and iodide.²⁶⁷ Thus 3,5-diphenyl-*2H*-thiopyran (**222**) was found to aromatize either on its own to thiopyrylium salts **396** or by *S*-methylation to 1-methyl-3,5-diphenylthiabenzene (**398**) via intermediate **397**,²⁶⁷ as shown in Scheme 18.



SCHEME 18

Other aromatizations of *2H*-thiopyrans with trityl perchlorate were accomplished in the following transformations: **399a** $\rightarrow$ **400a**,¹⁵⁵ **399b** $\rightarrow$ **400b**,¹⁵⁶ **14** $\rightarrow$ **401**,⁴² and **286** $\rightarrow$ **402**.⁴² The similar reaction **399c** $\rightarrow$ **400c**¹⁵⁵ is not an oxidation process.



- (a) $\text{R} = \text{H} = \text{Z}$; $\text{X} = 4\text{-MeO}$
 $\text{Y} = \text{Ac}, \text{CONH}_2, \text{CN}, \text{CON}=\text{CHNMe}_2$
 (b) $\text{R} = \text{Ph}$; $\text{X} = \text{Z} = \text{H}$; $\text{Y} = \text{CHO}$
 (c) $\text{R} = \text{H}$; $\text{X} = 4\text{-MeO}$; $\text{Y} = \text{Ac}$
 $\text{Z} = \text{EtO}, \text{EtS}$

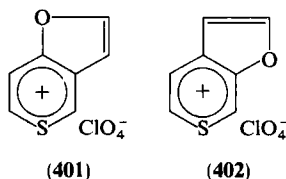


TABLE IX
AGENTS USED FOR AROMATIZATION OF 4*H*-THIOPYRANS TO THIOPYRYLIUM SALTS

Agent	References	Agent	References
O ₂ + AcOH	363	Ph ₃ CCl	367
Cl ₂	361	Ph ₃ Cl	272
I ₂	361	Ph ₃ C ⁺ BF ₄ ⁻	272, 286
HClO ₄	40, 105, 105a, 199, 236, 362, 364, 366, 368	Ph ₃ C ⁺ ClO ₄ ⁻	7, 90, 272, 367
		PCl ₅	5, 90
MeI + MeNO ₂	39	393	367
Me ₂ SO ₄	39	407	367
Et ₃ O ⁺ BF ₄ ⁻	39	C ₇ H ₇ ⁺ BF ₄ ⁻	365, 367
		AgNO ₃	367

Various agents used for aromatization of 4*H*-thiopyrans are listed in Table IX. Perchloric acid and trityl salts are the most frequently applied reagents.

Simple 4*H*-thiopyran (**7**)^{5,90,361} or its monosubstituted derivatives⁷ were oxidized to corresponding thiopyrylium ions of type **221** with several agents. A remarkable difference was observed in the behavior of **7** toward halogens: chlorine and iodine caused aromatization, whereas bromine only added to the substrate.³⁶¹

2,6-Di-*tert*-butyl-4*H*-thiopyran (**363**) as well as its 4-methyl derivative **243** were readily aromatized to thiopyrylium salts **403** using trityl tetrafluoroborate.²⁸⁶ 2,4,6-Triphenyl-4*H*-thiopyran (**45**) (R = Ph) was analogously converted to salts **404** by the action of methyl iodide, dimethyl sulfate, triethyloxonium tetrafluoroborate,³⁹ perchloric acid,³⁶² or oxygen in acetic acid.³⁶³

3-Methyl-2,4,6-triphenyl-4*H*-thiopyran (**47**) and 2,4-diphenyl-3-methyl-6-*tert*-butyl-4*H*-thiopyran (**58**) reacted with perchloric acid in acetic acid or with oxygen to give perchlorates **405a**^{105,362,364} and **405b**.^{98,363} Analogously, 2,4,5,6-tetraphenyl-4*H*-thiopyran (**226a**) gave salt **406a**.⁴⁰ 3,5-Dimethyl-2,6-diphenyl-4*H*-thiopyran (**409a**) with tropylium tetrafluoroborate yielded salts **410a**.³⁶⁵ Cyclopentano- and cyclohexano-4*H*-thiopyrans **21** exhibited a

³⁶¹ E. Molenaar and J. Strating, *Tetrahedron Lett.*, 2941 (1965).

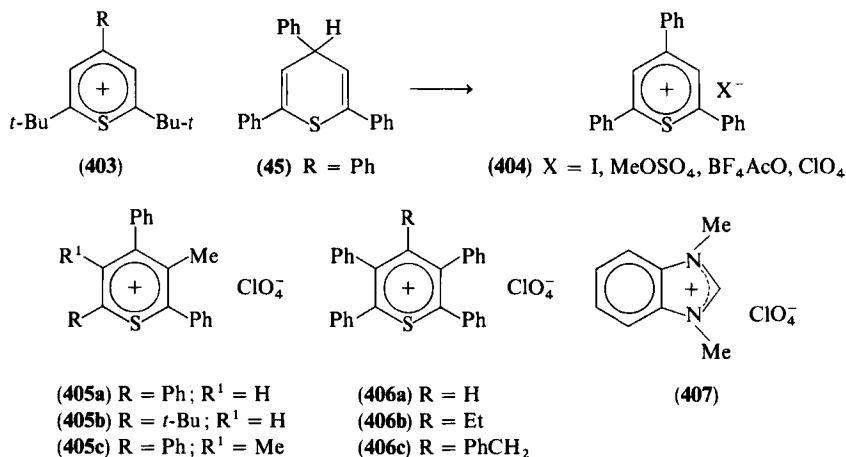
³⁶² V. G. Kharchenko, I. I. Kozhevnikova, A. A. Shcherbakov, G. G. Aleksandrov, and Yu. T. Struchkov, *Khim. Geterotsikl. Soedin.*, 324 (1980).

³⁶³ V. G. Kharchenko, N. I. Kozhevnikova, S. N. Chalaya, L. G. Chichenkova, and N. N. Ivanova, *Khim. Geterotsikl. Soedin.*, 405 (1981).

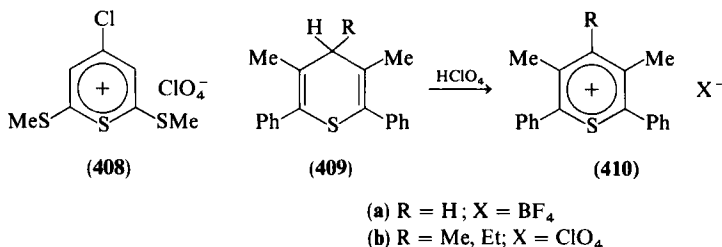
³⁶⁴ V. G. Kharchenko, N. I. Kozhevnikova, and N. V. Voronina, *Khim. Geterotsikl. Soedin.*, 562 (1979).

³⁶⁵ V. G. Kharchenko, S. N. Chalaya, and L. G. Chichenkova, *Khim. Geterotsikl. Soedin.*, 643 (1975).

similar behavior, giving corresponding thiopyrylium perchlorates **229**.³⁶⁶ The aromatization of tricyclic 4*H*-thiopyran **49** ($n = 2$, $R = H$) to ion **227a** was accomplished with other reagents such as silver nitrate, trityl chloride, tropylium tetrafluoroborate as well as with heterocyclic perchlorates **392** and **407**.³⁶⁷



4-Benzyl-2,4,6-triphenyl-4*H*-thiopyran (**245i**) reacts with perchloric acid with loss of the 4-benzyl group to afford perchlorate **404**.²³⁶ A similar elimination of the substituents was found for 4-benzyl derivatives **253**.³⁶⁸ The reported conversion of 4,4-dichloro-4*H*-thiopyran (**336b**) to perchlorate **408**, involving the loss of a 4-chlorine,³²⁵ is not an oxidation process. Similar transformations are also reported.³⁶⁹



³⁶⁶ V. G. Kharchenko, S. K. Klimenko, and M. N. Berezhnaya, *Khim. Geterotsikl. Soedin.*, 489 (1974).

³⁶⁷ A. F. Blinokhvatov, Z. N. Parnes, V. G. Kharchenko, and D. N. Kursanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1831 (1974).

³⁶⁸ V. G. Kharchenko and A. A. Rassudova, *Zh. Org. Khim.* 9, 2177 (1973).

³⁶⁹ S. Yoneda, T. Sugimoto, O. Tanaka, Y. Moriya, and Z. Yoshida, *Tetrahedron* 31, 2669 (1975).

The aromatization of 3,4,5-trisubstituted 2,6-diphenyl-4*H*-thiopyrans, e.g., **55** → **405c**,^{40,362,364} **226b,c** → **406b,c**,⁴⁰ and **409b** → **410b**³⁶² occurred with perchloric acid alone or in conjunction with molecular oxygen.³⁶⁴

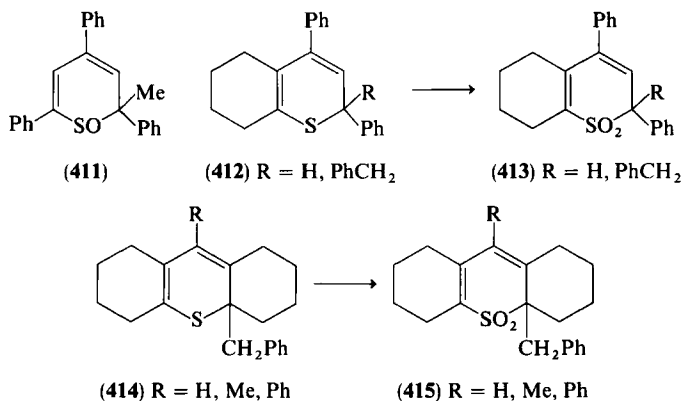
3. Aromatization of Selenopyrans to Selenopyrylium Salts

4-*H*-Selenopyran (**8**) was converted to selenopyrylium perchlorate **256** or chloride with trityl perchlorate or phosphorus pentachloride, respectively.⁹⁰

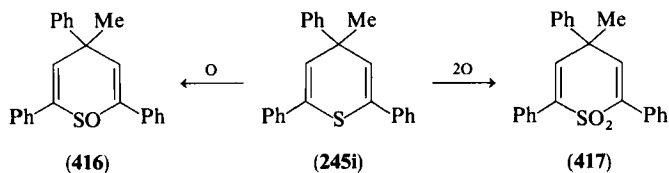
4. Oxygenation of Thiopyrans to Their *S*-Oxides

2*H*- as well as 4*H*-thiopyrans are, as a rule, oxygenated to the corresponding sulfones by hydrogen peroxide. The products are, in general, stable. Interruption after the addition of the first equivalent of oxygen gave the appropriate sulfoxides.³⁹

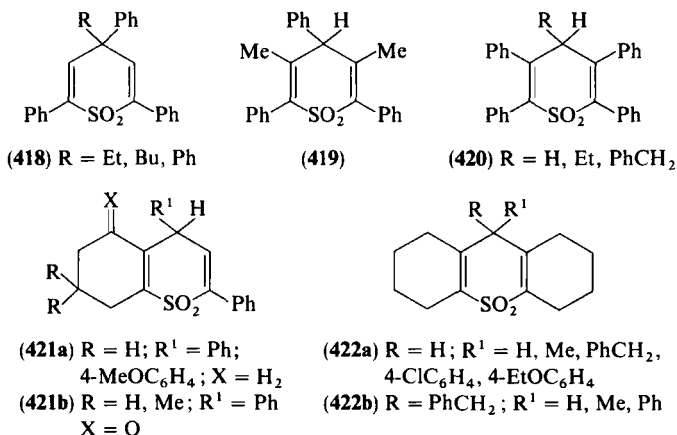
2-Methyl-2,4,6-triphenyl-2*H*-thiopyran (**246i**) reacts with hydrogen peroxide in acetic acid to produce sulfoxide **411**,³⁹ whereas condensed 2*H*-thiopyrans **412** and **414** gave the corresponding sulfones **413**¹⁰⁰ and **415**,³⁶⁸ respectively.



4-Substituted 2,4,6-triphenyl-4*H*-thiopyrans **245** are oxidized to their sulfones^{38,39} or sulfoxides.³⁹ The oxygenation of **245i** to **416** or **417** at room or elevated temperatures is a typical example.³⁹



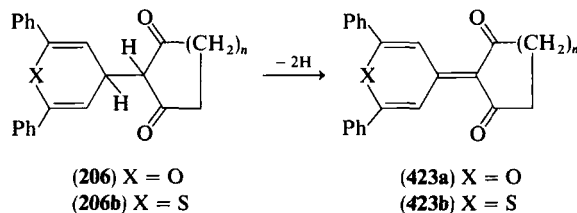
Analogous sulfones **418** were obtained by using H_2O_2 -AcOH and **245a**,³⁹ **245b**,³⁸ or a mixture of both isomers **245j** and **246j**.³⁹ The same procedure was used in the following transformations: **55** $\rightarrow$ **419**,¹⁰³ **226a-c** $\rightarrow$ **420**,⁴⁰ **232** $\rightarrow$ **421a**,¹⁰³ **20** $\rightarrow$ **421b**,^{61,99,370} **22** or **253** or **340** $\rightarrow$ **422a**,^{95,326} and **253** $\rightarrow$ **422b**.³⁶⁸



5. Dehydrogenation

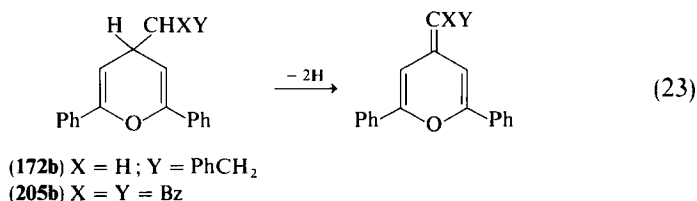
When two or more hydrogen equivalents are removed from a substrate, the term *dehydrogenation* will be employed.

a. *Dehydrogenation of 4H-Pyrans.* 4-Dioxocycloalkyl-2,6-diphenyl-4H-pyrans **206a** were smoothly oxidized with potassium ferricyanide in the presence of sodium hydroxide to give 4-dioxocycloalkylidenes **423a** in high yields.²⁵⁰



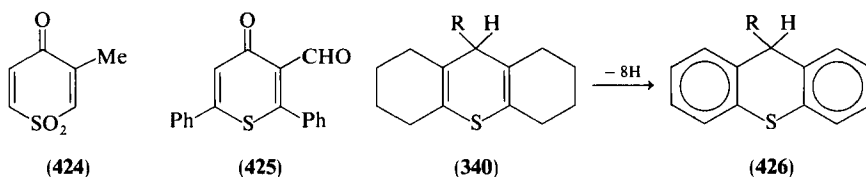
The dehydrogenation of 4H-pyrans **172b**²³⁶ and **205b** with molecular oxygen²⁴⁵ gave the products shown in Eq. (23)

³⁷⁰ V. G. Kharchenko, L. I. Markova, N. S. Smirnova, G. I. Rybina, and K. M. Korshunova, *Zh. Org. Khim.* 13, 182 (1977).



2,6-Diarylpyrylium ions also are dehydrogenating agents.^{232,250} Thus 2,2',6,6'-diaryl-4,4'-bis-4*H*-pyrans **163** were dehydrogenated by such agents to 4,4'-dipyranylidene derivatives **164** by a one-electron mechanism involving radical cation intermediates like **378**.²³² 2,2',4,4',6,6'-Hexamethyl derivative **163a** was oxidized with perbenzoic acid, but the reaction products were not identified.²¹⁸

b. *Dehydrogenation of Thiopyrans.* The oxidation of 4-chloro-2*H*-thiopyran derivatives **365** (R = R¹ = H, R² = Me) and **283** (X = CHO) with selenium dioxide gave the appropriate 4-thiopyrones **424**³⁷¹ and **425**,²⁹⁹ respectively. The mechanism is discussed in reference 299.



The catalytic dehydrogenation of dicyclohexeno-4-methyl-4*H*-thiopyrans **340** (R = H, Me) on palladium-charcoal or with sulfur led to aromatization of both carbocycles and only dibenzo derivatives **426** (R = H, Me) were obtained.^{95,102}

The ferricyanide oxidation of 4*H*-thiopyrans **206b** to corresponding dioxocyclohexylidene derivatives **423** proceeds in the same manner as in the pyran series.²⁵⁰ Simple 4-thiopyrone (**325**) and mesoxalic acid were isolated after oxidation of 4-hydroxy-4*H*-thiopyran (**2**) with potassium permanganate.⁴

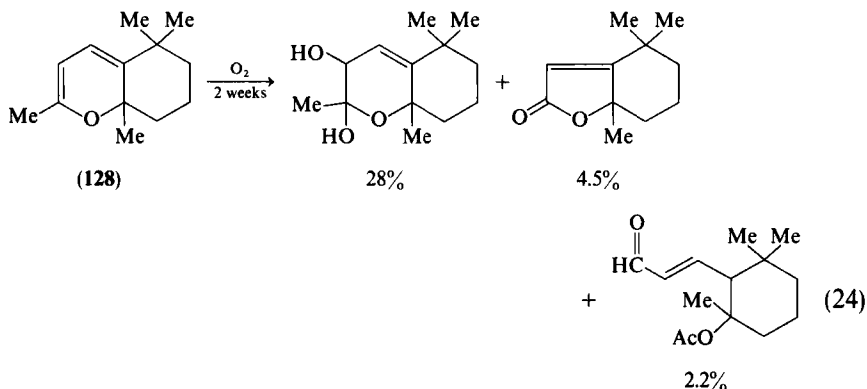
6. Miscellaneous Oxidations

Some 2*H*-pyrans are capable of autooxidation.^{172,372} Thus whereas 2,2,4,6-tetraphenyl-2*H*-pyran (**310a**) was completely inert,³⁷² the condensed

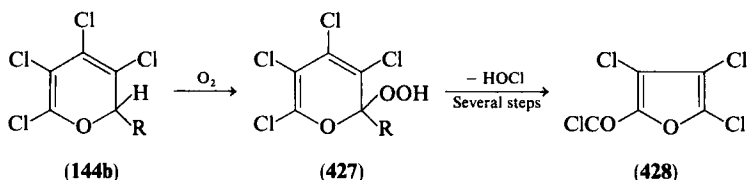
³⁷¹ Y. Gaoni, *Tetrahedron Lett.*, 2167 (1976)

³⁷² D. L. Pavia, *Diss. Abstr. Int. B* **30**, 570 (1969).

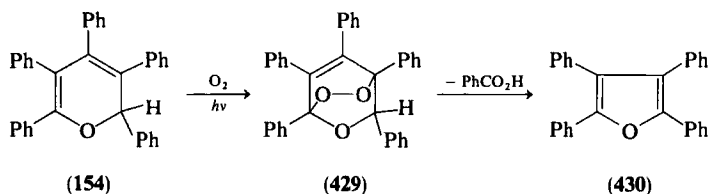
aliphatic 2*H*-pyran **128** gave addition, ring-closure, and ring-contraction products,^{171,172} as shown in Eq. (24).



A similar autooxidative ring contraction was recognized in the oxidation of 2-substituted 3,4,5,6-tetrachloro-2*H*-pyrans (**144b**) to furan derivatives **428**, proceeding probably via peroxide **427**.³²



Photochemically induced addition of molecular oxygen to 2,3,4,5,6-pentaphenyl-2*H*-pyran (**154**) in the presence of its 4*H* isomer **155** led to endoperoxide **429**, which was successfully converted on heating with potassium iodide in acetic acid to tetraphenylfuran (**430**).²¹¹



2,2,4,6-Tetramethyl-2*H*-pyran (**176**) is inert toward ozonolysis in contrast to its double bond isomer **308a**.¹⁹⁰ Vicinal dihydroxy-4*H*-pyran **342** was oxidized with periodic acid to the corresponding dialdehyde.³²⁸

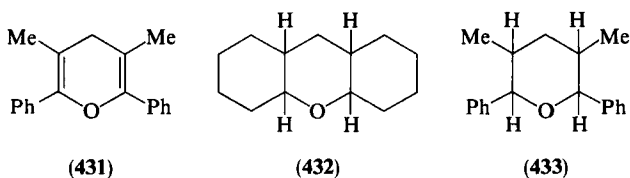
Oxidative decomposition of 2*H*-pyrantetracarboxylic acid **149** with hydrogen peroxide or nitric acid gave traces of succinic and oxalic acids, respectively.¹⁹⁴ 3-Methyl-4*H*-thiopyran (**3**) was reported to be oxidized with potassium permanganate to oxalic and acetic acids.⁶

B. DISPROPORTIONATION

Disproportionation has been observed frequently with thiopyrans and rarely with 4*H*-pyrans, and all cases involve a tetragonal carbon center (position 2 or 4) bearing at least one C—H bond. Some molecules of the substrate are aromatized to corresponding thiopyrylium or pyrylium ions and others reduced to dihydro or tetrahydro products. The relative abilities of pyrans and thiopyrans to disproportionate were interpreted within a proposed hydride transfer mechanism by a CNDO/2 method.⁴⁵

1. *Disproportionation of 4H-Pyrans*

2,3,5,6-Tetrasubstituted 4*H*-pyrans **153** and **431** were found to disproportionate with trifluoroacetic acid³⁵⁹ and with boron trifluoride–hydrogen bromide reagent³⁶⁰ to mixtures of pyrylium salts **395a,b** and tetrahydropyrans **432**³⁵⁹ or **433**,³⁶⁰ respectively.



A hydride-transfer mechanism involving protonation of the substrate has been postulated.³⁶⁰

2. *Disproportionation of Thiopyrans*

All thiopyrans not stabilized by electron-withdrawing substituents tend to disproportionate, especially in acid. This process is accelerated by hydrogen chloride,^{93,373–376} other hydrogen halides,^{93,360} a HCl–FeCl₃ reagent,^{22,377}

³⁷³ V. G. Kharchenko, S. K. Klimenko, T. I. Krupina, and A. A. Rassudova, *Khim. Geterotsikl. Soedin.*, Sb. 3, 82 (1971) [CA 77, 88226 (1972)].

³⁷⁴ V. G. Kharchenko, M. E. Stankevich, A. R. Yakoreva, and E. G. Lilienfeld, *Khim. Geterotsikl. Soedin.*, 422 (1971).

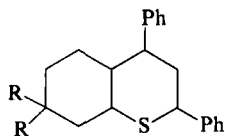
³⁷⁵ V. G. Kharchenko, M. E. Stankevich, N. M. Kupranets, A. R. Yakoreva, V. I. Kleimenova, and S. K. Klimenko, *Zh. Org. Khim.* 8, 193 (1972).

³⁷⁶ V. G. Kharchenko, M. E. Stankevich, A. R. Yakoreva, A. A. Rassudova, and N. M. Yartseva, *Khim. Geterotsikl. Soedin.*, 916 (1972).

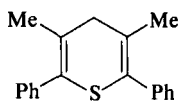
³⁷⁷ V. G. Kharchenko, S. K. Klimenko, and T. I. Krupina, *Khim. Geterotsikl. Soedin.*, Sb. 3, 76 (1971) [CA 77, 88225 (1972)].

^{377a} R. H. Everardus, R. Gräffing, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* 97, 69 (1978).

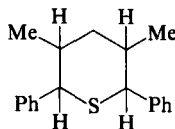
trifluoroacetic acid,^{365,374,375} boron trifluoride etherate,^{360,365} and phosphorus polysulfides.^{102,104}



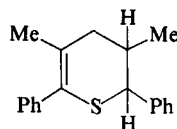
(434) R = H, Me



(435)



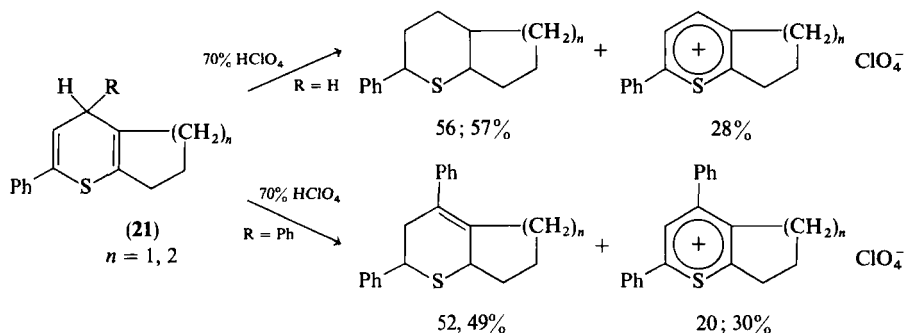
(436)



(437)

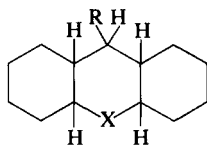
2*H*-Thiopyran **412** (R = H) disproportionates with 60% HClO₄ at elevated temperature to mixtures of thiopyrylium perchlorate **229** (R = Ph) and tetrahydrothiopyran **434** (R = H); 70% HClO₄ causes pure aromatization **412** → **229**.¹⁰⁰

4*H*-Thiopyrans also disproportionate to the corresponding thiopyrylium salts, but the second product has been either a dihydrothiopyran^{96,362,365} or, more frequently, a tetrahydrothiopyran.^{22,93,96,98,105a,373-375,377} A typical example is demonstrated in Scheme 19 for the disproportionation of condensed 4*H*-thiopyrans **21**.⁹⁶ 4-Unsubstituted derivatives **21** (R = H) afforded exclusively tetrahydro products, whereas 4-phenyl compounds **21** (R = Ph) gave dihydro products, probably due to double bond stabilization by conjugation with the 4-phenyl group. The first type of behavior was also observed for 4*H*-thiopyrans **21** (R = 4-MeOC₆H₄),⁹³ **45**,^{93,374,375} **55**,³⁷⁴ and **58**.^{105a} Other observations have, however, suggested that the degree of disproportionation might depend on reaction conditions. Thus 3,5-dimethyl-2,6-diphenylthiopyran (**435**) gives, in addition to the corresponding thiopyrylium salt, 2,3,5,6-tetrahydro derivative **436** on heating with perchloric acid,³⁷⁵ with hydrogen bromide, or trifluoroacetic acid at room temperature,³⁶⁵ whereas 2,3-dihydro derivative **437** was formed with boron trifluoride etherate³⁶⁵ and also with perchloric acid.³⁶²

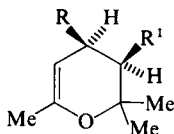


SCHEME 19

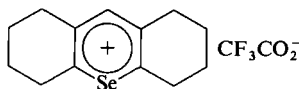
Tricyclic 4*H*-thiopyrans **340** ($R = H, Me, Et$) exhibited a different behavior toward various reagents and disproportionated either to the corresponding perhydro derivatives **438a** and appropriate thiopyrylium salts of the **227** type with acids^{22,93,98,373,377} or to **438a** and thioxanthenes⁴²⁶ ($R = H, Me$) spontaneously ($R = H$)¹⁰² or in the presence of phosphorus polysulfide ($R = H, Me$),¹⁰⁴ respectively.



(438a) $X = S$
(438b) $X = Se$



(439a) $R = R^1 = Me$
(439b) $R = Ph; R^1 = H$



(440)

3. Disproportionation of 4*H*-Selenopyrans

The disproportionation of dicyclohexano-4*H*-selenopyran (**62**) to the expected products **438b** ($R = H$) and **440** is effected by trifluoroacetic acid.¹⁰⁶

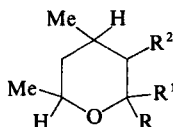
C. HYDROGENATION AND REDUCTION

Partial and total hydrogenations as well as hydrogenolyses of various pyrans and thiopyrans have been accomplished. Other reductions are rare.

1. Hydrogenation of 2*H*-Pyrans

Catalytic hydrogenation of 2*H*-pyrans has led to the expected saturated pyrans and occasionally also to open chain hydrogenolysis products. The formation of the latter compounds is due to the valence-bond isomerism of the starting 2*H*-pyrans with dienones, especially at higher temperatures (see Section V,E,1). Thus dihydropyran derivatives **439a,b** were prepared by partial hydrogenation of corresponding 2*H*-pyrans **187** and **182b**.²³⁷ Hydrogenation of 2,2-dibutyl-4,6-dimethyl-2*H*-pyran **124** ($R = Bu$) on a Raney nickel catalyst at elevated pressure and temperature as well as of condensed 2*H*-pyran **128** on a platinum catalyst in acetic acid at room temperature gave exclusively tetrahydropyrans **441b**³¹¹ and **441c**,¹⁶⁷ respectively. Similar transformations of mixtures of 2,2,4,6-tetramethyl-2*H*-pyran **176** and its double bond isomer **308a** led to tetrahydropyran **441a** and/or open chain products **442**, **443**, and **444**, depending on the pressure and temperatures used.^{189,190} Contrary to these findings, only open chain ketone

445 was obtained after hydrogenation of 2,6-diethyl-2,4-dimethyl-2*H*-pyran **184** ($R = Et$) or of a mixture of isomers **184** and **315a** on Raney nickel at $40^\circ C$.^{238,312}



(**441a**) $R = R^1 = Me$; $R^2 = H$

(**441b**) $R = R^1 = Bu$; $R^2 = H$

(**441c**) $R = Me$; $R^1, R^2 = CMe_2(CH_2)_3$



(**442**)



(**443**)

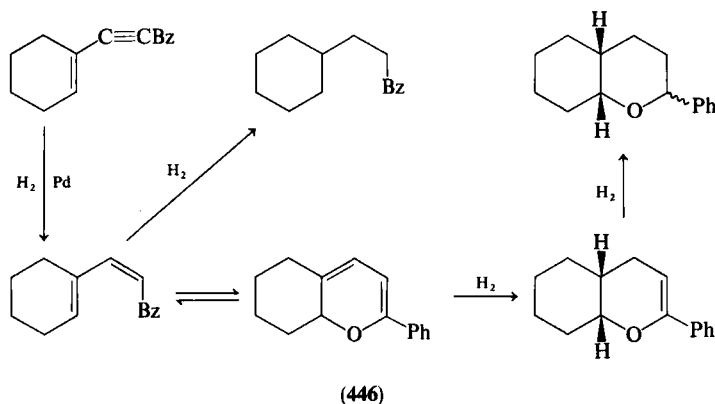


(**444**)



(**445**)

Successive hydrogenations involving labile condensed 2*H*-pyran **446**^{208,378} are shown in Scheme 19A.



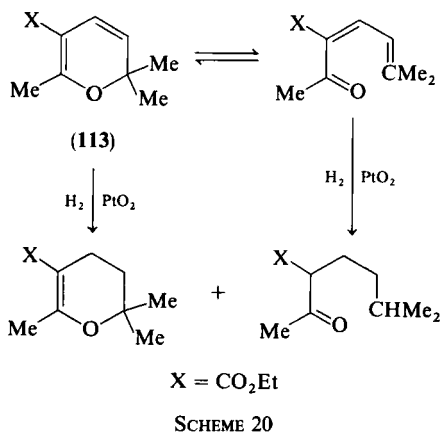
SCHEME 19A

The similar hydrogenation of 4-ethoxycarbonyl-2,2,6-trimethyl-2*H*-pyran **133** ($R = Me$, $X = EtO$) also gave both cyclic and open-chain products,¹⁷⁸ as shown in Scheme 20.

Analogously, the unconjugated double bond in condensed 2*H*-pyran derivative **352** was easily hydrogenated.³³⁵

A reported formation of 2,4,6-triphenyl-2*H*- or 4*H*-pyran by hydrogenation of enedione **40**²¹⁷ might proceed by the hydrogenolysis of hemiacetal **41**.

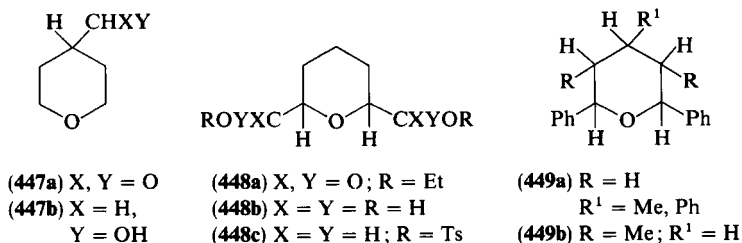
³⁷⁸ E. N. Marvell, T. Gosink, P. Churchley, and T. H. Li, *J. Org. Chem.* **37**, 2989 (1972).



2. Hydrogenation of 4*H*-Pyrans

The hydrogenation of unsubstituted 4*H*-pyran (**5**) to tetrahydropyran was used for the structure proof of **5**.¹⁸ The similar transformation of 4-formyl-4*H*-pyran **348** ($R = \text{H}$) afforded either aldehyde **447a** or alcohol **447b** on Pd-CaCO₃ catalyst³³⁶ or on Raney nickel,³³⁸ respectively. Analogously, 2,6-disubstituted tetrahydropyrans **448a-c** were prepared in 91–95% yields by hydrogenation of corresponding 4*H*-pyrans on palladium⁷³ or on Adams platinum catalyst.³⁷⁹ The use of a rhodium-charcoal catalyst at 40°C and 20 atm enabled hydrogenation of 2,6-diphenyl-4*H*-pyran **172** ($R = \text{H}$) to 2,6-dicyclohexyltetrahydropyran. With 2,4,6-trisubstituted derivatives **172** ($R = \text{Me}, \text{Ph}$) as well as 3,5-dimethyl-2,6-diphenyl-4*H*-pyran (**431**), the 2,6-phenyl groups were not hydrogenated, and tetrahydropyrans **449a**³⁸⁰ and **449b**^{360,380} were isolated in 32–45% yields.

The hydrogenation of 2-diethylamino-6-methoxy-3-methyl-4*H*-pyran (**96a**) on Pd-charcoal led to hydrogenolytic ring cleavage, yielding 60% of



³⁷⁹ V. Czornodola, *Rocz. Chem.* **16**, 459 (1936).

³⁸⁰ V. G. Kharchenko, N. S. Smirnova, S. N. Chalaya, A. S. Tatarinov, and L. G. Chichenkova, *Zh. Org. Khim.* **11**, 1543 (1975).

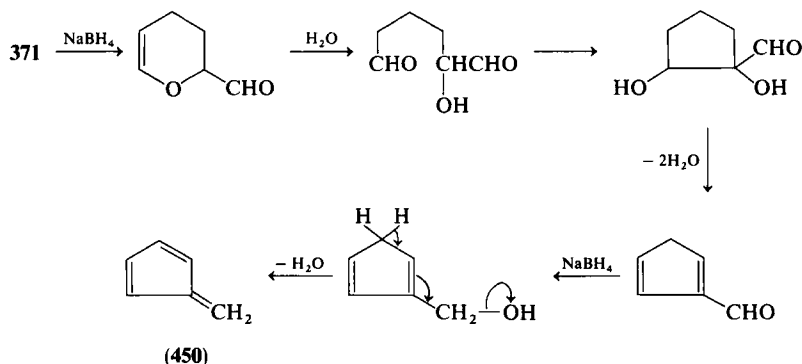
methyl 5-diethylamino-4-methylpentanoate.¹⁴⁴ The mild procedure with 3,5-diformyl-4-ethynyl-4*H*-pyran (**85d**) on Pd-BaSO₄ afforded 90% of the corresponding 4-ethyl derivative **85b**.¹²⁷ The hydrogenation of 2,2',4,4',6,6'-hexamethyl-4,4'-bis-4*H*-pyran (**163a**) was reported to stop after the consumption of 3.06 equivalents of hydrogen, but no products were isolated.

3. Other Reductions of Pyrans

The 2*H*-pyran ring in condensed derivative **128** was cleaved with LAH to give dienol **127**.¹⁶⁵ Analogous reductive ring openings with this reagent also were observed with 2*H*-pyrans **176** and **316**.¹⁶⁵

The reduction of bis-2,6-hydroxycarbonyl-4*H*-pyran (**32**) (R = H) to the corresponding dihydropyrandicarboxylic acid was accomplished with sodium amalgam.³⁷⁹

The formation of fulvene (**450**) by sodium borohydride reduction of 2-formyl-4*H*-pyran (**371**) in water³⁴⁷ may be explained by the mechanism shown in Scheme 21.



SCHEME 21

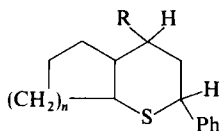
2-Hydroxy-2,4,6-triphenyl-4*H*-pyran (**40**) reacted with potassium borohydride, possibly with the participation of its valence-bond isomer **41**, to provide 2,4,6-triphenyl-4*H*-pyran (**151c**).⁸⁸

The keto group in condensed 4*H*-pyran derivative **264** was successfully reduced by reduction of the tosyl hydrazide with sodium borohydride.²⁹⁰

4. Hydrogenation of 2*H*-Thiopyrans

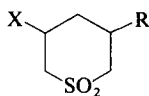
Isomeric 2*H*-thiopyrans **230** (R = Ph) and **231** were hydrogenated to tetrahydrothiopyrans **451a** (yields 50–71%) on 10% Pd-charcoal at elevated

pressure and temperature.³⁸¹ Analogously, sulfone **452a** was obtained from 3-phenyl-2*H*-thiopyran *S,S*-dioxide (**289**).^{300,301} The hydrogenations of 2*H*-thiopyran sulfones **118** and their double bond isomers over nickel gave the expected tetrahydro products **452b**.³⁸²



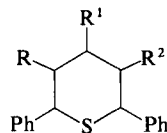
(**451a**) R = Ph, 4-MeOC₆H₄,
3,4-(MeO)₂C₆H₃
n = 1, 2

(**451b**) R = H, PhCH; n = 1, 2



(**452a**) R = Ph, X = H

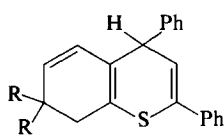
(**452b**) R = Me; X = Et₂N,
N(CH₂CH₂)₂NH
N(CH₂CH₂)₂O



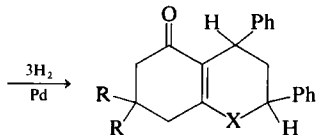
(**453**) R = H, Me;
R¹ = H, Me, Et, Ph;
R² = H, Me

5. Hydrogenation of 4*H*-Thiopyrans

Various 4*H*-thiopyrans undergo hydrogenation to the corresponding tetrahydrothiopyrans.³⁸³ Thus on using 10% Pd-C catalyst at enhanced pressure and temperature, **453** and **451b** were obtained from 4*H*-thiopyrans **45** (R = H, Me, Ph), **47** and **435** in 72–82% yields³⁸⁰ and from **21** (R = H, PhCH₂; n = 1,2) in 60–90% yields.³⁸¹ 4*H*-Thiopyrans **454** containing one additional carbon-carbon double bond afforded exhaustively hydrogenated products **434**,³⁷⁰ whereas oxo-4*H*-thiopyrans **20** (X = S) accepted only two hydrogen equivalents to give unsaturated ketones **455a** on different catalysts.^{370,384} Sulfone **421a** (R¹ = Ph) exhibited the same behavior to provide ketone **455b**.³⁸⁴ Partial hydrogenation of **435** to **437** was accomplished.³⁶⁵



(**454**) R = H, Me



(**455a**) R = H, Me; X = S

(**455b**) R = H, X = SO₂

³⁸¹ N. S. Smirnova, S. K. Klimenko, M. N. Berezhnaya, T. B. Stolbova, and V. G. Kharchenko, *Zh. Org. Khim.* **11**, 440 (1975).

³⁸² L. Skatteboel, B. Boulette, and S. Solomon, *J. Org. Chem.* **33**, 548 (1968).

³⁸³ V. G. Kharchenko, L. I. Markova, and N. S. Smirnova, *Katal. Protessov Poluch. Prevrashch. Sernistyk. Soedin.*, 78 (1979) [CA **91**, 211207 (1979)].

³⁸⁴ N. S. Smirnova, L. I. Lelynk, K. M. Korshunova, I. Ya. Evtushenko, and V. G. Kharchenko, *Zh. Org. Khim.* **10**, 1947 (1974).

6. Other Reductions of 4*H*-Thiopyrans

The Clemmensen reduction of condensed 4*H*-thiopyrans **340** ($R = H, Me$) with zinc and hydrochloric acid gave tetrahydro derivatives **438**.³⁷³ Triethylsilane and trifluoroacetic acid was used for analogous reductions of 4*H*-thiopyrans **45**, **47**, and **409** ($R = H, Me, Et, Ph$) to **453**.³⁶² 3,5-Dideutero derivatives of **453** were obtained in the same way in the presence of *O*-deuteriotrifluoroacetic acid.³⁶²

The carbonyl group in condensed 4*H*-thiopyrans **20a** was selectively reduced with LAH to give diastereomeric mixtures of hydroxy derivatives.^{61,370}

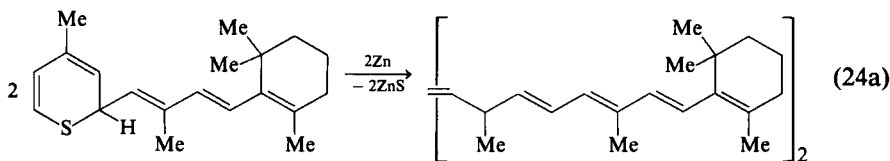
7. Reduction of 4*H*-Selenopyrans

Dicyclohexano-4*H*-selenopyran (**62**) and its 4-substituted derivatives were converted by triethylsilane and trifluoroacetic acid to stereoisomers of tetrahydro products **439** ($R = H, Ph, 2-FC_6H_4, PhCH_2$).³⁸⁵

D. DESULFURIZATION OF THIOPYRANS

As with other organic sulfides, 2*H*- or 4*H*-thiopyrans undergo desulfurization with Raney nickel^{39,184,236,281} or zinc amalgam.^{183,184a-186} The latter reagent is specific, allowing the number of double bonds to remain unchanged, whereas the former is not.

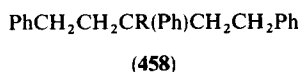
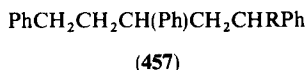
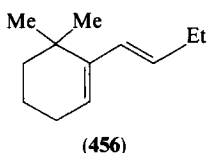
The desulfurization of 2-substituted 4-methyl-2*H*-thiopyrans, accompanied by dimerization of primary intermediates, is caused by $ZnHg_x$. This approach was explored for the synthesis of polyenes,¹⁸³⁻¹⁸⁶ including β -carotene (Eq. 24a).



The number of double bonds may be conserved or decreased with the Raney nickel catalyst. Thus bicyclic 2*H*-thiopyran **142** gave monocyclic diene (**456**).¹⁸⁴ Partially reduced hydrocarbons **457** ($R = Me, 4-Me_2NC_6H_4$) and/or **458** ($R = Me, PhCH, 4-Me_2NC_6H_4$) were prepared from

³⁸⁵ A. F. Blinokvatov, O. V. Markovtseva, N. A. Nefedova, V. G. Kharchenko, and Z. N. Parnes, *Khim. Geterotsikl. Soedin.*, 564 (1981).

2-substituted 2,4,6-triphenyl-2*H*-thiopyrans **246i**³⁹ and **246k**²⁸¹ or from 4-substituted 2,4,6-triphenyl-4*H*-thiopyrans **245i**,³⁹ **245k**,²⁸¹ and **245l**,²³⁶ respectively.

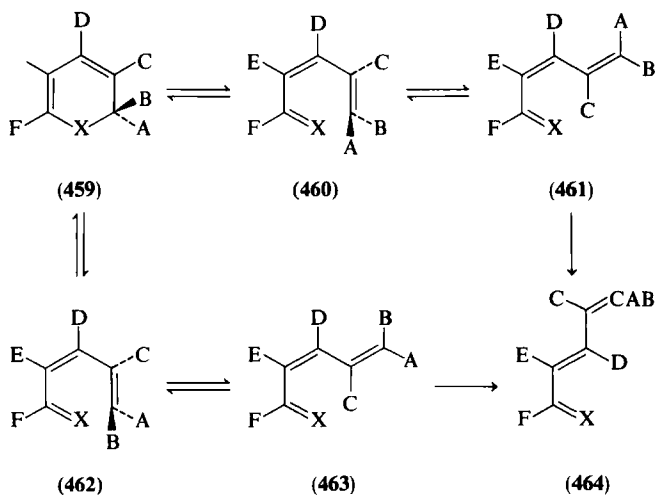


E. ISOMERIZATION

A pyran or a thiopyran ring can reversibly or irreversibly isomerize to open-chain or cyclic products. Isomerization seems to be more common for pyrans than for thia analogs and for 2*H* relative to 4*H* isomers. Isomerizations may be divided into four types, i.e., valence-bond tautomerism, endocyclic hydrogen shifts, exocyclic shifts, and migrations of nonhydrogen substituents.

1. Valence-Bond Tautomerism

Valence-bond tautomerism, a typical feature of 2*H*-pyrans but rare among 2*H*-thiopyrans, may be generally formulated as in Scheme 22.



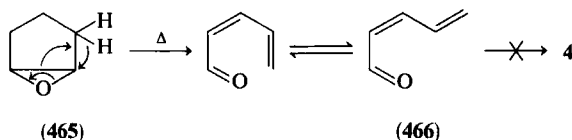
X = O, S

SCHEME 22

The electrocyclic process involves a rather complex equilibrating system consisting of a number of open-chain configurational and conformational isomers, e.g., species **460–463** as well as one heterocyclic form **459**. Although much information regarding the tautomerism is available, the details of the mechanism shown in Scheme 22 are not completely elucidated. Stereochemical aspects have still not been fully recognized. In some cases the secondary *Z–E* isomerizations, e.g., **461** → **464** and **463** → **464**, may be side reactions causing the irreversibility of the process.

a. *Tautomerism of 2H-Pyrans, cis Dienals, and cis Dienones.* The ability to isolate or at least identify a given 2H-pyran is limited by ring-chain tautomerism (dynamic isomerism), e.g., whether the equilibrium shown in Scheme 22 is sufficiently shifted in favor of heterocycle **459** (X = O) under the conditions of experiment (thermodynamic control) and/or whether the life time of **459** is long enough to be observed (kinetic control). Suggestions exist that **460** and **462** may not be stable conformers.¹⁶⁴

If both thermodynamic and kinetic factors operate simultaneously in favor of open-chain forms like **460** and **463**, then 2H-pyran **459** may not be identifiable. This may be the reason why attempts to prepare unsubstituted 2H-pyran (**4**) from *cis*-2,4-pentadienal (**466**) have failed (for other attempts to prepare **4**, see reference 386). Thus even if **466** had been generated by thermolysis of epoxycyclopentene **465**, no traces of **4** were detected.²⁸ Moreover, **466** seems to be thermodynamically more stable than cyclic form **4** according to *ab initio* MO calculations.⁵⁶



Several other dienones were observed to be incapable of effective ring closure to 2H-pyran valence tautomers of **459**.^{164,175,387} In other cases cyclic forms such as **460** and **463** were too unstable to be detected,^{30,164,388} but their existence, although in negligible concentrations, was proved on the basis of the structure of mutually isomerizing different open-chain forms^{28,99,388–391} or as adducts with tetracyanoethene³⁰ and maleic anhydride.^{237,392} The com-

³⁸⁶ G. Fodor and C. P. H. Siumg, *Justus Liebigs Ann. Chem.*, 1742 (1974).

³⁸⁷ E. P. Prokofev, Zh. A. Krasnaya, and K. M. Litvak, *Izv. Akad. Nauk SSSR, Ser. Khim.* **28**, 711 (1979).

³⁸⁸ R. Stokhuyzen and C. Chieh, *J.C.S. Perkin II*, 481 (1976).

³⁸⁹ P. Schiess, *Helv. Chim. Acta* **55**, 2365 (1972).

³⁹⁰ A. Roedig, F. Frank, and G. Röbbke, *Justus Liebigs Ann. Chem.*, 630 (1974).

³⁹¹ A. Roedig and H. A. Renk, *Justus Liebigs Ann. Chem.*, 1214 (1974).

³⁹² F. Fournier, J. Berthelot, N. K. Cuong, and J. J. Basselier, *Tetrahedron* **35**, 2629 (1979).

TABLE X
EQUILIBRIUM AND RATE CONSTANTS FOR VALENCE-BOND TAUTOMERISM OF
2H-PYRANS 459 (E = H; X = O)

Substituents					Reaction (Scheme 22)	Constant <i>k</i> or <i>K</i>	Temperature (K)	References
A	B	C	D	E				
H	Me	H	Me	Me	459 ^a → 461	3 × 10 ⁻³ /sec	286	207
Me	Me	H	Me	Me	461 ⇌ 459	0.14 ^b	356	396
					459 → 461	1.6 × 10 ⁻⁴ /sec	287.6	165
Me	Ph	H	Me	Ph	459 → 461	5.35 × 10 ⁻⁴ /sec	287.6	165
Me	(CH ₂) ₃ CMe ₂		H	Me	459 ⇌ 461 ^c	4.61	327	395
						1.52	386	395
					459 → 461 ^d	1.3 × 10 ⁻⁴ /sec	291	395
					461 ⇌ 459 ^e	1.4 × 10 ⁻³ /sec	291	395

^a Detected by NMR at -22°C.

^b In triethylamine.

^c Δ*H*^o = 23 kJ/mol.

^d Activation energy = 83.7 kJ/mol.

^e Activation energy = 104.6 kJ/mol.

positions of some valence-bond tautomeric mixtures were estimated quantitatively,^{88,111,164,175,179,208} others were not ascertained.^{87,166,378,391,393,394}

The extreme opposite examples where heterocyclic forms 459 are the only tautomers present, e.g., 2H-pyrans 120, 124, 128, 133, 135, and 137, were mentioned in Section III,I.

Equilibrium and rate constants for the ring opening of stable 2H-pyrans 128³⁹⁵ and 176,^{165,396} the less stable 316,¹⁶⁵ and extremely labile compound 459 (A = D = F = Me, B = C = E = H)²⁰⁷ are summarized in Table X. It was demonstrated that the ring opening 201c → 202c for R¹ = H proceeded relatively slowly under thermodynamic control.^{258a,259}

In general, enhancement of temperature^{177,208,395-397} or solvent polarity^{179,396,398} and perhaps UV irradiation^{167,398a} shifted the tautomeric equilibria toward dienone forms 461 and/or 463. Contrary to earlier reports,^{236,399} it

³⁹³ W. Surber, V. Theus, L. Colombi, and H. Schinz, *Helv. Chim. Acta* **39**, 1299 (1956).

³⁹⁴ A. T. Balaban and C. D. Nenitzescu, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2064 (1960).

³⁹⁵ E. N. Marvell, G. Caple, T. A. Gosink, and G. Zimmer, *J. Am. Chem. Soc.* **88**, 619 (1966).

³⁹⁶ T. C. Chadwick, *Diss. Abstr. Int. B* **32**, 5685 (1972).

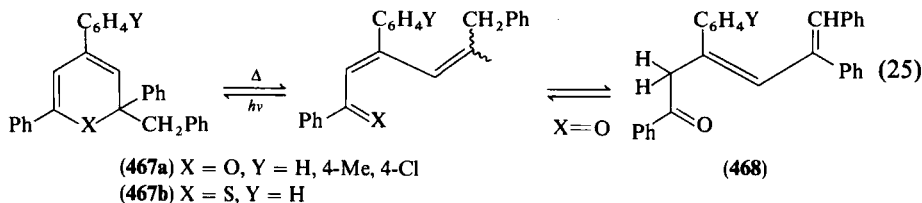
³⁹⁷ J. Royer, A. Safieddine, and J. Dreux, *Bull. Soc. Chim. Fr.*, 1646 (1972).

³⁹⁸ Zh. A. Krasnaya, E. P. Prokofev, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 123 (1978).

^{398a} A. C. Dvornikov, Zh. A. Krasnaya, and Ya. N. Malkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 390 (1981).

³⁹⁹ R. S. Becker and J. Kolc, *J. Phys. Chem.* **72**, 997 (1968).

was demonstrated that 2-benzyl-2,4,6-triaryl-2*H*-pyrans **467a** on heating in methanol gave isomerized dienones **468a** while the latter were photochemically converted back to the starting heterocycles **467a** in 70% quantum yields by 310 nm irradiation (Eq. 25).^{392,400}



However, condensed 2*H*-pyran **126** was photochemically converted to corresponding dienone **128**.¹⁶⁷

A pH decrease of aqueous solutions of 2-hydroxy-2,4,6-triphenyl-2*H*-pyran (**40**) increased the concentration of valence-bond tautomer **41** in mixtures of **40** and **41**.⁸⁸

2-Dimethylamino-2*H*-pyran derivative **135** (R = R' = Me, X = MeO) was produced by melting crystalline open-chain form **134**.¹⁷⁹

The influence of substituent effects on the relative populations of valence-bond tautomers **459**, **461**, and **463** have been examined. Thus simple dienals **461** and **463** (A = B = F = H) did not close to 2*H*-pyrans **459**.^{29,401,402} 2,2-Disubstitution (A and B ≠ H), on the other hand, destabilized intermediate conformations **460** and **462**, causing them to be nonplanar and so facilitating their closure to a heterocycle (**459**).^{165,167,174,208,395,396,402a} Cyclic forms **459** seem to exist only in cases where their valence isomeric cis dienones possess no stable planar conformation type of **460** or **462**,¹⁶⁴ but 2,2-disubstitution alone is evidently not sufficient, as illustrated by unstable 2,2,6-trimethyl-2*H*-pyran.²³⁷ *Ab initio* MO calculations on 2,2-dimethyl-2*H*-pyran **459** (A = B = Me, C = D = E = F = H, X = O) suggested that valence tautomer **461** would still be thermodynamically more stable, although the calculated molecular energy differences were smaller than those of **4** and **466**.⁴⁰³

When the 2,2-disubstitution (A and B ≠ H) was extended by introducing an additional nonhydrogen substituent at position 3 (C ≠ H)^{167,174,175,182,208,387,395,398,402a} or at position 4 (D ≠ H),^{164,165,258a,259,396,402a,404} the equilibrium shown

⁴⁰⁰ N. K. Cuong, F. Fournier, and J. J. Basselier, *Bull. Soc. Chim. Fr.*, 2117 (1974).

⁴⁰¹ S. Sarel and J. Rivlin, *Isr. J. Chem.* **1**, 221 (1963).

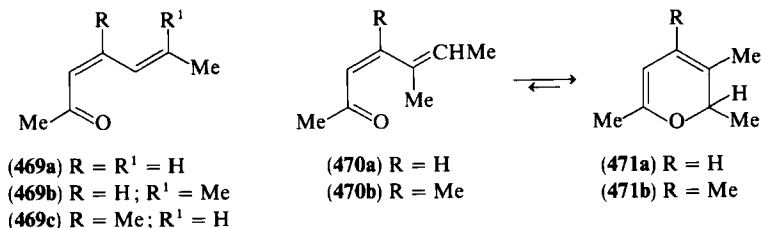
⁴⁰² J. C. Anderson, D. G. Lindsay, and C. B. Reese, *Tetrahedron* **20**, 2091 (1964).

^{402a} A. Duperrier and J. Dreux, *Tetrahedron Lett.*, 3127 (1970).

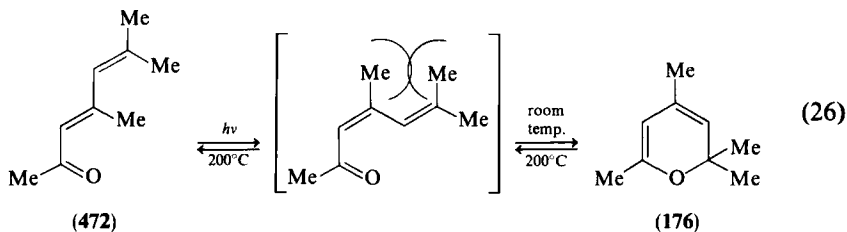
⁴⁰³ S. Böhm and J. Kuthan, *Collect. Czech. Chem. Commun.* **48**, 1007 (1983).

⁴⁰⁴ A. F. Kluge and C. P. Lillya, *J. Org. Chem.* **36**, 1988 (1971).

in Scheme 22 was shifted completely at room temperature toward the 2*H*-pyran **459**. This effect has been explained by the destabilization of open-chain conformers **461** or **463** due to the nonbonding repulsive interaction between nonhydrogen substituents, e.g., C...X, A...D or B...D, respectively.^{164,393,404} Thus dienones **469a-c** were found to give no 2*H*-pyrans because the aforementioned interactions were absent. On the other hand, 4,5-disubstituted ketone **470a** was in equilibrium with corresponding 2*H*-pyran **471a**, in which **471a** prevailed (87%).^{164,404}



2,3,4,6-Tetramethyl-2*H*-pyran (**471b**) contained no valence tautomer **470b** in benzene.²¹² Photoinduced *E* → *Z* isomerization of **472** led exclusively to 2,2,4,6-tetramethyl-2*H*-pyran (**176**), as shown in Eq. (26).^{397,404}



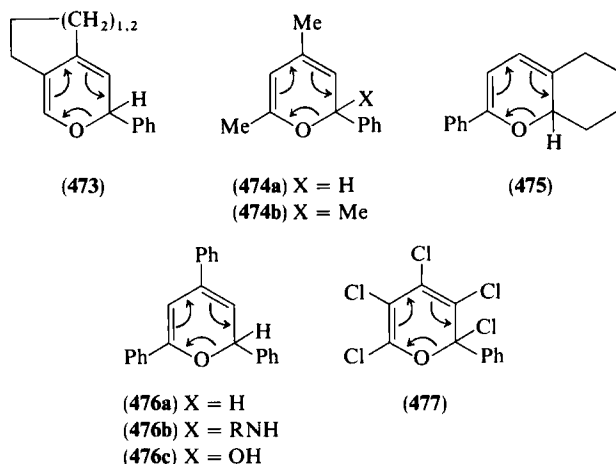
The steric bulk of other alkyl substituents in **461** and/or **463** shifted the equilibria shown in Scheme 22 toward the 2*H*-pyrans (**459**).³¹

Analogous substituent effects were postulated for 2*H*-pyrans **459** under conditions that placed them in equilibrium with trans dienones **464**.³⁹³

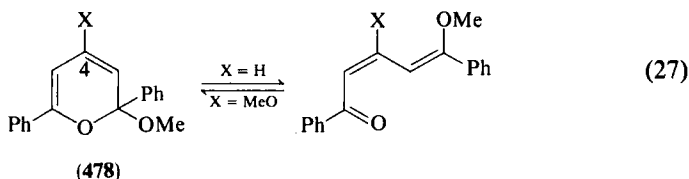
The effects of conjugating substituents were recognized in the cases of 3,5- and 2,6-disubstitution. Such substituents in positions 5 and/or 3 (E and C = COR, CO₂R, CN, Ph) stabilize the 2*H*-pyran form **459** with respect to open-chain forms **461** and **463**, especially for substituents having electron-withdrawing character. This rationalizes the stabilities of such 2*H*-pyrans as **11**,^{35,126} **133**,^{111,175,176,387,398a,405} **135**,^{179,398} **137**,¹⁷⁹ **139**,¹⁸¹ **141**,¹⁸² **273**,²⁹⁴ as well as those shown in Eq. (1).⁸⁹

⁴⁰⁵ R. G. Salomon, J. R. Burns, and W. J. Dominic, *J. Org. Chem.* **41**, 2918 (1976).

Similar substituents at positions 2 and/or 6 (A, B, or F = Ph, CN, etc.) causes the opposite effect, e.g., the destabilization of *2H*-pyrans **459** with respect to their valence-bond tautomers **461** and **463** by more extended conjugation in the latter.^{402a} Attempts to isolate *2H*-pyrans **40**,⁸⁸ **120**,^{160,161} **201**,²⁴⁸ **473**,^{30,405} **474a**,³⁸⁹ **474b**,⁴⁰⁶ **475**,^{208,378} **476a**,^{208,268} **476b**,⁴⁰⁷ and (**477**)³⁹¹ were unsuccessful mainly on these grounds. The same lability was exhibited by several *2H*-pyrans of types **133** and **135**, which lacked substituents at the 3-position.¹⁷⁶



Another effect of the 4-methoxy group for *2H*-pyrans is seen in the different behavior of **478**^{258a,259} shown in Eq. (27) and the successful preparation of **323**.³¹⁹

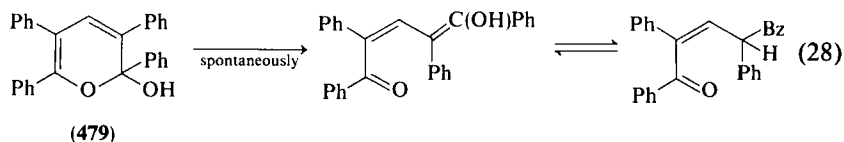


Strong repulsion between bulky 2,3- and 5,6-phenyl groups in *2H*-pyran **479** accounted for its instability, (Eq. 28).⁴⁰⁸ Similar reasons were evidently responsible for the lability of 2,3,4,5,6-pentaphenyl-*2H*-pyrans **154**^{211,400} and **195**.²³⁶

⁴⁰⁶ G. Köbrich, *Angew. Chem.* **72**, 348 (1960).

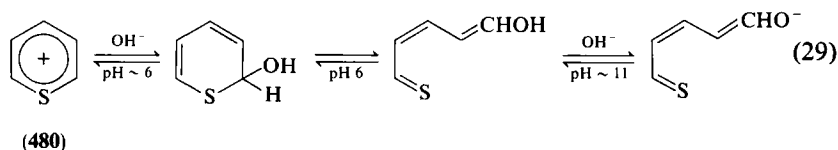
⁴⁰⁷ A. R. Katritzky, R. T. C. Brownlee, and G. Musumarra, *Tetrahedron* **36**, 1643 (1980).

⁴⁰⁸ J. J. Basselier, *Ann. Chim. (Paris)* [13] **6**, 1131 (1961).



Although some experimental findings support the preference of one of the two possible disrotatory pathways, e.g., **459** → **461** and **459** → **463**,^{165,396} the factors controlling the general stereospecificity of the process in Scheme 22 are not yet well understood.

b. Tautomerism of 2*H*-Thiopyrans and Dienethiones. The equilibrium of labile 2-hydroxy-2*H*-thiopyran (**480**) and its nonionized and ionized valence tautomers is pH-dependent, Eq. (29).²⁶⁶



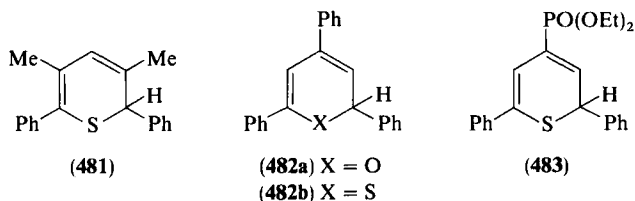
The photochemical behavior of 2-benzyl-2,4,6-triphenyl-2*H*-thiopyran (**467b**) is similar to that of its 1-oxa analog **467a** (see Eq. 25) except for the degree of reversibility.^{399,409}

2. Endocyclic Hydrogen Shifts

The exceptionally easy isomerization of 2-methyl-3,4,5,6-tetrachloro-2*H*-pyrans **144b** ($R^2 = \text{Me}$) to its 4*H* isomer **145b** at room temperature³² was mentioned in Section III,J.

2,6-Diphenyl-3,5-dimethyl-4*H*-thiopyran (**435**) was found to isomerize to its 2*H* isomer **481** under the influence of a HCl–AcOH or HCl–Et₂O mixture⁹² or hydrogen bromide and iodide.⁹³

2,4,6-Triphenyl-4*H*-pyran (**151c**) on heating in acetic acid gave intermediate **482a**, which immediately isomerized to dienone **152c**.²⁶⁸ Analogous

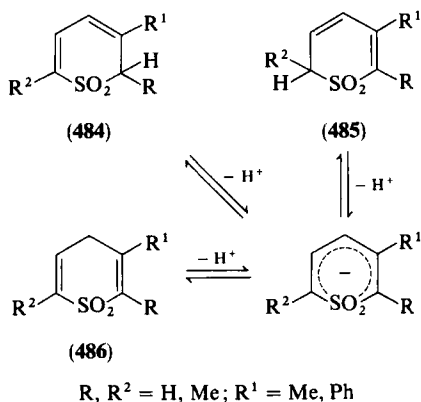


⁴⁰⁹ R. S. Becker and J. Kolc, *J. Phys. Chem.* **72**, 997 (1968).

hydrogen shifts in 4*H*-thia analog **45** ($R = \text{Ph}$) and its 4-deutero derivative were reported to provide 2*H* isomer **482b** or its 2-deutero derivative.²⁶⁸ The former experiment has not been reproduced,³⁶³ and the proposed mechanism²⁶⁸ has been questioned.³⁶³

Thermal 4*H* $\rightarrow$ 2*H* isomerization of 2,6-diphenyl-4*H*-thiopyranphosphonate **255** to **483** was accomplished by heating for several days.²⁸⁸

2*H*-Thiopyran *S*-dioxides equilibrate with their isomers by deprotonation with sodium alkoxides according to Scheme 23, e.g., $484 \rightleftharpoons 485$ ⁴¹⁰ and $484 \rightleftharpoons 486$ for $R = R^2 = \text{H}$ and $R^1 = \text{Ph}$.³⁰⁰ The equilibrium $484 \rightleftharpoons 485$ was also observed during the flash vacuum thermolysis of 3-phenyl-2*H*-thiopyran *S*-dioxide (**289**).⁴¹¹



SCHEME 23

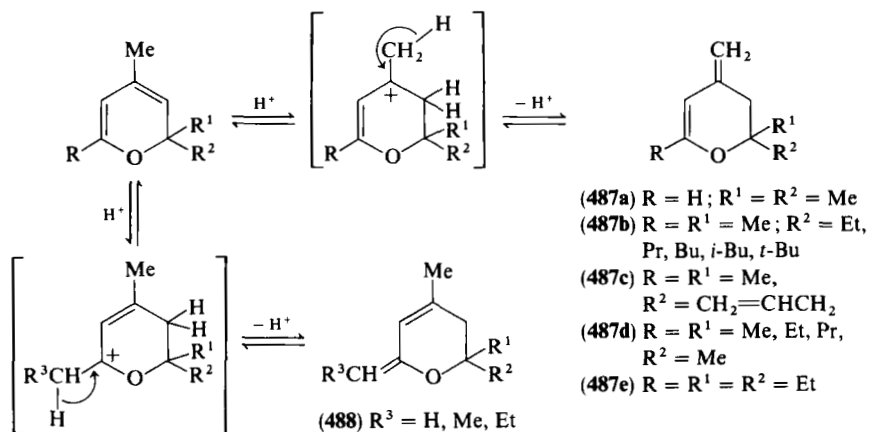
3. Exocyclic Hydrogen Shifts

Isomerization involving exocyclic hydrogen shifts is typical for 4-alkyl- and 4-hydroxy-2*H*-pyrans, rare for analogous 2*H*-thiopyrans.

a. Isomerization of 4-Alkyl-2*H*-pyrans. The formation of 4-alkylidene and/or 6-alkylidene dihydropyran derivatives **487** and **488** has often accompanied the preparation of the title compounds especially in an acidic medium as demonstrated in Scheme 24 for **487a**,³²³ **487b**,³⁹⁷ **487d**,²⁴⁷ **487e**,^{247,309} and **488d,e**.²⁴⁷ 2,2,4,6-Tetramethyl-2*H*-pyran **176** exhibited anal-

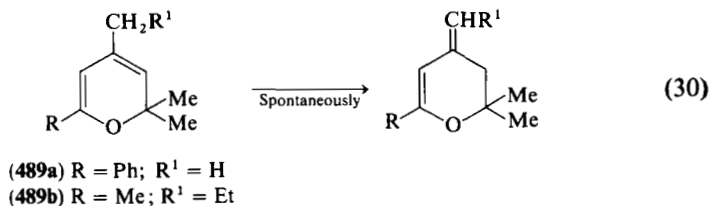
⁴¹⁰ S. Bradamante, A. Mangia, and G. Pagani, *Tetrahedron Lett.*, 3381 (1970).

⁴¹¹ J. D. Finlay, C. R. Hall, and D. J. H. Smith, *Tetrahedron Lett.*, 1149 (1977).

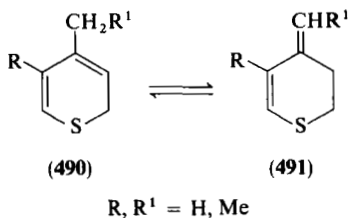


SCHEME 24

ogous behavior, e.g., **176** $\rightarrow$ **308a**, with acids,^{165,310,323,397} by heating,³⁹⁷ and on UV irradiation.⁴⁰⁴ 2*H*-Pyrans **489** isomerize spontaneously (Eq. 30).²³⁷



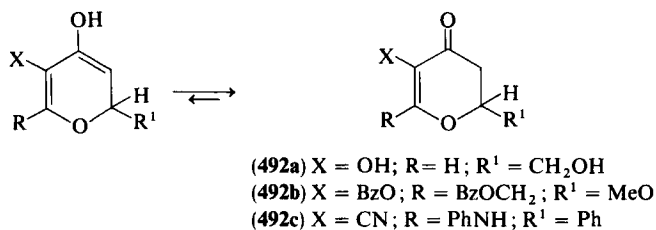
b. Isomerization of 4-Alkyl-2*H*-thiopyrans. 3,4-Disubstituted 2*H*-thiopyrans **490** in HMPT or diisopropylamine–DMSO mixtures partly isomerize to 8–15% 4-alkylidene derivatives **491**.²¹ The same behavior was exhibited by analogous thieno-2*H*-thiopyrans.²¹



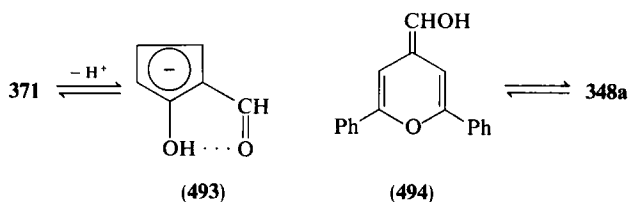
c. Isomerization of 4-Hydroxy-2*H*-pyrans. Some of the title compounds isomerize to 2,3-dihydro-4-pyrones **492a**,²⁹⁸ **492b**,⁴¹² and **492c**.⁴¹³

⁴¹² F. W. Lichtenthaler, S. Ogawa, and G. Heidel, *Chem. Ber.* **110**, 3324 (1977).

⁴¹³ M. Augustin, G. Jahreis, and W. D. Rudolf, *Synthesis*, 472 (1977).



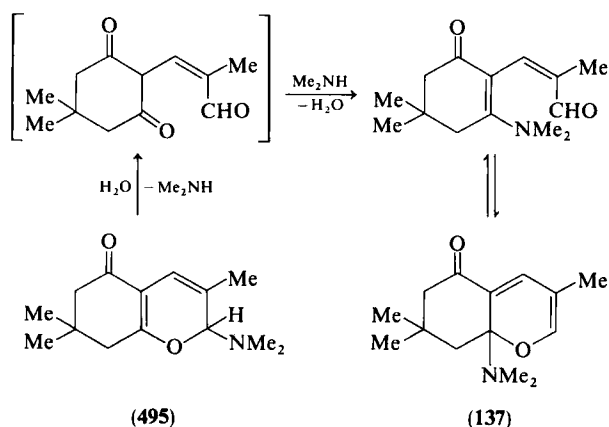
d. *Isomerization of 4H-Pyrans.* 2-Formyl-4*H*-pyran (**371**) was deprotonated by hydroxide ion; the heterocyclic ring contracts to a substituted cyclopentadienyl anion (**493**).³⁴⁸ 2,6-Diphenyl-4-formyl-4*H*-pyran (**348a**) in DMSO equilibrates with corresponding enol **494** to a 1:1 mixture of both tautomers.³³²



4. Migrations of Nonhydrogen Substituents

a. *Isomerizations of 2H-Pyrans.* The migration of the 2-dimethylamino group in condensed 2*H*-pyran **495** to the 6-isomer **137** in aqueous medium proceeded as shown in Scheme 25.¹⁷⁹

The isomerization of 2,3,4,5-tetrachloro-2*H*-pyrans **120a** (R = H, Ph) to **121** and **122** (R¹ = H) (see Section III,I) were explained as migrations of the chloride ion.^{160,161}



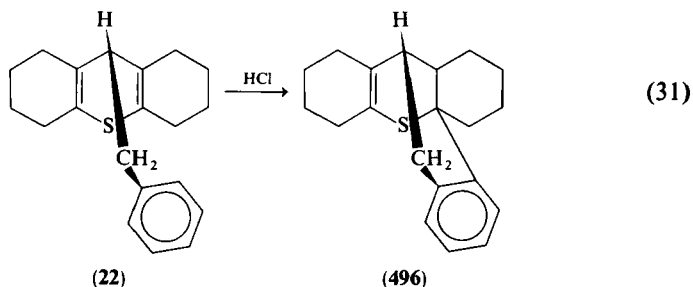
SCHEME 25

b. *Photochemical 1,3 Shifts of a 4-Benzyl Group in 4H-Pyrans.* The isomerization of 4-benzyl-2,4,6-triaryl-4*H*-pyrans **183** to 2-benzyl-2*H* isomers **467a** takes place on UV irradiation.^{236,392,400,414-416} The migration of the benzylic group proceeds in excited singlet states of the starting species as a concerted suprafacial process.³⁹²

c. *Photochemical 1,3 Shifts of a 4-Benzyl Group in 4H-Thiopyrans.* The transformation is analogous to that for the preceding oxapyrans and is known for 2,4,4,6-tetrasubstituted and hexasubstituted starting species, e.g., **2451** → **2461**²³⁶ and **253** → **414**,³⁶⁸ respectively.

5. Miscellaneous

The isomerization of 4-benzyl-4*H*-thiopyran (**22**) with hydrogen chloride to **496** proceeds by an intramolecular electrophilic substitution of the benzyl group (Eq. 31).⁵⁴



F. RING-OPENING REACTIONS

Hydrolytic ring cleavage and analogous transformations with alcohols, amines, hydrazine, and hydroxylamine derivatives are now considered. Other ring openings have been treated in Section V,D.

1. Hydrolysis of 4*H*-Pyrans

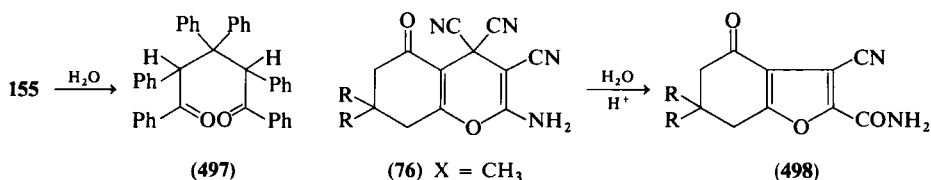
Various substituted 1,5-diones were prepared by hydrochloric acid hydrolysis of 2,6-diphenyl-4*H*-pyran (**151a**) (R = Ph),²³⁴ 2,4,6-trisubstituted 4*H*-pyrans **151b**,²⁰⁶ **151c**,²³⁶ and **172a**,²³⁶ 4-benzyl-2,4,6-triphenyl-4*H*-pyran

⁴¹⁴ N. K. Cuong, F. Fournier, and J. J. Basselier, *C.R. Acad. Sci., Ser. C* **271**, 1626 (1970).

⁴¹⁵ H. Bounani and J. Gayoso, *C.R. Acad. Sci., Ser. C*, 399 (1973).

⁴¹⁶ H. G. Henning and R. Kruger, *Z. Chem.* **20**, 261 (1980).

(165), and other 2,4,4,6-tetrasubstituted species.^{234,236} Hexaphenyl-4*H*-pyran (155) generated from phenylmagnesium bromide and appropriate pyrylium ion was found to be extremely labile toward hydrolysis, giving 1,5-diketone 497 as the only isolated product.²³⁴

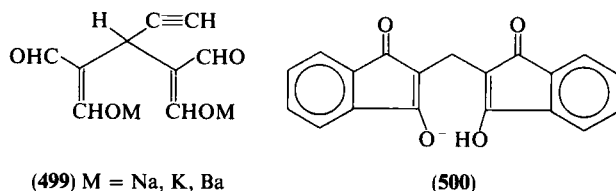


However, products of a similar transformation of dimeric 4*H*-pyran 163a were not identified.²¹⁸

2-Dimethylamino-6-methoxy-3-methyl-4*H*-pyran (96a) underwent an acidic hydrolysis with diluted HCl or TsOH to 2-methylglutaric acid derivatives MeO₂CCH₂CH₂CH(Me)COX with X = MeO or Me₂N.¹⁴⁴

Condensed 4*H*-pyrans 76 (X = CN) undergo acidic hydrolysis by ring contraction to furan derivatives 498. The detailed mechanism of the process was discussed.⁴¹⁷

Ring opening of 4*H*-pyrans in alkali were also described. Thus 3,5-diformyl-4-ethynyl-4*H*-pyran (85b) with aqueous alkali hydroxides was transformed to dienolate salts 499, and the process was followed spectrophotometrically.⁶² Analogous reactions of polycyclic 4*H*-pyrans, e.g., 30a → 29a, and 13 → 500,³⁷ also took place.

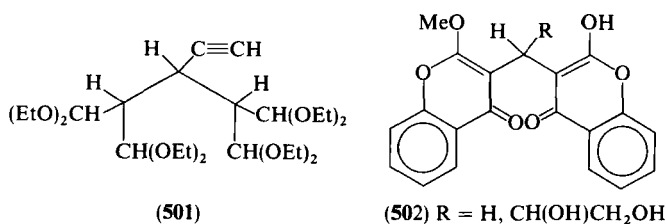


2. Alcoholysis of 4*H*-Pyrans

3,5-Diformyl-4*H*-pyran (85b) reacted with ethanol to give tetraacetal 501.⁶² Condensed 4*H*-pyrans 36 with boiling methanol or sodium methanolate gave exclusively the corresponding monomethyl ethers 502.^{82,125}

⁴¹⁷ H. Junek and H. Aigner, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* 25, 1423 (1970).

Ketol **146**, on the other hand, was formed after the reaction of spirocyclic *4H*-pyran **147** with methanolic hydrogen chloride.¹⁹¹



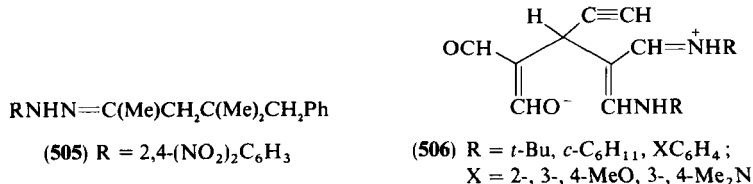
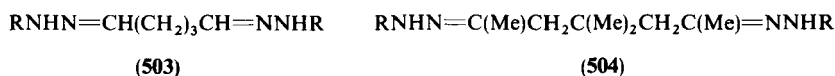
3. Reaction of *2H*-Pyrans with Hydrazine Derivatives

Condensed *2H*-pyran **128** reacted with semicarbazide in acid to give the semicarbazone of *cis*- β -ionone (**126**),¹⁶⁷ via free ketone **126**.

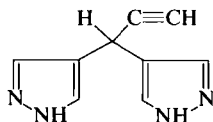
4. Reactions of *4H*-Pyrans and *4H*-Thiopyran with Amines, Hydrazines, and Hydroxylamines

Unsubstituted *4H*-pyran (**5**) and *4H*-thiopyran (**7**) with 2,4-dinitrophenylhydrazine afford identical bishydrazones **503**.^{18,19} Analogous product **504** was obtained from *4H*-pyran derivative **68** (X = EtO, Y = Me), whereas a slightly modified precursor possessing Y = Ph provided monohydrazone **505**.⁸⁶

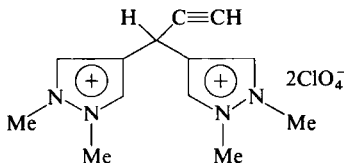
4H-Pyran **85b** readily gave with various primary amines RNH₂ at room temperature ring-opened products formulated as **506**.⁶² If hydrazine hydrochloride or *N,N'*-dimethylhydrazine and perchloric acid were used instead of the amines, the ring opening was accompanied by a secondary ring closure to lead to bispyrazolyl derivatives **507** or **508**, respectively.⁴¹⁸



⁴¹⁸ F. Wille and W. Schwab, *Monatsh. Chem.* **109**, 337 (1978).



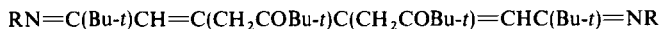
(507)



(508)

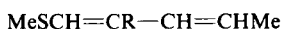
Condensed dioxo-4*H*-pyran **30a** with hydroxylamine gives an oxime $C_{13}H_{17}N_3O_3$.²

Spirocyclic 4*H*-pyran derivative **18** undergoes opening of both rings with phenylhydrazine or with hydroxylamine hydrochloride to provide corresponding dihydrazone **509a** or dioxime **509b**, respectively.⁵²



(509a) R = PhNHN

(509b) R = OH



(510a) R = H

(510b) R = Me

5. Miscellaneous

Unsubstituted 2*H*-pyran (**6**) was converted to dienyl sulfide **510a** along with a small amount of the methyl homolog **510b** by treating with sodium in HMPTA or naphthylsodium in THF followed by alkylation with methyl iodide. The conversion probably proceeded via a short-lived anion.⁴¹⁹

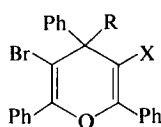
G. SUBSTITUTION REACTIONS

Substitutions may be electrophilic or nucleophilic according to the reagent used. Electrophilic chlorination or bromination usually takes place at position 3 and/or 5 where a relatively high π -electron density is located in all pyran-like heterocycles. In a second process, electrophilic attack occurs only after deprotonation of a starting substrate with a strong base; substitution in the 2-, 4-, or 6-positions is typical. Nucleophilic substitution usually takes place if a pyran or thiopyran has in the 2-, 4-, or 6-position a chlorine, methoxy, or an amine leaving group.

⁴¹⁹ R. Gräffing and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **98**, 520 (1979).

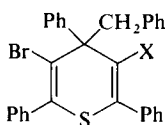
1. *Simple Electrophilic Substitutions of Pyrans and 4H-Thiopyrans*

2,4,4,6-Tetraphenyl-4*H*-pyran (**25**) easily gave with bromine in carbon disulfide the more stable 3,5-dibromo derivative **511a**.^{58,420} Analogous 4-benzylated 4*H*-pyran **165** gave with NBSI (*N*-bromosuccinimide) monobrominated products **511b**.⁴²¹ The bromination of 4-benzyl-2,4,6-triphenyl-4*H*-thiopyran (**467b**) with the same reagent afforded either mono- (**512a**) or dibrominated species **512b**.⁴²¹ Similarly, the reaction of 4-chloro-2,6-diphenyl-3-formyl-2*H*-pyran (**283a**) with NCSI (*N*-chlorosuccinimide) in pyridine afforded 5-chlorinated compound **513**.²⁹⁹ Of course, a radical pathway cannot be entirely excluded.



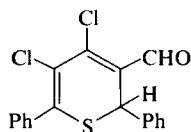
(**511a**) R = Ph; X = Br

(**511b**) R = PhCH₂; X = H



(**512a**) X = H

(**512b**) X = Br



(**513**)

A report on the Friedel-Crafts acetylation of 3-methyl-4*H*-thiopyran (**3**)⁶ should be considered with caution because of lack of a sufficient structure proof for **3**.

2. *Electrophilic Substitutions via Deprotonated Pyrans and Thiopyrans*

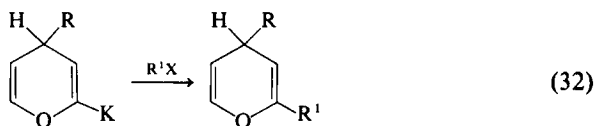
The parent heterocyclic structure may be activated toward electrophilic agents by prior deprotonation either to a corresponding organometallic derivative or to a more ionic species possessing a heterocyclic π -electronic octet. Electrophilic attack on the conjugate base is less regioselective than on the parent. The choice of the two alternative pathways of substitution seems to be determined by the deprotonating reagents, polarity of solvents, and reaction conditions.

a. *Deprotonation.* Diethyl 2,6-diphenyl-4*H*-pyranphosphonate (**217**) (R = Ph, R¹ = Et) and its thia analog **255** were successfully deprotonated with butyllithium and deuterated with *O*-deuteriomethanol at -78°C to give 4-deuterated **217**²⁶⁵ and 4-deuterated **255**, respectively, together with its 2-deuterated thio-2*H* isomer **483**.²⁸⁸

⁴²⁰ A. P. De Carvalho, *C.R. Acad. Sci.* **199**, 1430 (1934).

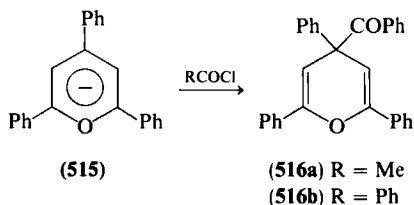
⁴²¹ U. Eisner and T. Krishnamurthy, *J. Org. Chem.* **37**, 150 (1972).

b. *Alkylation, Acylation, and Silylation of Pyrans.* Unsubstituted 4*H*-pyran (**5**) and its 4-methyl derivative were converted with a butyllithium-potassium *tert*-butoxide mixture or with trimethylsilylmethylpotassium to corresponding 4*H*-pyran-2-ylpotassium intermediates capable of alkylation or silylation to 2-substituted 4*H*-pyrans **514a,b** in up to 48% yields (Eq. 32).⁴²² 2,4,6-Triphenyl-4*H*-pyran (**45**, R = Ph) exhibited, on the other hand, a measurable acidity of the 4-hydrogen ($pK_A = 37 \pm 2$)⁴²³ and together with 2*H*-isomer **225** gave with sodium amide in liquid ammonia or with *tert*-butyllithium in THF the anionic species of probable structure **515**. The latter was easily alkylated or acylated with methyl iodide, benzyl chloride, acetyl chloride, and benzoyl chloride exclusively at position 4 to provide 4*H*-pyrans **245i,l** as well as **516a,b**.⁴²⁴ The acidity of **45** having R = Ph ($pK_A = 19.5$)⁴²³ was simulated by CNDO/2 calculations.⁴²⁵



(514a) R = H; R^1X = MeI, Me_3SiCl

(514b) R = Me; R^1X = EtBr, Me_3SiCl , $\text{Me}_3\text{SiCH}_2\text{Br}$



(516a) R = Me

(516b) R = Ph

c. *Alkylation, Acylation, and Sulfurization of Thiopyrans.* Unsubstituted 2*H*-thiopyran (**6**) is capable of various deprotonation reactions on the parent skeleton.^{377a,426-429} The reaction was extended to condensed 2*H*-pyran systems.^{428,430} As shown in Scheme 26, the alkylation of

⁴²² M. Schlosser and P. Schneider, *Angew. Chem.* **91**, 515 (1979).

⁴²³ R. R. Schmidt, U. Burkert, and R. Prowo, *Tetrahedron Lett.*, 3477 (1975).

⁴²⁴ R. R. Schmidt and U. Burkert, *Tetrahedron Lett.*, 4355 (1973).

⁴²⁵ A. F. Pronin, V. G. Kharchenko, and A. A. Bagaturyants, *Khim. Geterotsikl. Soedin.*, 994 (1977).

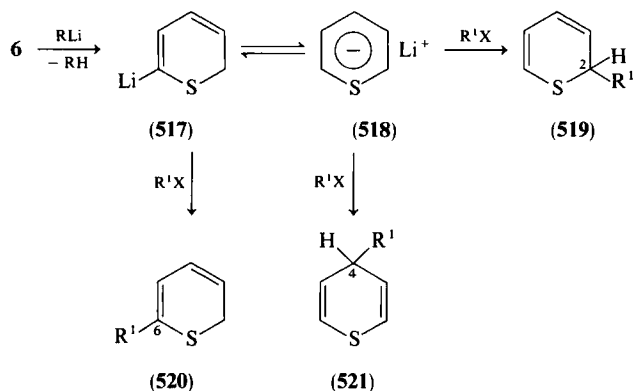
⁴²⁶ R. Gräfin, H. D. Verkruijsse, and L. Brandsma, *J.C.S. Chem. Commun.*, 596 (1978).

⁴²⁷ R. Gräfin and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **97**, 208 (1978).

⁴²⁸ R. Gräfin and L. Brandsma, *Synthesis*, 578 (1978).

⁴²⁹ R. Gräfin, H. D. Verkruijsse, and L. Brandsma, *J. Chem. Soc.*, 596 (1978).

⁴³⁰ R. Gräfin and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **99**, 23 (1980).



SCHEME 26

6 after deprotonation with lithium bases may lead to 6-substituted 2H-thiopyrans **520**, 2-substituted 2H-thiopyrans **519**, and/or to 4-substituted 4H isomers **521**. Lithium compounds **517** or **518** undergo electrophilic attack by the alkylating agent.^{377a,427,428} On the other hand, sodio- and potassioamides generate predominantly the thiopyran anion **518**.^{426,427,429} The isomerization **517** → **518** was also caused by addition of powerfully solvating agents, such as HMPTA, to the deprotonating mixture.⁴²⁷ Kinetic factors influence the composition of the resulting products.^{427,429}

The results of the alkylation of **6**^{377a,426,427,429} are summarized in Table XI. In addition to the above factors, the regioselectivity of electrophilic attack on **518** was strongly affected by the structure of the alkylating agents, e.g., methyl iodide, ethyl bromide, cyclohexyl bromide, and *tert*-butyl bromide.

TABLE XI
PRODUCTS OF DEPROTOALKYLATION OF 2H-THIOPYRAN (**6**)

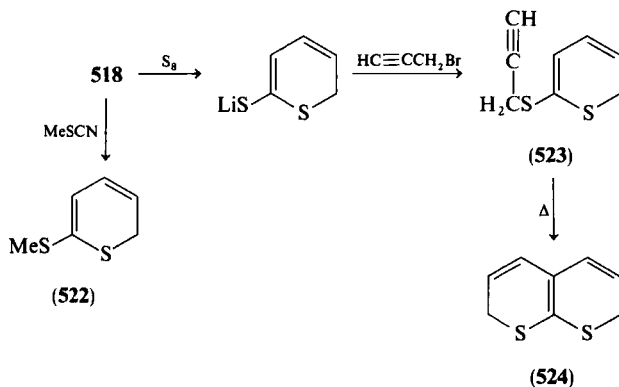
Deprotonating agent	Alkylating agent	Total yields (%)	Products	References
BuLi, THF	MeI	72	520	427
LDA ^a , THF	MeI	— ^b	520 + 521	427
BuLi, THF, HMPTA				
<i>i</i> -Pr ₂ NH	MeI	74	521	427
KNH ₂ , NH ₃ (l)	<i>t</i> -BuBr	54	519	426, 429
NaNH ₂ , NH ₃ (l)	<i>c</i> -C ₆ H ₁₁ Br	82	519 + 521 ^c	426, 429

^a Lithium diisopropylamide.

^b Not reported.

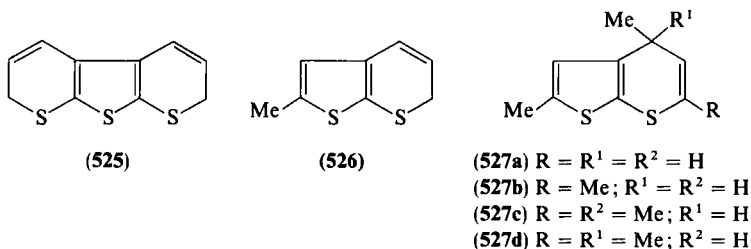
^c Ratio 85:15.

As shown in Scheme 27, 6-lithio-2*H*-thiopyran (**517**) further underwent thiomethylation and sulfurization accompanied by 3-propynylation to afford 6-substituted 2*H*-pyrans **522**^{377a} and **523**.⁴²⁸ The latter was thermally converted to bicyclic 2*H*-pyran system **524**⁴²⁸ by the general procedure mentioned in Section III,F.



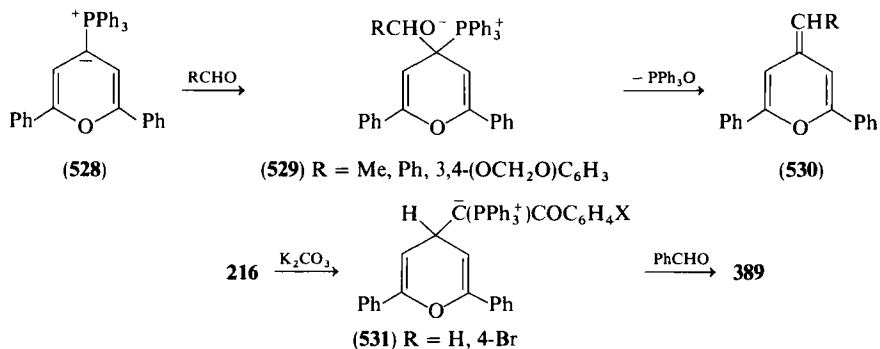
SCHEME 27

The same approach was used in the synthesis of tricyclic bis-2*H*-pyran system **525** from thieno-2*H*-pyran **15**.⁴²⁸ The deprotomethylation of **15** was also shown to proceed via intermediates like **517** and **518** and gave various methylated products **526** and **527a-d**.⁴³⁰

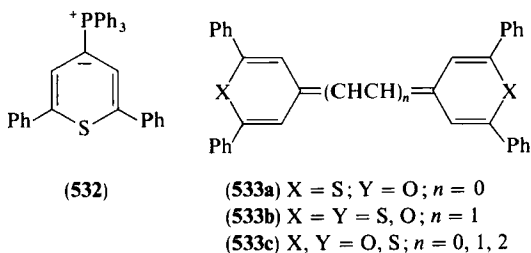


d. *Wittig-Horner Reactions with 4*H*-Pyranylphosphonium Salts and with 4*H*-Thiopyranyl Phosphonates.* Wittig reagent **528** generated *in situ* from salt **215a** with phenyllithium gave with aldehydes 4*H*-pyranylidene derivatives **530**.²⁴¹ In case of R = Ph, intermediate **529** was trapped.²⁴¹ Reagents **531** obtained from phosphonium salts **216** and potassium carbonate gave ketones **389** with benzaldehyde.²⁵¹

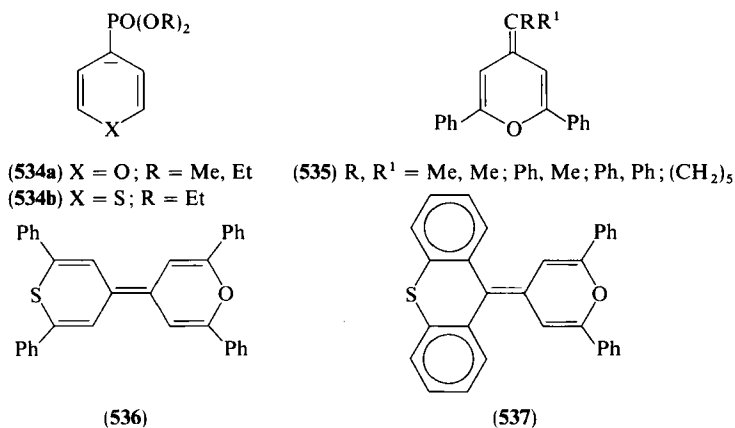
Reagent **528** and 2,6-diphenylthiopyrylium perchlorate afford 4,4'-bis-4*H*-pyranylidene (**533a**).^{262a} Analogous transformations of various



pyrylium and thiopyrylium salts with **528** or with its thia analog **532**, prepared in a similar way,²⁶² allowed conversions to products like **533**.^{262a}



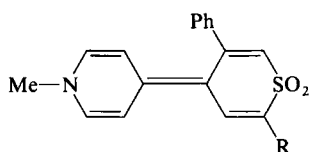
The Wittig-Horner reagents **534a,b** generated from **217** (R = Ph, R¹ = Me, Et)^{265,431} afforded variously substituted **530** having R = Me, Ph, 2,4-(MeO)₂C₆H₃, 3,4-(MeO)₂C₆H₃, *o*- and *p*-C₆H₃, 9-anthryl, 2-thienyl, and 2-quinolyl with corresponding aldehydes as well as **535** and products like **536**



⁴³¹ S. V. Krivun, S. N. Baranov, and O. F. Voziyanova, *Zh. Obshch. Khim.* **43**, 359 (1973).

and **537** with appropriate ketones.^{265,431} The use of different 4-formyl-methylenepyrans, 4*H*-pyranilidenebutenaldehydes, as well as corresponding thia analogs, together with **255**²⁸⁸ led to optically interesting derivatives **533b**⁴³² and **533c**.⁴³³

e. *Arylation of 2*H*-Thiopyran *S,S*-Dioxides.* When dioxides **484** were deprotonated with potassium hydrogen carbonate in the presence of 4-bromopyridinium iodide, the 4-substitution in **484** occurred, and dihydropyridine derivatives **538** were isolated.^{434,435} Analogous compounds **539a,b** were obtained in the same way.⁴³⁵



(**538**) R = H, Me

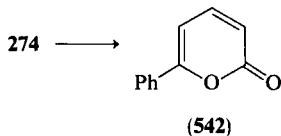
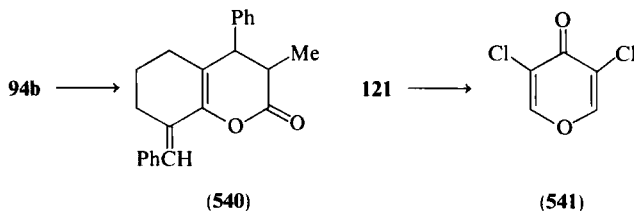


(**539a**) R = R² = H; R¹ = Ph

(**539b**) R = Me; R¹ = H; R² = Ph

3. Nucleophilic Substitution of Pyran and Thiopyran Derivatives

a. *Hydrolysis.* 2-Dimethylamino-4*H*-pyran **94b** with dilute acetic acid and acetate ion gave 3,4-dihydropyrene **540** (80%).¹⁴² 2,4,4,5-Tetrachloro-4*H*-pyran (**121**) was easily hydrolyzed with water to 2,3-dichloro-4-pyrone



⁴³² G. A. Reynolds and C. H. Chen, *J. Org. Chem.* **46**, 184 (1981).

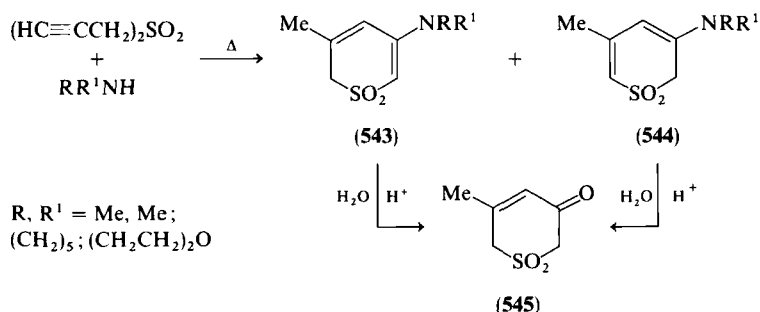
⁴³³ G. A. Reynolds and C. H. Chen, *J. Heterocycl. Chem.* **18**, 627 (1981).

⁴³⁴ G. Pagani and S. Maiorana, *Chim. Ind. (Milan)* **53**, 259 (1971).

⁴³⁵ G. Pagani, *J.C.S. Perkin Trans. II*, 1184 (1973).

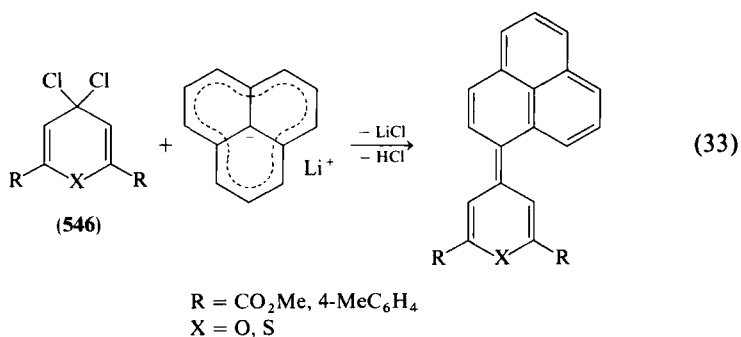
(541).¹⁶⁰ 2,2-Dimethoxy-6-phenyl-2*H*-pyran (274) with sodium hydroxide in DMF provided 34% of 6-phenyl-2-pyrone (542).²⁹⁵

Unsaturated ketone 545 was obtained in a 98% yield by acid hydrolysis of a mixture of isomeric 2*H*-thiopyran *S,S*-dioxides 543 and 544 generated³⁸² as shown in Scheme 28 (see Section III,F,6).



SCHEME 28

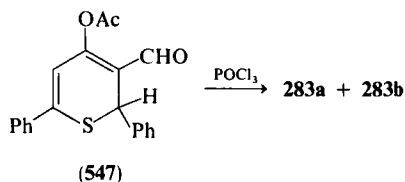
b. Other Nucleophilic Substitutions. 4,4-Dichloro-4*H*-pyran and analogous 4*H*-thiopyrans 546 react with fenalidlithium as shown in Eq. (33).⁴³⁶



The substitution of the 4-acetoxy group in 2*H*-thiopyran-3-carboxaldehyde 547 with phosphorus oxychloride was accompanied by decarbonylation, affording a mixture of 2*H*-pyrans 283a and 283b.²⁹⁹ An aminolysis of unsaturated dichloropyrans was patented.⁴³⁷

⁴³⁶ I. Murata, T. Nakazawa, and S. Tada, *Tetrahedron Lett.*, 4799 (1971).

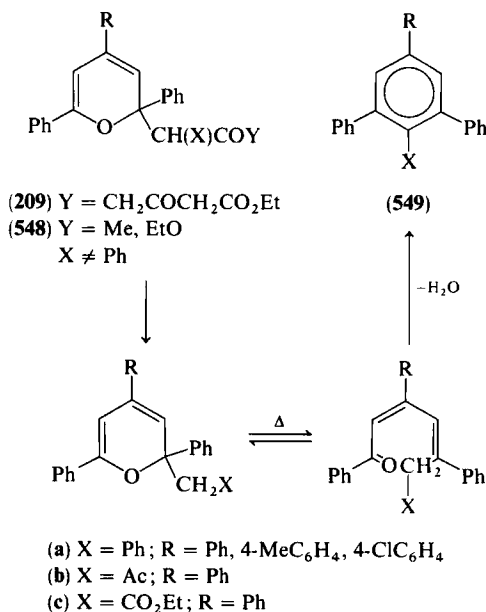
⁴³⁷ A. A. Gevorkyan, Sh. O. Badanyan, and A. A. Manukyan, USSR Patent 387,987 (1973) [CA 79, 126309 (1973)].



H. CONVERSION TO CARBOCYCLIC SYSTEMS

1. *Intramolecular Cyclizations via Valence-Bond Tautomers of 2H-Pyrans and 2H-Thiopyrans*

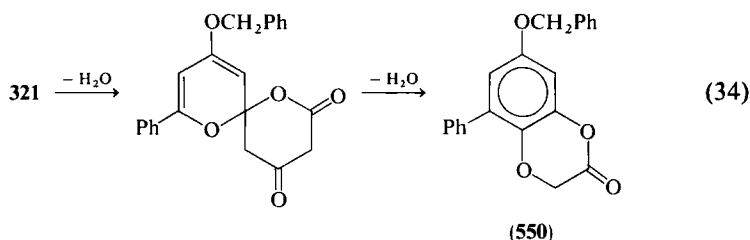
If a 2H-pyran or 2H-thiopyran derivative **459** possesses in substituents A or B an active methylene fragment, for example PhCH_2 , RCOCH_2 or NO_2CH_2 , the corresponding valence-bond tautomers **460** or **462** may undergo intramolecular ring closure to substituted benzenes. The equilibria shown in Scheme 22 are shifted toward such products.



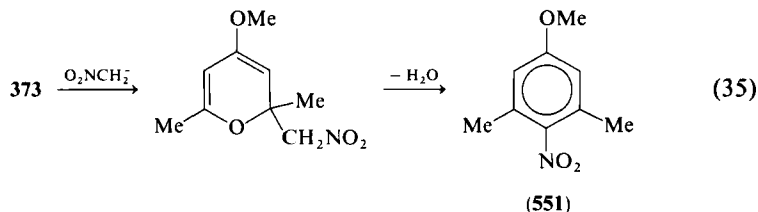
SCHEME 29

a. *Conversions of 2H-Pyrans.* 2-Substituted 1,3,5-triarylbenzenes **549a**,^{233,236,400} **549b**,²⁵³ and **549c**,^{9,253} were prepared from 2H-pyrans by intramolecular ketolization (Scheme 29). The transformations were accomplished with bases,^{9,233,236,253} acids,²³⁶ or thermally.⁴⁰⁰ In cases of X $\neq$ Ph, the starting 2H-pyran β -dicarbonyl derivatives **548b**,²⁵³ **548c**,²⁵³ or **209**⁹ underwent the loss of the COX residue by the action of bases. Condensed 4H-pyran **191** gave triphenyltetraline by heating with sodium alkoxide.⁴³⁸

Analogously, the formation of lactone **550** from 2H-pyran **321**³¹⁷ may be explained by Eq. (34).



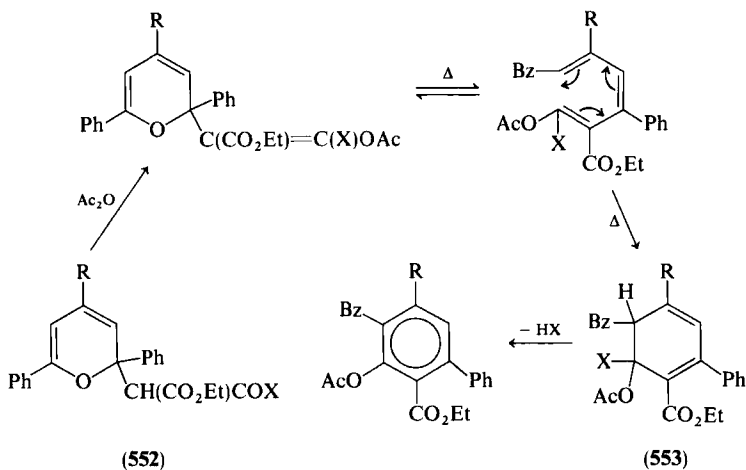
The formation of 2,6-dimethyl-4-methoxy-1-nitrobenzene (**551**) from intermediate 2,6-dimethyl-4-methoxy-2H-pyran (**323**) and nitromethide ion³¹⁹ involves aromatization to pyrylium ion **373** followed by the expected process shown in Eq. (35).



Sometimes the formation of benzene derivatives can be explained by cycloaddition rather than by ketolization. Thus the excellent preparation of substituted benzophenones **553** from 2H-pyrans **552** on heating with acetic anhydride²⁵³ is interpreted as in Scheme 30.

b. *Conversion of 2H-Thiopyrans.* 2-Benzyl-2,4,6-triphenyl-2H-thiopyran (**2461**) was transformed to 1,2,3,5-tetraphenylbenzene (**549**, X = Ph, 58%) by sodium alkoxides.^{236,438}

⁴³⁸ K. Dimroth, H. Kroke, and K. H. Wolf, *Justus Liebigs Ann. Chem.* **678**, 202 (1964).

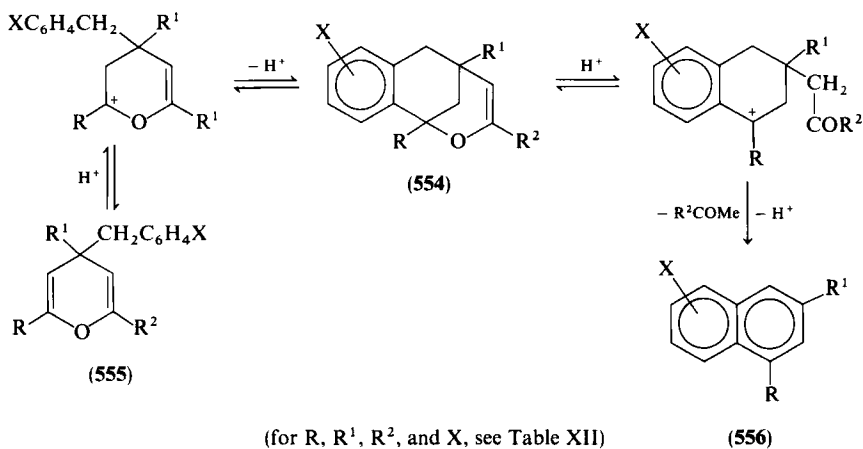


$\text{R} = \text{Me, EtO}$
 $\text{X} = \text{Ph, 2-thienyl}$

SCHEME 30

2. Intramolecular Rearrangements of Protonated 4H-Pyrans and 4H-Thiopyrans

The title derivatives with strong acids generate heterocyclic carbocations that may lead to intramolecular electrophilic substitution in ortho sites of 4-benzyl or 4-benzyl-like substituents.



(for R , R^1 , R^2 , and X , see Table XII)

SCHEME 31

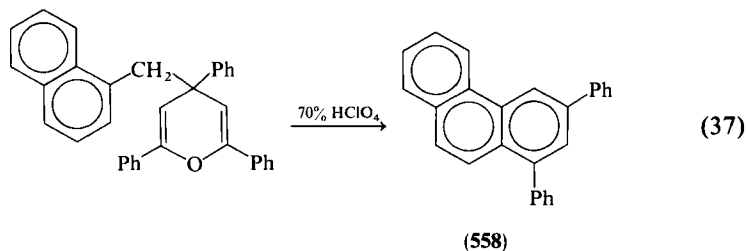
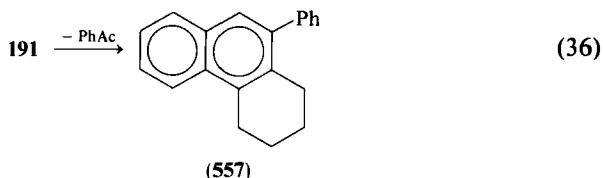
TABLE XII
SOME NAPHTHALENES **556** PREPARED FROM 4*H*-PYRANS **555**^{438,439}

Substituents ^a				Yield (%)
R	R ¹	R ²	X	
Me	Me	Me	H	70
Me	Ph	Me	H	89
Me	<i>t</i> -Bu	Me	H	71
Ph	Ph	<i>t</i> -Bu	H	93
Ph	Ph	Ph	H	87
Ph	Ph	Ph	MeO	91
4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	H	45

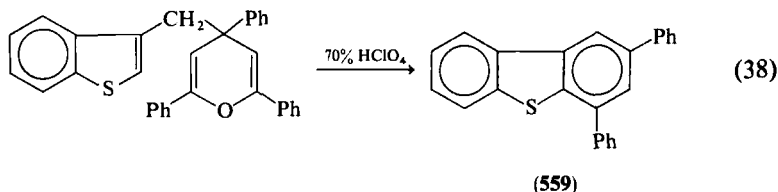
^a See Scheme 31.

a. *Rearrangements of 4*H*-Pyrans.* 2,4,6-Trisubstituted 4-benzyl-4*H*-pyrans **555** react with 70% perchloric acid^{236,439} to form 1,3-disubstituted or 1,3,7-trisubstituted naphthalenes **556** by a prototropic mechanism involving intermediates **554**⁴³⁸ as shown in Scheme 31.

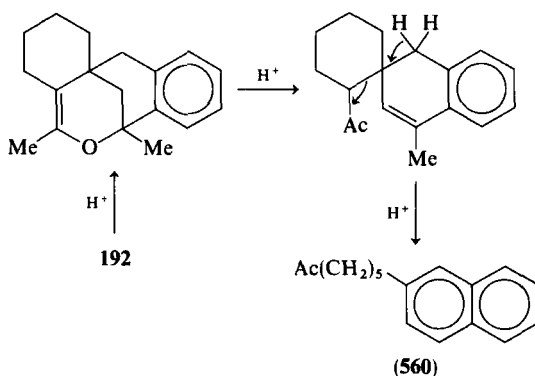
The rearrangement accompanied by the elimination of ketone R²COMe gave, as a rule, good yields of naphthalenes **556** (Table XII)^{438,439} and was extended to the synthesis of polycondensed aromatic systems **557**, **558**, and (**559**), as demonstrated by Eqs. (36–38).



⁴³⁹ K. Dimroth and K. H. Wolf, *Angew. Chem.* **72**, 778 (1960).



The somewhat different prototropic transformation of condensed 2*H*-pyran **192** to ketone **560**⁴³⁸ requires an explanation involving at least two neutral intermediates, as suggested in Scheme 32.



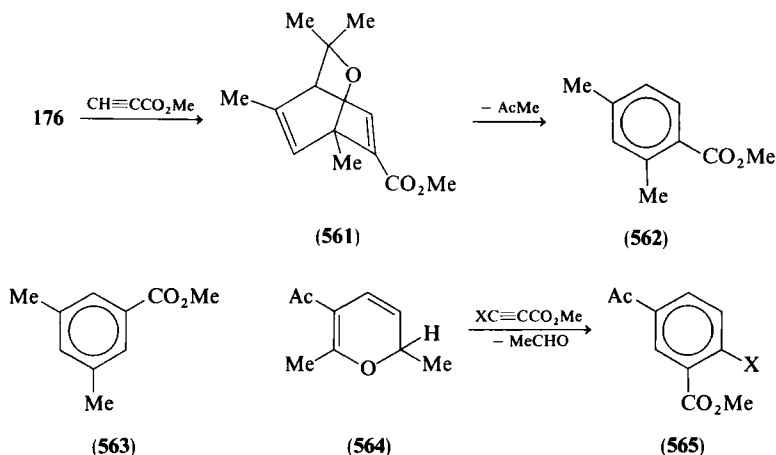
SCHEME 32

b. *Rearrangements of 4H-Thiopyrans.* 4-Benzyl-2,4,6-triphenyl-4*H*-thiopyran (**245I**) with 70% perchloric acid gave expected 1,3-diphenyl-naphthalene **556** ($R = R' = \text{Ph}$, $X = \text{H}$) in up to 54% yield.^{236,438} The probable mechanism is analogous to that shown in Scheme 31; an intermediate like **554** was trapped as compound **496** after treatment of condensed 4*H*-thiopyran **22** with hydrogen chloride [see Eq. (31) in Section V,E,5].

3. Spontaneous Decomposition of Cycloadducts of 2*H*-Pyrans with Acetylenic Dienophiles

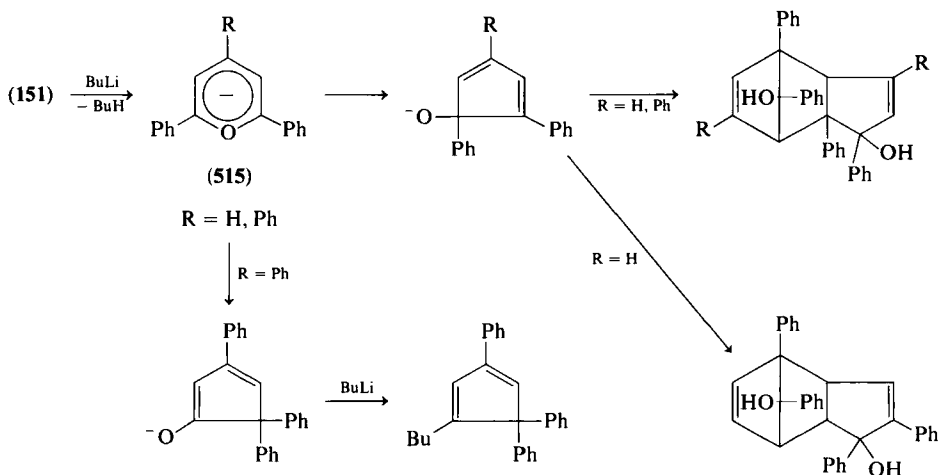
Relatively stable 2,2,4,6-tetramethyl-2*H*-pyran (**176**) exhibited a high regiospecificity toward methyl propargylate to afford $[4\pi + 2\pi]$ adduct **561**, which spontaneously decomposed to methyl 2,4-dimethylbenzoate (**562**) in 73% yield.⁴⁰⁵ Similarly, labile 3-acetyl-2,6-dimethyl-2*H*-pyran (**564**) gave with acetylenic methyl carboxylates benzenoid derivatives **565**. On the other

hand, labile 2,4-dimethyl-2*H*-pyran exhibited in this reaction somewhat less regiospecificity, providing a 4:1 mixture of isomeric methyl esters **562** and **563**.



4. Conversion of 4*H*-Pyrans to Cyclopentadienes

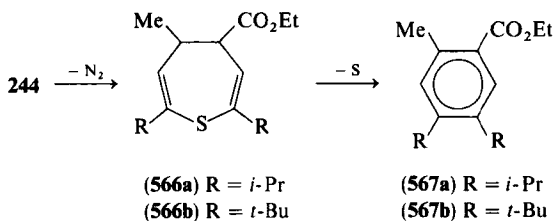
4*H*-Pyrans **151a** ($\text{R} = \text{Ph}$) and **151c** gave with excess butyllithium at -30 to -120°C **515**-like anions, which isomerized to substituted cyclopentadiene anions and then, either dimerized or reacted with the reagent (Scheme 33).⁴²³



SCHEME 33

5. Other Decompositions of 4*H*-Thiopyrans

The transformation of diazoester **244** ($R^1 = \text{Me}$, $R = i\text{-Pr}$) to substituted ethyl benzoate **567a**, catalyzed with palladium(II), proceeded as a spontaneous desulfurization of unstable thiopin derivative **566a**.²⁸⁵ The isolation of the similar intermediate **566b** will be mentioned in Section G,3.



I. CONVERSION TO OTHER HETEROCYCLES

Most important is the conversion of 4*H*-pyrans to pyridines. Ring contraction and ring expansion reactions of 2*H*-pyrans and 2*H*-thiopyrans also occur.

1. Conversion of 4*H*-Pyrans to 1,4-Dihydropyridines

4*H*-Pyrans are transformed to the corresponding π -isoelectronic 1,4-dihydropyridine derivatives by ammonia,^{2,37,68,69} ammonium acetate,^{76,440,441} primary amines,^{37,62,68,442} hydroxylamine,³⁷ arylhydrazines,^{311,313} urea,⁴⁴⁰ and thiourea.⁴⁴⁰ The open-chain intermediates are rarely isolated.⁶²

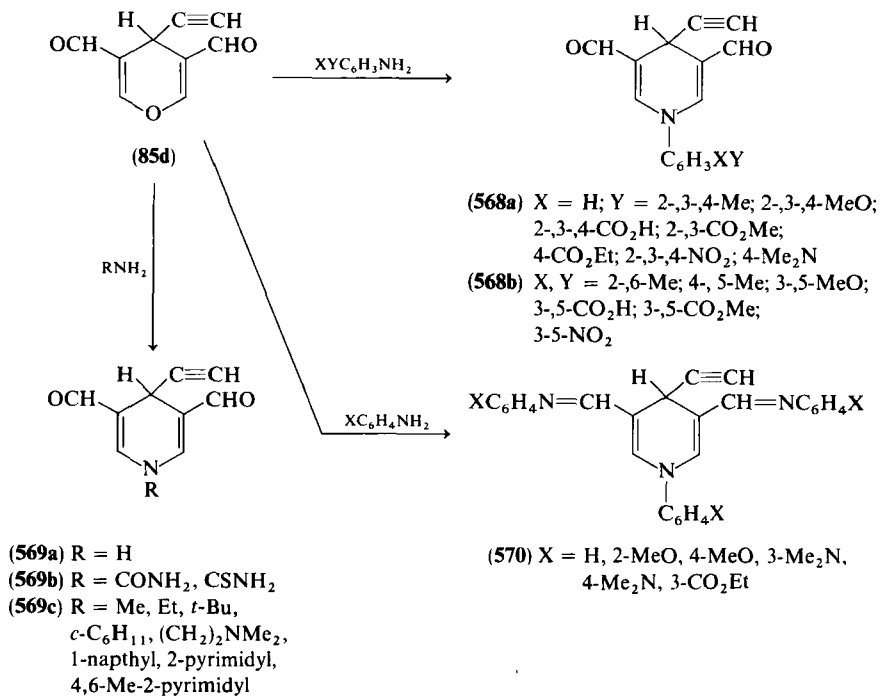
A large number of 1,4-dihydropyridines were prepared from 3,5-diformyl-4-ethynyl-4*H*-pyran (**85d**). Thus compounds **568a,b** and **569a-c** were isolated after the reaction of **85d** with primary amines,^{62,442} ammonium acetate,⁴⁴⁰ urea, and thiourea.⁴⁴⁰ As shown in Scheme 34, some aromatic amines react with both 3,5-aldehydic groups to afford 1,4-dihydropyridine Schiff bases **570**.^{62,442}

3,5-Dicarbonyl 4*H*-pyran derivatives can be converted to 1,4-dihydropyridines. 3,5-Diketones **86** ($R = R^1 = \text{H}$; $R^2 = \text{H, Ph}$), **13**, and bislactone **34b** afforded appropriate azaheterocycles **571**,² **572**,³⁷ and **573**.⁷⁶ More complex 1,4-dihydropyridines **574** were synthesized analogously.^{68,69}

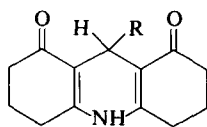
⁴⁴⁰ F. Wille and W. Schwab, *Chem. Ber.* **110**, 985 (1977).

⁴⁴¹ C. Seoane, J. L. Soto, and P. Zamorano, *J. Heterocycl. Chem.* **18**, 309 (1981).

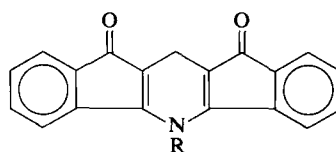
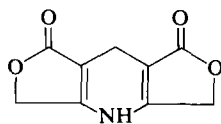
⁴⁴² F. Wille, W. Schwab, and J. Kroner, *Monatsh. Chem.* **110**, 613 (1979).



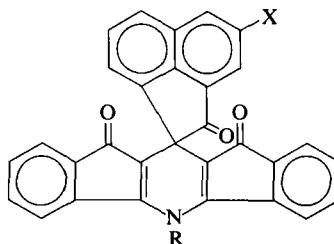
SCHEME 34



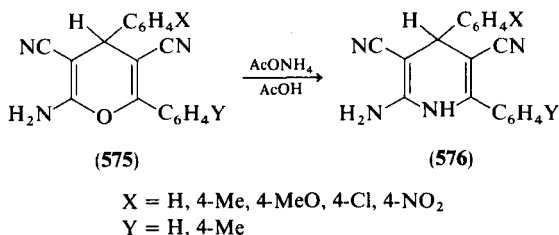
(571)

(572) R = H, Et, Bu, CH₂CH₂OH, OH

(573)

(574) R, X = H, H; Ph H; H, NO₂

2-Amino-3,5-dicyano-4*H*-pyrans **575** gave 1,4-dihydropyridines **576** in the same way, whereas analogous 3-esters were fully aromatized.⁴⁴¹

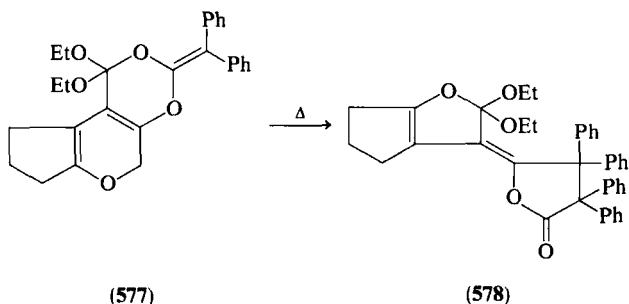


4-*H*-Pyrans **69** and **326** (R = Pr) provide dihydropyridines with arylhydrazines,^{311,313} but a structure proof is lacking.

2. Ring Contraction in 2*H*-Pyrans and 2*H*-Thiopyrans

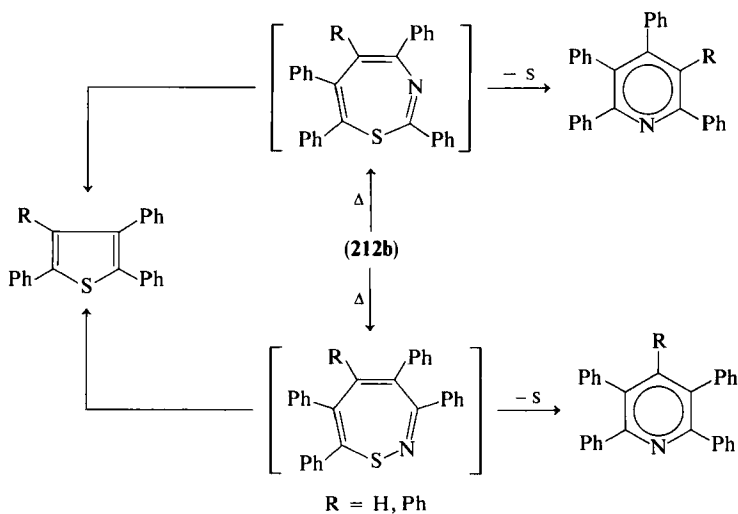
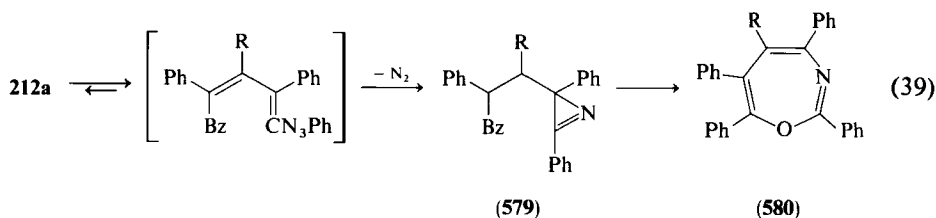
The oxidation of 2-substituted 3,4,5,6-tetrachloro-2*H*-pyrans **143b** with molecular oxygen at 20°C was accompanied by contraction of the six-membered ring to 2-furylcarbonyl chlorides **428**,³² (Section V,A,6). The formation of compounds **430**²¹¹ and **498**⁴¹⁷ represents other 2*H*-pyran ring contractions.

Condensed 2*H*-pyran derivative **577** rearranges to **578** at 150–160°C in 30 min.⁴⁴³



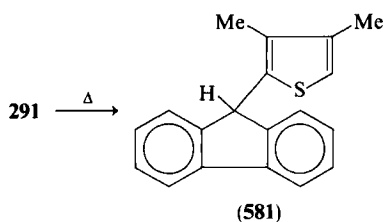
2-Azido-2*H*-pyran derivatives **212a** (R = H) eliminates nitrogen on standing to give azirine **579** (Eq. 39). When R = Ph, intermediate **579** was too labile to be trapped.²⁵⁴ Analogous azido-2*H*-thiopyrans **212b** decomposed only at elevated temperature to provide thiophene and pyridine derivatives,²⁵⁴ as shown in Scheme 35.

⁴⁴³ R. W. Saalfrank, *Tetrahedron Lett.*, 295 (1975).



SCHEME 35

Complex 2*H*-thiopyran derivatives **291** afforded 25% of isomeric thiophene **581** on heating at 240°C in a nitrogen atmosphere.³⁰²



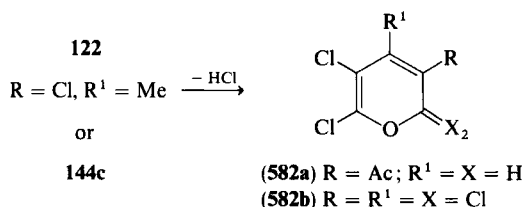
3. Ring Expansion in 2*H*-Pyrans and 2*H*-Thiopyrans

Decomposition of 2-azido-2*H*-pyran (**212a**) generated seven-membered heterocyclic system **580** when starting **212a** had R = Ph or by heating **579** (R = H).²⁵⁴

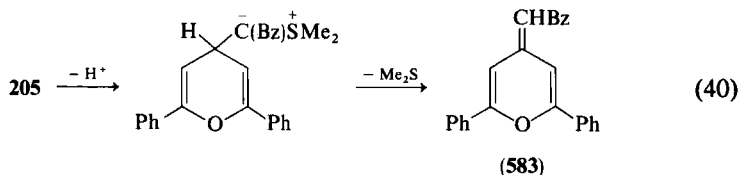
2*H*-Thiopyran diazoester **244** ($R = t\text{-Bu}$) was converted catalytically to relatively stable thiopine **566b** with π -allylpalladium chloride²⁸⁶; at 140°C **566b** gave **567b**.

4. Pyranylidene Derivatives from Pyrans

3-Acetyl-2-methyl-2,5,6-trichloro-2*H*-pyran (**122**: $R = \text{Cl}$, $R^1 = \text{Me}$) and 3,4,5,6-tetrachloro-2-trichloromethyl-2*H*-pyran (**144c**) eliminated hydrogen chloride to provide 2-methylene derivatives **582a**¹⁶² and **582b**.^{188,444}

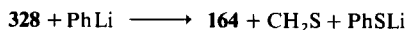


2,6-Diphenyl-4*H*-pyranylideneacetophenone (**583**) was prepared from the dimethylsulfonium ylide on heating with dilute hydroxide as shown in Eq. (40).²⁵²



Analogously, 4-chloromethylene-4*H*-pyran was prepared in about 50% yield by vacuum thermolysis of 4-dichloromethyl-4*H*-pyran **604** ($X = \text{O}$) on a sodium methoxide-silica gel-fiberglass catalyst.⁴⁴⁵

Bis-4,4'-pyranylidene derivative **164** ($R = \text{Ph}$) was prepared from dimeric 4*H*-pyran compounds **328** as follows:³²²

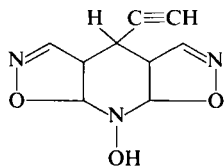


5. Miscellaneous

The diformyl derivative **85d** with hydroxylamine hydrochloride on heating gave tricyclic product **584**.⁴¹⁸

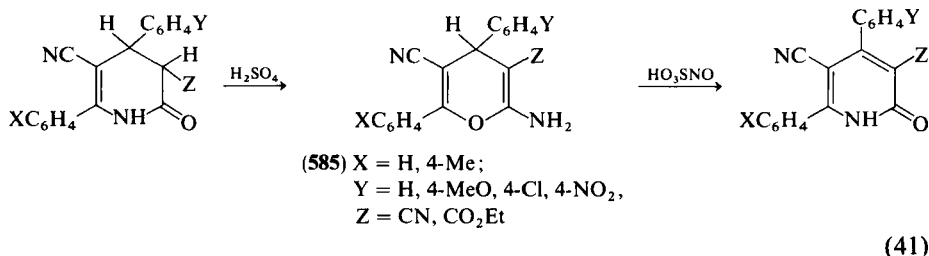
⁴⁴⁴ A. Roedig and H. Göpfert, *Chem. Ber.* **113**, 806 (1980).

⁴⁴⁵ K. Dimroth, W. Kinzebach, and M. Soyka, *Chem. Ber.* **99**, 2351 (1966).



(584)

The conversion of polysubstituted 4*H*-pyran derivatives **585** to corresponding pyridones and dihydropyridones was accomplished as in Eq. (41).⁴⁴¹

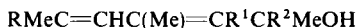


(41)

J. ADDITION REACTIONS

1. Simple Additions

a. *Additions of Grignard Reagents to 2*H*-Pyrans.* Organometallics shift the valence-bond tautomerism shown in Scheme 22 (Section V,E,1) toward dienone forms **461** and **463**, which then react to give the corresponding dienols.⁴⁴⁶ 2,3,4,6-Tetramethyl-2*H*-pyran (**471b**) and 2,2,4,6-tetraalkyl-2*H*-pyrans **176** and **184** (R = Et) give with methylmagnesium iodide unsaturated alcohols **586a-c** (79–86%).⁴⁴⁶ The assumed course of the addition was supported by treating **471b** with a ¹³C labeled Grignard reagent. Such organometallic reactions may apparently accompany the preparation of 2*H*-pyrans from pyrylium salts and 2-pyrones (Sections IV,A,3 and IV,G,1), especially if excess reagent is used.



(586a) R = R¹ = Me; R² = H

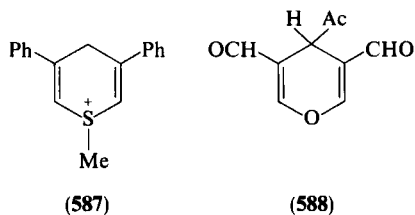
(586b) R = R² = Me; R¹ = H

(586c) R = R² = Et; R¹ = H

b. *Addition of Alkyl Halogenides to 2*H*-Thiopyrans.* As mentioned in Section V,A,2, methyl iodide added to 3,5-diphenyl-2*H*-thiopyran

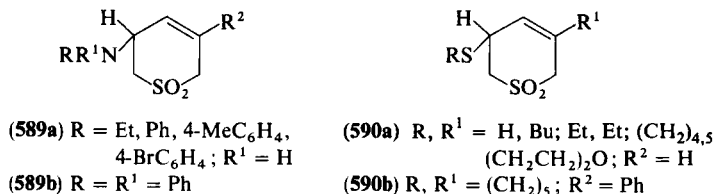
⁴⁴⁶ J. Royer and J. Dreux, *Justus Liebigs Ann. Chem.* **741**, 109 (1970).

(222) in the presence of silver tetrafluoroborate to give *S*-methylthiosulfonium salts **397**.^{267,274} The latter are in equilibrium with the 4*H* isomer (**587**).²⁶⁷



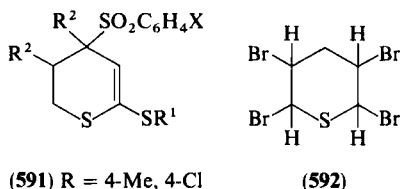
c. *Addition of Water and Amines to Pyrans and 2H-Thiopyran S,S-Dioxides.* The reported hydration of the triple bond in 4-ethynyl-4*H*-pyran derivative **85d** with diluted acetic and sulfuric acids in the presence of mercury(II) sulfate, affording 4-acetyl compound **588**,¹¹⁷ could not be repeated.⁶²

2*H*-Thiopyran *S,S*-dioxide (**9**) accepted several amines RR^1NH by addition in the presence of triethylamine to give cyclic sulfones **589a** in variable yields.²⁶ Similarly, 3-phenyl derivative **289** gave **589b** with piperidine, whereas no addition took place with sodium methoxide.³⁰⁰



d. *Addition of Thiols and Sulfinic Acids to 2H-Thiopyrans.* *S,S*-Dioxides **9** and **289** accept some thiols by addition, providing expected adducts **590a**²⁶ and **590b**,³⁰⁰ respectively.

3,4,6-Trisubstituted 2*H*-thiopyrans **299** add to arylsulfinic acids $XC_6H_4SO_2H$ to afford sulfones **591**. The addition was catalyzed with protons, and the detailed mechanism was discussed in reference 304.



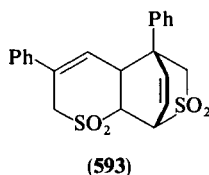
e. *Halogenations.* 4*H*-Pyrans-2,6-dicarboxylic acids **32** afford dibromo adducts with bromine.⁷¹ The structures of analogous products from

2-hydroxy-2,4,6-triphenyl-2*H*-pyran (**41**) and bromine or iodine were not elucidated.²⁶⁰

Unsubstituted 4*H*-thiopyran (**7**) gave with bromine 2,3,5,6-tetrabromo derivative **592**, whereas chlorine and iodine caused aromatization to thio-pyrylium halogenides **221**.³⁶¹

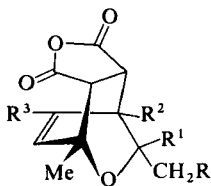
2. Cycloadditions

a. *Dimerization*. 3-Phenyl-2*H*-thiopyran *S,S*-dioxide (**289**) self-dimerizes to cycloadduct **593**.³⁰⁰



b. *Oxygenation*. The photochemical $[2\pi + 4\pi]$ addition of molecular oxygen to 2,3,4,5,6-pentaphenyl-2*H*-pyran (**154**) at -70°C gave 3,6-endo-peroxide **429**.²¹¹

c. *Diels-Alder Cycloadditions of Electrophilic Ethenes to 2*H*-Pyrans*. Maleic anhydride reacted easily with 2,2,3,4,6-pentamethyl-2*H*-pyran, with other methylated 2*H*-pyrans (**176** and **471b**), as well as with 4-substituted 2-benzyl-2,6-diphenyl-2*H*-pyrans **467a** to give $[2\pi + 4\pi]$ cycloadducts of probable structures **594a,b**,²³⁷ **594c**,²¹² and **594d**.⁴⁴⁷ Analogously, labile 2*H*-pyran **133** ($R = \text{Me}$; $R^1 = \text{H}$; $X = \text{EtO}$) was trapped as adduct **595**.¹⁷⁸

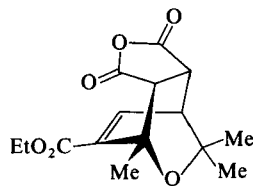


(594a) $R = \text{H}$; $R^1 = R^2 = R^3 = R^4 = \text{Me}$

(594b) $R = R^3 = \text{H}$; $R^1 = R^3 = R^4 = \text{Me}$

(594c) $R^1 = R^2 = \text{H}$; $R^2 = R^3 = R^4 = \text{Me}$

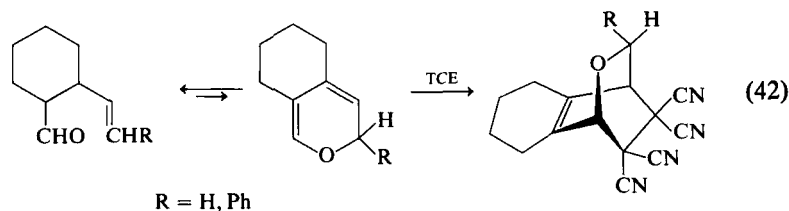
(594d) $R = R^1 = R^2 = R^4 = \text{Ph}$; $R^3 = \text{Ph}$, 4-MeC₆H₄



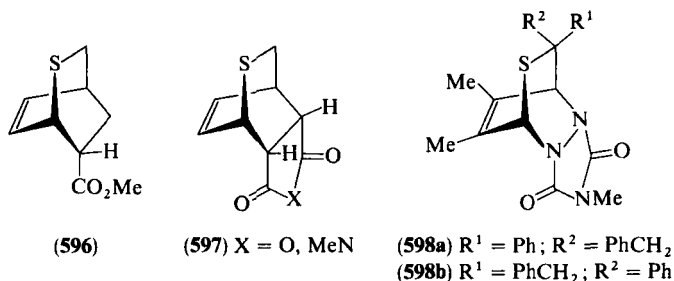
(595)

⁴⁴⁷ F. Fournier, S. Altenburger-Combrisson, N. K. Cuong, and J. J. Brasselier, *Tetrahedron* **35**, 2633 (1979).

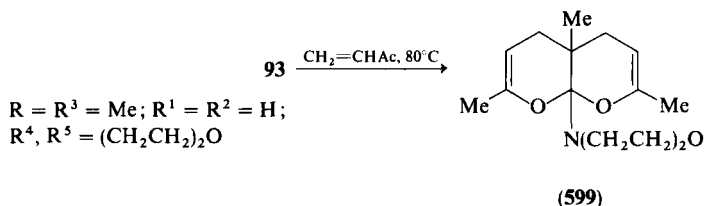
The same approach was used for the trapping of thermodynamically unstable *2H*-pyran species, as shown in Eq. (42).^{28,30} Analogous adducts with TCE were prepared from the *2H*-pyran **467a** via intermediate charge-transfer complexes.⁴⁴⁷



d. *Diels-Alder Cycloadditions of Electrophilic Ethenes to 2H-Thiopyrans.* The unsubstituted compound **6** easily underwent $[4\pi + 2\pi]$ cycloadditions with methyl acrylate, maleic anhydride, and *N*-phenylmaleimide to afford **596** and **597**; the structures were elucidated by NMR shift reagents.⁴⁴⁸ A mixture of stereoisomeric adducts **598a,b** was obtained from *2H*-thiopyran derivative **368** and *N*-methylazodicarboximide.³⁴⁵



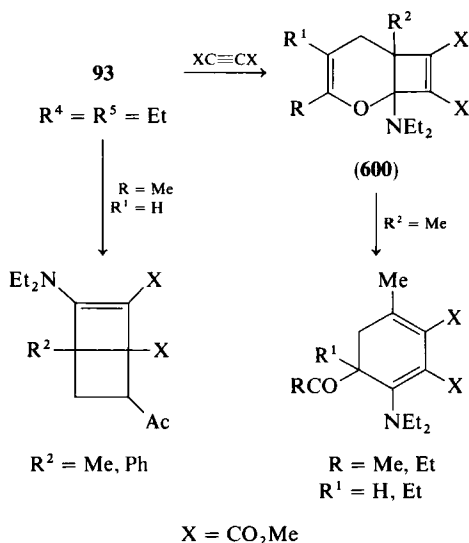
e. *Cycloadditions of Electrophilic Dienes to 4H-Pyrans.* Methyl vinyl ketone reacted with 3,6-dimethyl-2-morpholino-*2H*-pyran to afford bicyclic dihydropyran **599**.¹⁴⁰



f. *Cycloaddition of Electrophilic Acetylenes to Pyrans.* As mentioned in Section V,H,3, some *2H*-pyrans, such as **176** and **564**, reacted with

⁴⁴⁸ R. H. Fleming and B. M. Murray, *J. Org. Chem.* **44**, 2280 (1979).

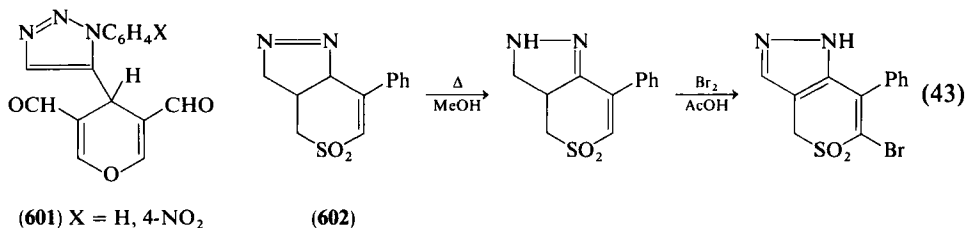
methyl acetylenecarboxylate or dimethyl acetylenedicarboxylate to give labile $[4\pi + 2\pi]$ adducts that spontaneously decomposed to various aromatics.⁴⁰⁵ The formation of both kinds of products shown in Scheme 36, apparently isolated after the reaction of 2-diethylamino-4*H*-pyrans **93** with acetylenes, was explained by a secondary isomerization of primary $[2\pi + 2\pi]$ cycloadducts **600**.⁴⁴⁹



SCHEME 36

g. Cycloadditions with Arylazides and Diazomethane. Phenyl- and 4-nitrophenylazides add to the 4-ethynyl group in 4*H*-pyran **85d** to provide expected triazoles **601**.⁶²

3-Phenyl-2*H*-thiopyran *S,S*-dioxide **289** and diazomethane gave 1,3-cycloadduct **602**, which underwent further chemical transformations as shown in Eq. (43).⁴⁵⁰

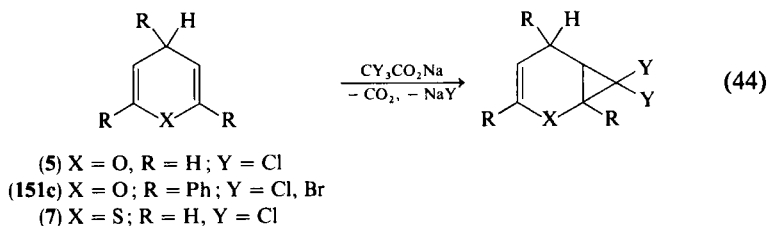


⁴⁴⁹ J. Ficini, J. Besseyre, and C. Barbara, *Tetrahedron Lett.*, 3151 (1975).

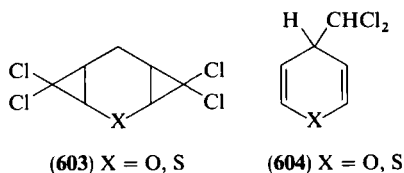
⁴⁵⁰ S. Bradamante, S. Maiorana, A. Mangia, and G. Pagani, *Tetrahedron Lett.*, 2971 (1969).

3. Additions of Carbenes

Dichloro- and dibromocarbenes generated by thermolysis of sodium trihaloacetates add to one double bond in *4H*-pyrans **5** and **151c** as well as in *4H*-thiopyran (**7**), as shown in Eq. (44).⁴⁴⁵



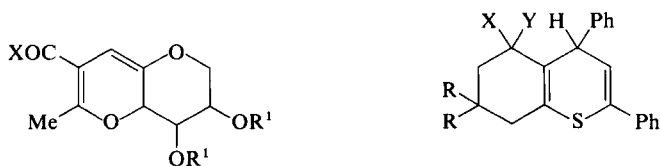
Unsubstituted substrates **5** and **7** give with dichlorocarbene a mixture of products including dicycloadducts **603** and simple adducts to position 4, e.g., **604**.⁴⁴⁵



K. FUNCTIONAL GROUP TRANSFORMATIONS

1. Transformations of Hydroxy Groups

The vicinal hydroxy groups in condensed *2H*-pyran derivatives **342** were transformed to ethers **605a** and acetals **605b** with methyl iodide and silver oxide or with acetone, respectively.³²⁸ Analogously, both hydroxy groups in the 4-(1',2'-dihydroxy)ethyl derivative of *4H*-pyran **36** were acetylated with acetic anhydride in pyridine and transformed to dimethylmethylen acetal with acetone.¹³⁵ The hydroxy group in *4H*-pyran **607a** was oxidized, resulting in aldehyde **607b**, with chromium trioxide.⁸⁶ The hydroxy group in diastereo-



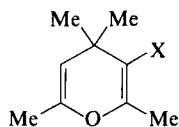
(605a) R¹ = R² = Me; X = Me, MeO

(605b) R¹, R² = CMe₂; X = Me, OH, MeO

(606a) X = OH; Y = H; R = H, Me

(606b) X, Y = PhCH; R = H, Me

(606c) X, Y = PhNNH; R = H, Me

(607a) X = CH₂OH

(607b) X = CHO

(607c) X = CH=CHBz

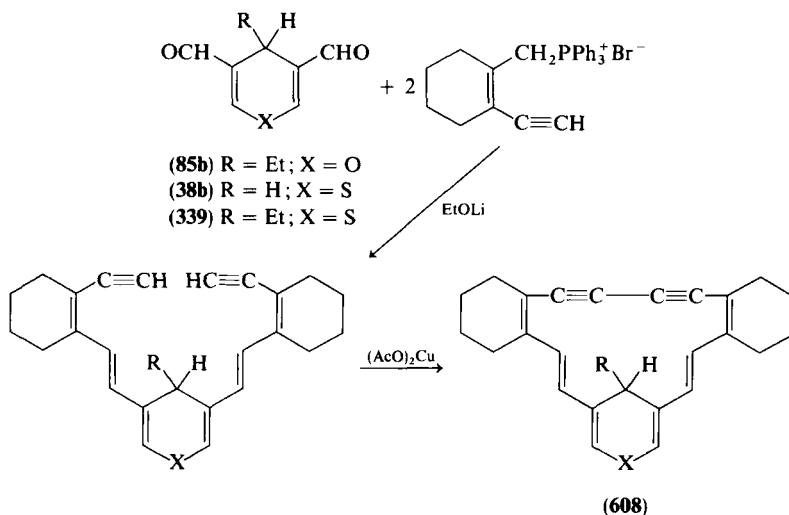
(607d) X = CO₂H

meric 4*H*-thiopyrans **606a** was acetylated with acetyl chloride in pyridine to give only one of the two possible acetates.⁶¹ Dehydration of **606a** on heating with traces of acetic anhydride afforded expected unsaturated 4*H*-thiopyran **454**.³⁷⁰

2. Transformations of the Carbonyl Group

The carbonyl group in condensed 4*H*-pyran **263b** was reduced by condensation with tosylhydrazine followed by borohydride.²⁹⁰ The aldehyde group in **607b** was aldolized with acetophenone to unsaturated ketone **607c** or oxidized to carboxylic acid **607d** with molecular oxygen.⁸⁶

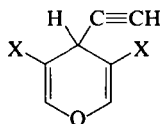
The reaction of both aldehydic groups in 3,5-diformyl-4-ethyl-4*H*-pyran (**85b**) and in analogous 4*H*-thiopyrans **38b** and **339** with a carbocyclic Wittig reagent was successfully explored in the syntheses of hetero[17]annulene **608** (Scheme 37).⁸⁵ Analogous 3,5-diformyl derivative **85d** reacted with phenylhydrazines to give Schiff bases **609**.⁴¹⁸ Hydroxylamine and **85d** at room



SCHEME 37

temperature afforded dioxime **609b**, which was converted to 3,5-dicyano derivative **609c** with thionyl chloride.⁴¹⁸

The carbonyl groups in 4*H*-thiopyrans **20a** were easily reduced to diastereomeric hydroxy derivatives **606a**.^{61,370} The reaction of **20a** with benzylmagnesium chloride gave benzylidene derivatives **606b**³⁷⁰ and with phenylhydrazine the corresponding Schiff bases **606c**.^{61,99}



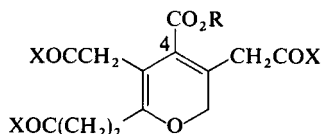
(**609a**) X = CH=NNHAr (Ar = Ph, 4-NO₂C₆H₄,
2,4-(NO₂)₂C₆H₃)

(**609b**) X = CH=NOH

(**609c**) X = CN

3. Transformations of the Carboxylic Acid Group

Carboxylic acid **342** gave with methyl iodide and silver oxide the methoxycarbonyl ester.³²⁸ 2*H*-Pyran tetracarboxylic acid **149** was converted¹⁹⁴ with diazomethane to tetramethyl tetraester **610a**. Methanol and ethanol in the presence of *p*-toluenesulfonic acid did not esterify the sterically hindered carboxylic acid group at position 4; only triesters **610b,c** were isolated. Ester **610b** and ammonia or benzylamine provided amides **610d**. The starting tetracarboxylic acid underwent partial decarboxylation at 200°C to afford tricarboxylic acid **611a**, which was esterified with methanol to **611b**.¹⁹⁴

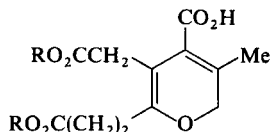


(**610a**) R = Me; X = MeO

(**610b**) R = H; X = MeO

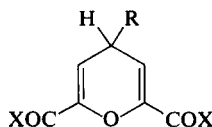
(**610c**) R = H; X = EtO

(**610d**) R = H; X = NH₂, PhCH₂NH



(**611a**) R = H

(**611b**) R = Me



(**612a**) R = H, Me; X = MeO

(**612b**) R = H; X = EtO

(**612c**) R = H; X = Cl

(**612d**) R = H; X = NH₂, PhNH

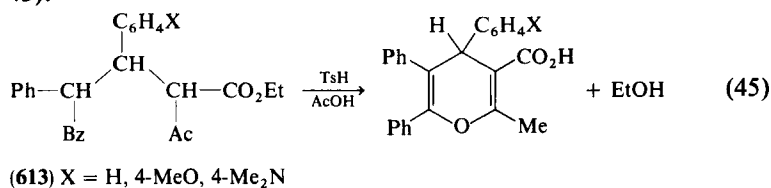
4*H*-Pyran-2,6-dicarboxylic acids **32** were converted to esters **612a,b** in the presence of sulfuric acid⁷¹ or after reaction with phosphorus pentachloride.²¹⁵ The acid (*R* = H) reacted with the latter reagent to give dichloride **612c**; amides **612d** were formed from the chloride with ammonia or aniline.⁷¹

p-Bromobenzyl ester **19b** was prepared from the corresponding 2*H*-thiopyrancarboxylic acid with *p*-bromophenyldiazomethane.⁵³

4. Transformations of the Ester Group

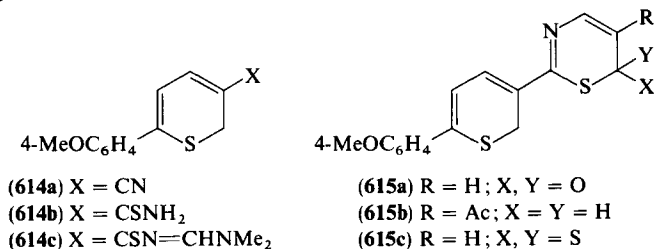
The 3-ethoxycarbonyl group in 4*H*-pyran **63** (*R* = Me, *R*¹ = Bu) was hydrolyzed on heating with ethanolic potassium hydroxide; this procedure with analogous 4*H*-pyrans **63** (*R*¹ = Me, Ph) was accompanied by decarboxylation.¹⁰⁷ Acid **607d** obtained by hydrolysis of ethyl ester **68** (*X* = EtO; *Y* = Me) did not decarboxylate to a definite product on heating with copper powder.⁸⁶

An unexpected hydrolysis of an ethoxycarbonyl group was observed in the attempt to accomplish cyclodehydration (Section III,A) using diketo esters **613** (Eq. 45).⁴⁵¹



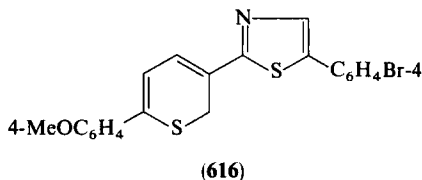
5. Transformations of Other Functional Groups

The 3-cyano group in 2*H*-thiopyran **614a** was transformed to various derivatives (**614b,c**).⁴⁵² One (**614c**), underwent cyclocondensations with ketene, methyl vinyl ketone, and 2',4-dibromoacetophenone, providing heterocyclic derivatives **615a,b** and **616**. Oxo derivative **615a** reacted with P₄S₁₀ to give **615c**.⁴⁵²



⁴⁵¹ M. A. Elkasaby, *J. Indian Chem. Soc. B* **14**, 739 (1976).

⁴⁵² J. P. Pradere, *C.R. Acad. Sci., Ser. C* **281**, 119 (1975).



L. PHOTOCHEMICAL REACTIONS

Photochemical reactions involving *4H*-pyrans are the best investigated: Knowledge of the photochemical behavior of simple *2H*-pyrans and especially of thiopyrans is limited.

1. Photochemical Transformations of *2H*-Pyrans and *2H*-Thiopyrans

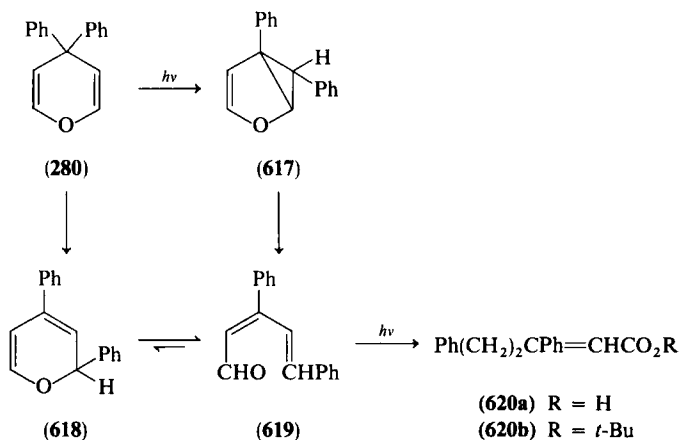
Benzo-*2H*-pyrans and their thia analogs, e.g., heterocycles not treated in this chapter, are photochemically labile and form reversible photochromic systems with open-chain and colored photoisomers. This behavior was observed for 2-benzyl-2,4,6-triphenyl-*2H*-species **467a,b** ($Y = H$)^{399,409} and naturally occurring *2H*-pyran **92a**^{452a} but only at about 77K. At room temperature, these as well as other *2H*-pyrans are photochemically stable. Only 2,2,4,6-tetramethyl-*2H*-pyran (**176**) was photochemically changed to its exocyclic double bond isomer **308a**.⁴⁰⁴ An irreversible photolysis of 2-azido-*2H*-thiopyran derivative **212b** ($R = H$) has been discussed in reference 254.

2. Photochemical Transformations of *4H*-Pyrans and *4H*-Thiopyrans

Photolysis of 4,4-diphenyl-*4H*-pyran (**280**) in *tert*-butyl alcohol gave a mixture of unsaturated aldehyde **619** and compounds **620a,b**.^{296,453} Surprisingly, the formation of aldehyde **619** apparently proceeded via intermediate **617** and not by the alternative pathway via isomeric *2H*-pyran **618** (Scheme 38). As mentioned in Sections V,E,4b and V,E,4c, 4-benzyl-2,4,6-triaryl-*4H*-pyrans and their thia analogs photoisomerize to 2-benzyl-*2H* species^{236,392,400,414-416} by a concerted 1,3-suprafacial migration of

^{452a} R. S. Becker and J. Michl, *J. Am. Chem. Soc.* **88**, 5931 (1966).

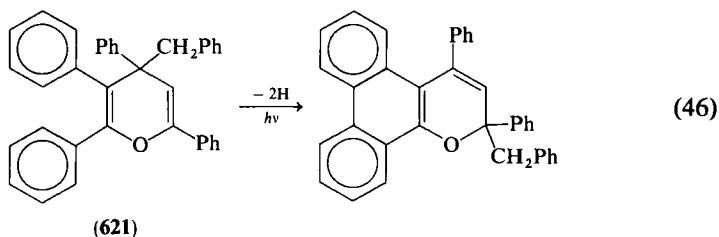
⁴⁵³ G. Lord, L. Foisy, L. Baril, D. Gravel, and G. Durocher, *Can. J. Chem.* **55**, 4010 (1977).



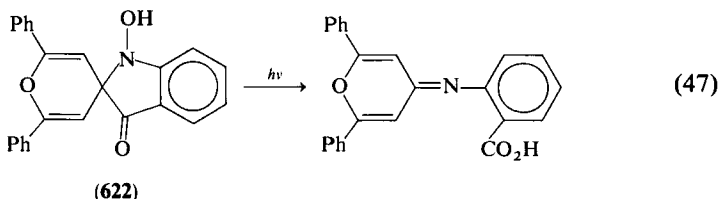
SCHEME 38

the 4-substituent.³⁹² The photochromic valence bond isomerizations $133 \rightleftharpoons 132$ (R = Me; X = Me, MeO) were studied in detail by pulse UV irradiation.^{398a}

The 1,3-migration of the 4-benzyl group of 4-benzyl-2,4,5,6-triphenyl-4*H*-pyran (**621**) was accompanied by photodehydrogenation of 5,6-substituents (Eq. 46).⁴⁰⁰



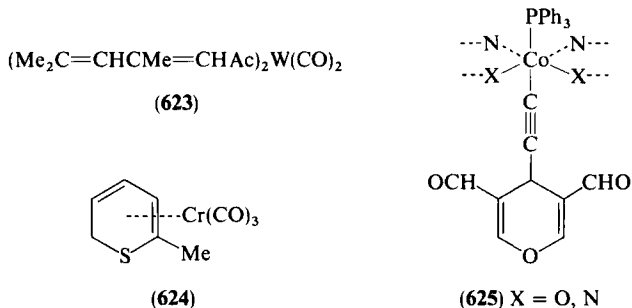
The photochemical transformation of the spirocyclic 4*H*-pyran derivative **622** shown in Eq. (47)³³³ resembles the reverse of the phototransformation $349 \rightarrow 350$. Upon reaction with PbO_2 **622** gave a stable nitroxide radical.⁴⁵⁴



⁴⁵⁴ A. T. Balaban, N. Negoita, and R. Baican, *Org. Magn. Reson.* **9**, 553 (1977)

M. FORMATION OF METALLIC COMPLEXES

2,2,4,6-Tetramethyl-2*H*-pyran (176) and $(\text{MeCN})_3\text{W}(\text{CO})_3$ gave zero-valence complex **623**. 6-Methyl-2*H*-thiopyran with $(\text{MeCN})_3\text{Cr}(\text{CO})_3$ afforded the π -complex of the parent heterocycle **624**.^{454a} 3,5-Diformyl-4-ethynyl-4*H*-pyran (**85d**) replaced an azido ligand in some cobalt complexes to give **625**.⁶²

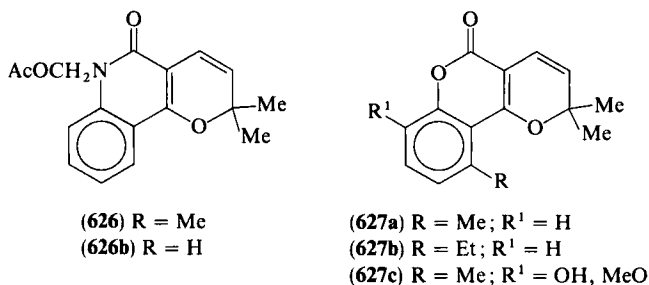


VI. Naturally Occurring Pyrans

Pyrans are very rare as natural products.⁴⁵⁵ Only some 2*H*-pyrans have been isolated from plants.

The structure as well as the synthesis of the alkaloid flindersine (**67b**)¹¹⁰ or **92a**,⁴⁵⁶ respectively, were mentioned in Sections III,D and III,E.

Zanthophyllum monophyllum was reported to contain zanthophylline (**626a**) and its dimethyl derivative (**626b**).⁴⁵⁷ The N-substituent in **626a,b** was very sensitive toward hydrolysis with dilute acids.



^{454a} K. Oefele, A. Wurzing, and W. Kalbfus, *J. Organomet. Chem.* **69**, 279 (1974).

⁴⁵⁵ D. E. Games, *Aromat. Heteroaromat. Chem.* **1**, 369 (1973) [*CA* **79**, 92047 (1973)].

⁴⁵⁶ J. W. Huffman and T. M. Hsu, *Tetrahedron Lett.*, 141 (1972).

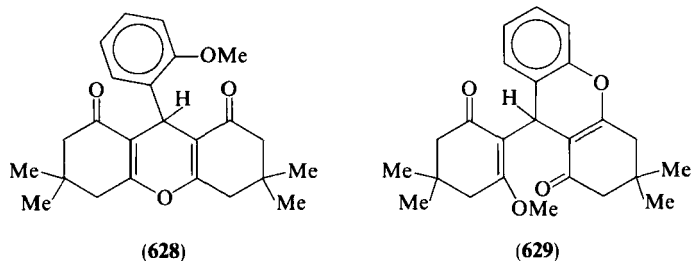
⁴⁵⁷ F. R. Stermitz and I. A. Sharifi, *Phytochemistry* **16**, 2003 (1977) [*CA* **88**, 60074 (1978)].

B. laxa contains both rioclinin (**627a**) and substituted derivatives (**627b,c**).⁴⁵⁸

Other *2H*-pyrans are artifacts of structurally similar natural compounds. Thus anhydrofulvic acid was prepared by dehydration of labile fulvic acid²⁹² [Eq. (12), Section IV,D,1]. So-called dehydrolapachones **352** and **354** were obtained by chemical transformations of naturally accessible "lapachol."^{334,335}

VII. Physical Properties

The methodology of a pyran structure elucidation is illustrated by attempts to distinguish between two alternative structures, **628** and **629**, assumed for the product of the reaction of 2-methoxybenzaldehyde with dimedone.¹³³



A. ELECTRONIC SPECTRA

Typical examples of $\pi \rightarrow \pi^*$ UV spectra are illustrated in Tables XIII–XVI. The use of absorption spectroscopy for diagnostic purposes is limited. Thus simple *2H*-pyrans, as a rule, show more complex and red-shifted absorption curves in comparison to those of similar *4H*-pyrans (Tables XIII and XIV). Analogous spectral behavior for simple *2H*- and *4H*-thiopyrans is perceptible from Tables XV and XVI. The introduction of conjugating aryl groups and other unsaturated substituents causes a significant overlap of original absorption bands with those of the aromatic systems as well as a bathochromic shift of the longest wave absorption maxima.

Because of the $\pi \rightarrow \pi^*$ character of the pyran and thiopyran absorption no important solvatochromic effects have been observed. But the occurrence of

⁴⁵⁸ F. Bohlmann and C. Zdero, *Phytochemistry* **16**, 1261 (1977) [*CA* **87**, 130453 (1977)].

TABLE XIII
 ABSORPTION MAXIMA FOR SOME 2*H*-PYRAN CHROMOPHORES

Substituent at position						$\lambda_{\max}$ (nm)	log ϵ	References
2	2	3	4	5	6			
H	Me	Me	H	H	Me	211	3.36	164
						284	3.59	
Me	Me	H	Me	H	Me	221	3.89	311
						265	3.18	
						272	3.22	
						278	3.22	
Me	Me	Me	H	Ph	Me	222	4.09	305
						263	3.88	
						286	3.84	
Me	Me	Me	H	Ac	Me	218	4.05	175
						254	3.88	
						325	3.53	
Ph	PhCH ₂	H	Ph	H	Ph	248	4.34	400
						262	4.38	
						338	3.98	
Ph	NCCH ₂	CN	Ph	CN	Ph	207	4.55	35
						245	4.47	
						375	4.49	
Ar ^a	NCCH ₂	CN	Ar ^a	CN	Ar ^a	318	4.45	126
						400	4.41	

^a Ar = 4-MeOC₆H₄.

valence bond tautomerism in the 2*H* series (see Section V,E,1) caused photochromism of 2*H*-pyrans **67b** and **467a,b** at low temperature.^{452a,392,399,409} The same but also solvent-dependent tautomerism **134** $\rightleftharpoons$ **135** and **136** $\rightleftharpoons$ **137** was found to lead to apparent solvatochromism and thermochromism in the UV spectra of 2-dimethylamino-2*H*-pyrans **135** and **137**.¹⁷⁹

The singlet energy of 2*H*-pyrans **467a** and the singlet-triplet energy gap were estimated to be 368 kJ/mol and 105–125 kJ/mol on the basis of fluorescence and phosphorescence measurements.^{392,454a}

2-Hydroxy-2*H*-thiopyran as a pseudobase was determined by UV spectrophotometry and discussed with HMO calculations together with other heterocycles.²⁸⁷ Ionization constants of 2*H*-thiopyran 1,1-dioxides **484** (R = H; R¹ = Ph; R² = H, Me) were determined spectrophotometrically in H₂O and MeOH at 25°C.^{458a}

^{458a} G. Gaviraghi and G. Pagani, *J.C.S. Perkin Trans. 2*, 50 (1973).

TABLE XIV
ABSORPTION MAXIMA FOR SOME 4*H*-PYRAN CHROMOPHORES

Substituent at position						$\lambda_{\max}$	log ϵ	References
2	3	4	4	5	6			
H	H	H	H	H	H	222	3.85	19
						238 ^a	3.71 ^a	18
Me	H	Me	Me	H	Me	218	3.79	311
						248	3.95	
						225	3.08	86
H	H	Ph	Ph	H	H	240	3.02	296
H	H	CHO	H	H	H	246 ^b	2.77	338
Ph	H	PhCH ₂	Ph	H	Ph	248	4.37	236
CHO	H	H	H	H	H	290–294	4.01–4.04	347
Et ₂ N	Ph	H	H	H	H	298	3.63	139
Me	CO ₂ Et	Me	H	CO ₂ Et	Me	214	4.04	86
						221	4.04	
						285	3.46	
H	CHO	Me	H	CHO	H	219	4.13	442
						232	3.77	
						295	3.80	
NH ₂	CN	Ph	H	CN	Ph	298	3.85	121
NH ₂	CN	CN	CN	Ac	Me	243	4.20	36
						272	3.89	
						385	3.82	

^a No maxima were reported for a methanolic solution.

^b In addition to another carbonyl $n \rightarrow \pi^*$ band at 310 nm (log ϵ = 2.04).

TABLE XV
ABSORPTION MAXIMA FOR SOME 2*H*-THIOPYRAN CHROMOPHORES

Substituent at position							$\lambda_{\max}$ (nm)	log ϵ	References
1	2	2	3	4	5	6			
—	H	H	H	H	H	MeS	335	3.71	304
—	H	(CH ₂) ₄	Ph	Ph	H	Ph	252	4.2	473
							360	3.9	
—	H	H	Ph	H	Ph	H	270	4.49	274
							364	3.69	
—	Me	Ph	H	Ph	H	Ph	257	4.32	39
							347	3.75	
—	PhCH ₂	Ph	H	Ph	H	Ph	258	4.32	236
							347	3.66	
O	Me	Ph	H	Ph	H	Ph	230	4.28	39
							253	4.36	
							297	3.89	
							340	3.57	
O ₂	H	H	H	H	H	H	225–234	3.34–3.38	26
							263–265	3.38–3.57	

TABLE XVI
 ABSORPTION MAXIMA FOR SOME 4*H*-THIOPYRAN CHROMOPHORES

Substituent at position							$\lambda_{\max}$ (nm)	log ϵ	References
1	2	3	4	4	5	6			
—	H	H	H	H	H	H	236–238 ^a	3.72	19
—	Ph	H	H	H	(CH ₂) ₄		278	3.39	
—	Ph	H	H	H	(CH ₂) ₄		240	4.2	473
—	Ph	H	H	Ph	H	Ph	295	3.2	
—	Ph	H	H	Ph	H	Ph	235	4.46	39
—	Ph	H	H	Ph	H	Ph	350	3.20	
—	Ph	H	Me	Ph	H	Ph	235 ^b	4.56	39
—	Ph	H	PhCH ₂	Ph	H	Ph	248 ^b	4.37	236
—	4-MeC ₆ H ₄	H	Ph	Ph	H	Ph	238 ^b	4.56	280
O	Ph	H	Me	Ph	H	Ph	245	4.36	39
O ₂	Ph	H	Me	Ph	H	Ph	233	4.32	39

^a Shoulder.^b The long wave absorption band is overlapped by a strong aromatic absorption near 240 nm.

The UV absorption of 4*H*-selenopyran (**8**) and metallic complexes **623** and **624** were also measured.³⁵¹

B. INFRARED SPECTRA

Infrared absorption spectra of pyrans and thiopyrans show a typical feature of conjugating molecular vibrators, e.g., a high degree of coupling within vibronic modes. Theoretical analysis of simple 4*H*-pyran (**5**) concludes that the doublet at 1634 and 1686 cm⁻¹ can be attributed to coupled antisymmetric and symmetric vibrations of the two double bonds.⁴⁵⁹ Absorption maxima for various pyran, thiopyran, and selenopyran derivatives are illustrated in Table XVII. Higher wave numbers of the appropriate absorption maxima are typical for 4*H* types and for oxygen heterocycles rather than for the corresponding 2*H* species and sulfur or selenium analogs. Maxima for functional groups, as a rule, exhibit the expected wave numbers, as shown in the footnotes of Table XVII for 4-formyl-4*H*-pyran **348b** (R = H). However, 2-formyl derivative **371** exhibits strong coupling in the whole skeleton of O = CHC(O⁻) = CHCH = CH.

⁴⁵⁹ H. S. Kimmel and W. H. Snyder, *Spectrosc. Lett.*, **4**, 15 (1971).

TABLE XVII
SOME INFRARED SPECTRAL CHARACTERISTICS OF PYRANS AND THIOPYRANS

Compound	$\tilde{\nu}_{\max}$ (cm ⁻¹)			References
	$\nu(\text{C}=\text{C})$		$\nu(\text{C}-\text{O})$ or $(\text{C}-\text{S})$	
2,3,4,6-Trimethyl-2 <i>H</i> -pyran	1680	1632	1122	212
5-Phenyl-2,3,6-trimethyl-2 <i>H</i> -Pyran	1660	1610	1200-1150	305
2-Benzyl-2,6-diphenyl-4-(<i>p</i> -tolyl)-2 <i>H</i> -pyran	1640	1620		400
4 <i>H</i> -Pyran	1686	1634	1253 1124	18, 459
	1700	1660	1280-1260	19
2,4,4,6-Tetramethyl-4 <i>H</i> -pyran	1724	1667		86
2-Formyl-4 <i>H</i> -pyran	1670		1191 1000	347
4-Formyl-4 <i>H</i> -pyran	1680 ^a	1620	1260	338
2,6-Diphenyl-4 <i>H</i> -pyran	1689	1642	1267	204
2-Dimethylamino-3-methyl-4 <i>H</i> -pyran	1715			139
3,5-Dicyano-4-ethynyl-4 <i>H</i> -pyran	1672 ^b	1608 1592		418
2 <i>H</i> -Thiopyran	1674	1650	750	19
4,5-Dimethyl-2-phenyl-2-phenylacetyl-2 <i>H</i> -pyran	1600 ^c	1590		345
Biscyclohexeno[<i>b,e</i>]-4 <i>H</i> -thiopyran	1664	1618	746	102
Biscyclohexeno[<i>b,e</i>]-4 <i>H</i> -selenopyran	1675	1446(?)		106

^a In addition to C=O absorption at 1725 cm⁻¹.

^b In addition to C≡N and C≡C absorptions at 2212 and 2110 cm⁻¹.

^c In addition to C=O absorption at 1710 cm⁻¹.

Infrared spectra of metallic complexes **623** and **624** were also investigated.^{454a}

C. NUCLEAR MAGNETIC RESONANCE

Typical proton chemical shifts and coupling constants are illustrated in Table XVIII.

A complete analysis of the ¹H-NMR spectra of all parent 4*H*-species **5**, **7**, and **8** was performed using A₂B₂X₂ systems for the neutral molecules or A₂B₂X for corresponding cations.⁴⁶⁰ Chemical shifts of olefinic protons in **5**

⁴⁶⁰ J. Degani, L. Lunazzi, and F. Taddei, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 131 (1965) [CA **63**, 15750 (1965)].

TABLE XVIII
¹H-NMR DATA FOR SOME PYRAN AND THIOPYRAN DERIVATIVES

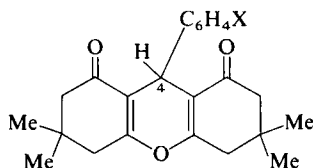
Compound	Chemical shifts ^a of substituent at position							References
	2	2	3	4	4	5	6	
2,2,4-Trimethyl-2 <i>H</i> -pyran	1.28s	1.28s	4.78qn (1.6, 1.6)	1.63d (1.6)	—	4.89dd (1.6, 5.6)	6.25m (5.6, 1.2)	289
2,3,6-Trimethyl-2 <i>H</i> -pyran	5.40q (6.5)	8.72d (6.5)	8.24s	4.50d (6.0)	—	5.10d (6.0)	8.33s	164
<i>t</i> -Butyl-2-methoxy-2 <i>H</i> -pyran-6-carboxylate	5.45	3.34	5.56	—	6.05	6.58	—	291
5-Acetyl-3,6-dimethyl-2-dimethylamino-2 <i>H</i> -pyran	5.76	2.37	1.67	6.30	—	2.25	2.25	180
6-Ethylthio-2 <i>H</i> -thiopyran	3.18dd	3.18dd (5.5, 1.1)	5.45m (9.4, 0.8)	5.95m (6.0, 9.4, 1.1)	—	6.23dd (6.0, 0.8)	2.8q 1.25t	149
3,5-Diphenyl-2 <i>H</i> -thiopyran	3.60t	3.60t (0.6–9)	7.2–7.8m	6.40q (0.6)	—	7.2–7.8m	6.54a (0.9)	274
3,5-Diphenyl-1-methyl-2 <i>H</i> -thiopyran tetrafluoroborate ^b	4.78d (0.1)	4.78d (0.1)	7.37–7.93m	7.23q (0.9)	—	7.37–7.93m	6.78d (0.7)	267
2,2,4,6-Tetramethyl-2 <i>H</i> -thiopyran	1.25s	1.25s	4.91m	1.75m	—	5.75m	1.93s	184
4-Acetoxy-2,6-diphenyl-2 <i>H</i> -thiopyran	5.10d	7.3–8.0m	5.62dd (6.0, 1.0)	2.28s	—	6.38d (1.0)	7.3–8.0m	299
2,4,4,6-Trimethyl-4 <i>H</i> -pyran	1.78s	—	4.41s	1.01s	1.01s	4.41s	1.78s	86
2-Diethylamino-3-phenyl-4 <i>H</i> -pyran	2.76t	—	—	3.02	3.02	4.82	6.30	139
	1.0q			(1.6, 3.2)		(6.0, 3.2)	(6.0, 1.6)	
4-Benzyl-2,4,6-triphenyl-4 <i>H</i> -pyran	7.1–7.7m	—	5.5	3.3	7.1–7.7	5.5	7.1–7.7	400
4-Benzyl-2,4,6-triphenyl-4 <i>H</i> -thiopyran	7.0–7.7	—	5.86	1.67	7.0–7.7	5.86	7.0–7.7	277, 460a
2,4,4,6-Tetraphenyl-4 <i>H</i> -thiopyran	7.13	—	6.00	7.13	7.13	6.00	7.13	342
6-Phenyl-2,3-tetramethylene-4 <i>H</i> -pyran	—			2.93d (4.2)	2.93d (4.2)	5.90t (4.2)	7.29	460b

^a Coupling constants (Hz) are given in parentheses.

^b Signal of MeS residue was singlet at 2.97 ppm.

were calculated (accuracy 0.02 and 0.31 ppm) using an additive system of increments.⁴⁶¹

Chemical shifts of 4-methyne protons in condensed 4*H*-pyran derivative **630** correlate well with Hammett σ constants for substituents X; polar substituent effects operating in molecules **630** were discussed.⁴⁶² The spectra of some ¹³C-labeled 2*H*-pyrans were also measured.³⁰⁹

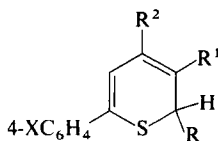


(630) X = 3-MeO, 3-OH, 3-NO₂, 4-Me₂N, 4-MeO,
4-OH, 4-Me, 4-Cl, 4-CO₂Me, 4-CN or 4-NO₂

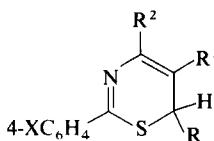
Chemical shifts of inert protons in hetero[17]annulenes **608** show that diamagnetic π -electron currents are more important in 4*H*-thiopyran than in 4*H*-pyran derivatives.⁸⁵

Solvent effect on ¹H-NMR spectra of condensed 4*H*-thiopyran derivatives **20a** were explored during consideration of the geometry of 4*H*-thiopyran rings in solutions.⁵⁵

Only limited reports on the NMR of other nuclides are available.^{136,176,180,182,258,463} Some ¹³C-NMR data for pyrans and thiopyrans are illustrated in Table XIX.



(631)



(632)

R = H;
R¹ = CHO, COMe, CO₂Me
or R, R¹ = CH(Me)CCl(Me)CO,
CH₂CCl(Me)CO;
R² = H, Me;
X = H, MeO

^{460a} T. Parasaran and C. C. Price, *J. Org. Chem.* **29**, 946 (1964).

^{460b} I. Ya. Evtushenko, B. I. Ionin, S. K. Klimenko, and V. G. Kharchenko, *Zh. Org. Khim.* **11**, 435 (1975).

⁴⁶¹ V. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron* **25**, 2023 (1969).

⁴⁶² M. Salmon, A. Jimenez, and R. Zawadski, *Org. Magn. Reson.* **5**, 5 (1973).

⁴⁶³ C. Rabiller, G. J. Martin, J. Pradere, J. C. Meslin, and H. Quiniou, *Org. Magn. Reson.* **14**, 479 (1980).

TABLE XIX
¹³C-NMR DATA FOR SOME PYRAN AND THIOPYRAN DERIVATIVES^{136,176,463}

Carbons of position	Chemical shifts ^a		
	2 <i>H</i> -Pyran 133 ^b	4 <i>H</i> -Pyran 88	2 <i>H</i> -Thiopyran 631 ^c
Ring			
2	77.8	158.0	22.6 (144.5)
3	120.7	90.0	123.9
4	119.8	58.3	144.7 (159.0)
5	102.7	90.0	116.1 (164.5)
6	165.6	158.0	149.4
Substituents			
2	27.4 (Me)	(See 6)	—
3	—	117.3 (CN)	190.4 (CHO)
4	—	156.3 (NCN)	—
5	166.2, 50.5	117.3 (CN)	—
6	19.8 (Me)	131.3, 130.2 128.4, 127.5 (Ph)	55.0, 129.4 114.1, 161.5 (4-MeOC ₆ H ₄)

^a In δ (ppm) with respect to TMS, coupling constants J_{HC} (Hz) are in parentheses.

^b R = R¹ = Me; X = MeO.

^c R = R² = H; R¹ = CHO.

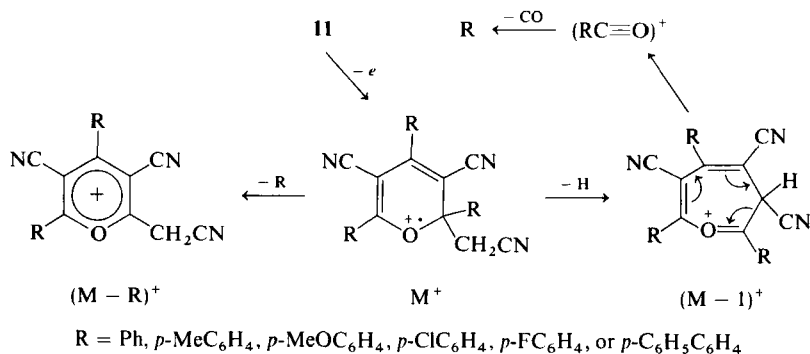
The valence-bond tautomerism of 2-dimethylamino-2*H*-pyrans **135** (see Section V.E.1) was followed by ¹³C-NMR.¹⁸⁰

¹³C-NMR spectra of the series of substituted 2*H*-thiopyrans **111** and **114** reveal a very good linear correlation between the ¹³C chemical shifts of **631** and ¹³C or ¹⁵N chemical shifts of analogous thiazines **632**, suggesting a high degree of structural similarity between both series.⁴⁶³

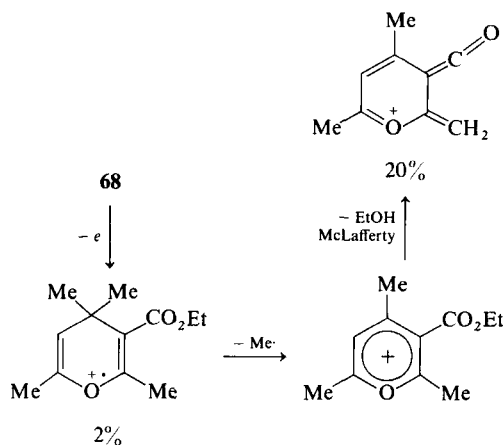
D. MASS SPECTRA

2,2,4,6-Tetrasubstituted 3,5-dicyano-2*H*-pyrans **11** decomposed mainly to ionic species (M - 1)⁺, (M - R)⁺, RCO⁺, and R⁺ (Scheme 39).^{35,126}

More reports on the mass spectrometric behavior of 4*H*-pyrans are available.^{36,62,86,112,121,333} The fragmentation patterns were studied in detail for 4*H*-pyran carboxylates of **68** (X = EtO, Y = Me) and **87b-d**, using high resolution measurements and detection of metastable ions.^{86,112} The main mode of fragmentation involved the loss of an alkyl or aryl 4-substituent to generate very stable pyrylium ions, as shown in Scheme 40.



SCHEME 39



SCHEME 40

Analogous fragmentations to thiopyrylium ions constitute a typical model for various *2H*-thiopyran derivatives^{155,304,345,464} along with other ions.^{155,299,304,345,465} A chromium complex was also measured.^{454a}

Mass spectra of *4H*-thiopyran derivatives contain strong peaks of molecular ions M^+ , but general fragmentation patterns have not yet been discussed.^{152,277,283}

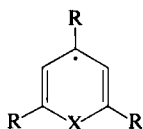
⁴⁶⁴ J. P. Pradere, G. Duguay, and H. Quiniou, *Org. Mass Spectrom.* **11**, 293, 364 (1976).

⁴⁶⁵ S. E. Cremer and A. V. Subbaratnam, *Chem. Commun.*, **33** (1967).

E. MISCELLANEOUS

The photoelectron spectrum of 4*H*-pyran (**5**) was measured⁴⁶⁶ and interpreted by various MO methods.^{56,466}

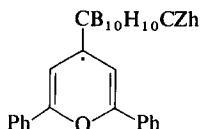
The EPR technique was successfully used for the detection of 4*H*-pyranil radicals **162d**,^{215,229,230,303a,467,468} **633a**,⁴⁶⁹ **633b**,⁴⁷⁰ and **634**,⁴⁷¹ as well as radical cations **378a,b**²²¹ or radical anions **635**.⁴⁷¹ A complete analysis of hyperfine splitting and spin densities was performed for **162d**,²²⁹ **633a**,⁴⁶⁹ **633b**,⁴⁷⁰ and (**635**).⁴⁷¹ Theoretical Hückel and McLachlan MO calculations of the spin densities were used to confirm twist conformations of radical **162d**²³⁰ and **633a**.⁴⁶⁹ The replacement of oxygen in **162a** by sulfur in **633a** caused a new distribution of the unpaired electron.⁴⁶⁹ The hyperfine splitting in radical anions **635** by the 4-hydrogen is larger than by the 3,5-protons.⁴⁷¹ In **634** the spin density is localized mainly in the 4-carborane residue.²⁴⁵ A stable spiro-pyranic aminyloxide radical from **622** was also detected by EPR.⁴⁵⁴



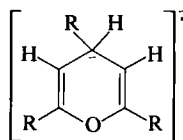
(**162d**) R = Ph; X = O

(**633a**) R = Ph; X = S

(**633b**) R = *t*-Bu; X = O



(**634**) R = *t*-Bu, Ph, 4-MeOC₆H₄



(**635**) R = *t*-Bu, Ph

Electrochemical investigations show that 4*H*-pyranil radicals **162** and **633** as well as corresponding radical anions **197** are reversibly oxidized to appropriate pyrylium ions at about -0.3 to -0.4 V.^{224,225,228,239}

Irreversible electrochemical oxidation of dimeric 4*H*-pyrans **163** to monomeric pyrylium ions at about $+0.6$ V was observed.^{225,227,228} The anodic oxidation of the dimers in the presence of aromatic hydrocarbons caused electroluminescence of the latter.^{228,472} The polarographic oxidation of carboranyl 4*H*-pyran **174a** (R = Ph) at a platinum microelectrode was found to

⁴⁶⁶ M. Blochi, F. Brogli, E. Heilbronner, T. B. Jones, H. Prinzbach, and O. Schweikert, *Helv. Chim. Acta* **61**, 1388 (1978).

⁴⁶⁷ V. I. Trofimov and I. I. Chkheidze, *Khim. Vys. Energ.* **1**, 324 (1967) [*CA* **68**, 12244 (1968)].

⁴⁶⁸ L. A. Polyakova, K. A. Bilevich, G. N. Dorofeenko, O. Yu. Okhlobystin, and I. I. Bubnov, *Dokl. Akad. Nauk SSSR* **212**, 370 (1973).

⁴⁶⁹ J. Degani, L. Lunazzi, G. F. Pedulli, C. Vincenzi, and A. Mangini, *Mol. Phys.* **18**, 613 (1970).

⁴⁷⁰ C. Hacquard and A. Rassat, *Mol. Phys.* **30**, 1935 (1975).

⁴⁷¹ V. B. Panov, M. V. Nekhoroshev, and O. Yu. Okhlobystin, *Zh. Org. Khim.* **15**, 2224 (1979).

⁴⁷² F. Pragst and R. Ziebig, *Electrochim. Acta* **23**, 735 (1978).

proceed via radical **634** ($R = Ph$).²⁴³ The classical polarographic method was used in the study of the dehydrogenation of 2,4,6-triphenyl-4*H*-pyran (**151c**) with molecular oxygen.³⁵⁷

Dielectric measurements provide dipole moments for 2*H*- and 4*H*-thiopyrans **7**, **21**, **22**, **47**, **49**, **230**, **231**, and **409**,⁴⁷³ as well as for some 4*H*-thiopyran *S,S*-dioxides **419** and **420**.⁴⁷⁴

Molecular refraction was used in a consideration of a 2*H*-pyran structure.⁴⁷⁵ Occasionally, liquid pyrans and thiopyrans have been characterized by refraction indices.^{19,24,144,189,238,314,427}

2-(*p*-Methoxystyryl)-3-phenyl-4-methoxypyran was patented as a material for the construction of organic conductors.⁴⁷⁶⁻⁴⁷⁹

ACKNOWLEDGMENTS

The author thanks Mrs. Zuzana Donnerová for indispensable help in collecting the literature and for technical assistance in preparing the manuscript.

⁴⁷³ E. N. Kharlamova, E. N. Guryanova, and V. G. Kharchenko, *Zh. Strukt. Khim.* **12**, 637 (1971); E. N. Kharlamova, E. N. Guryanova, S. K. Klimenko, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, 744 (1978).

⁴⁷⁴ V. V. Puchkova, E. N. Guryanova, V. G. Kharchenko, and A. A. Rassudova, *Zh. Org. Khim.* **9**, 1531 (1973).

⁴⁷⁵ K. von Auwers, *Justus Liebigs Ann. Chem.* **422**, 133 (1921).

⁴⁷⁶ Matsushita Electric Industrial Co., Ltd., British Patent 1,350,278 (1973) [*CA* **81**, 19272 (1974)].

⁴⁷⁷ M. Ikeda, H. Sato, E. Torii, K. Morimoto, and Y. Hasegawa, U.S. Patent 3,840,368 (1974) [*CA* **83**, 35710 (1975)].

⁴⁷⁸ M. Ikeda, H. Sato, E. Torii, K. Morimoto, and Y. Hasegawa, *Ger. Offen.* 2,149,293 (1973) [*CA* **79**, 47839 (1973)].

⁴⁷⁹ H. Sato and M. Ikeda, *J. Appl. Phys.* **43**, 4108 (1972).

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The Formation of Anionic σ -Adducts from Heteroaromatic Compounds: Structures, Rates, and Equilibria

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I. Introduction

A survey of the quantitative studies on nucleophilic heteroaromatic substitution¹ disclosed a complete lack of information on heterocyclic

¹ G. Illuminati, *Adv. Heterocycl. Chem.* **3**, 285 (1964).

Meisenheimer adducts as obtained by the reaction of heteroaromatic compounds with such familiar nucleophiles as RO^- ions, despite the fact that the most commonly accepted mechanism of nucleophilic aromatic substitution, involving Meisenheimer-type adducts as intermediates,^{2,3} was likely to apply to many heteroaromatic substrates under appropriate conditions. This observation stimulated a series of investigations in our laboratory on the formation of σ -adducts from the reactions of a variety of heteroaromatic compounds with nucleophilic reagents. A strong impetus in this field, which was shared by several research groups, came from the structural and reactivity studies carried out in the benzene series starting from the early papers in the mid-1950s⁴ and rapidly developing in the following years.⁵⁻¹²

The first papers concerning the formation of σ -adducts from the reaction of heteroaromatic compounds and alkoxide ions appeared in 1968¹³⁻¹⁵ and soon were extended from 6- to 5-membered rings.^{16,17} Investigations of considerable general interest in heterocyclic chemistry as well as in the whole of organic chemistry have been carried out ever since, using heterocyclic substrates with several types of nucleophilic reagents. Although the adduct formation reactions of heteroaromatic compounds usually have corresponding processes in polynitro-activated benzenes when the more familiar reagents such as alkoxide ions and amines are used, other reagents such as the amide ion and organolithium compounds lead to σ -adducts exclusively with azines. Unfortunately, most data are confined to structural studies, and those on rates and equilibria are scanty in the latter reactions.

Before defining the scope of the present chapter it is worth making a few general comments on the nature of the reactions and their products and on the use of terms.

In a most general way the formation of a σ -adduct from an aromatic or heteroaromatic substrate can be defined to consist of the formation of a new

² J. F. Bunnett and R. E. Zahler, *Chem. Rev.* **49**, 273 (1951).

³ J. F. Bunnett, *Q. Rev., Chem. Soc.* **12**, 1 (1958).

⁴ R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.* **16**, 61 (1966).

⁵ E. Bunce, A. R. Norris, and K. E. Russell, *Q. Rev., Chem. Soc.* **22**, 123 (1968).

⁶ M. R. Crampton, *Adv. Phys. Org. Chem.* **7**, 211 (1969).

⁷ M. J. Strauss, *Chem. Rev.* **70**, 667 (1970).

⁸ T. N. Hall and C. F. Poranski, in "The Chemistry of Nitro and Nitroso Groups" (H. Feuer, ed.), Part 2, Chapter 6. Wiley (Interscience), New York, 1970.

⁹ M. J. Strauss, *Acc. Chem. Res.* **7**, 181 (1974).

¹⁰ J. A. Zoltewicz, *Int. Rev. Sci.: Org. Chem., Ser. Two* **3**, 63-85 (1976).

¹¹ C. F. Bernasconi, *Acc. Chem. Res.* **11**, 147 (1978).

¹² S. S. Gitis and A. Ya. Kaminskii, *Russ. Chem. Rev. (Engl. Transl.)* **47**, 1061 (1978).

¹³ C. A. Fyfe, *Tetrahedron Lett.*, 659 (1968).

¹⁴ G. Illuminati and F. Stegel, *Tetrahedron Lett.*, 4169 (1968).

¹⁵ J. E. Dickeson, L. K. Dyall, and V. A. Pickles, *Aust. J. Chem.* **21**, 1267 (1968).

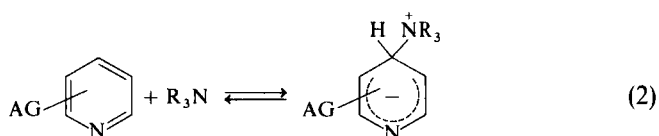
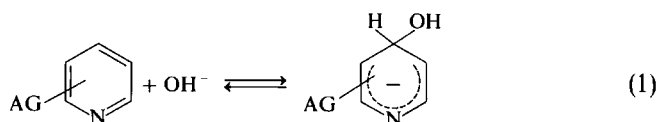
¹⁶ G. Doddi, G. Illuminati, and F. Stegel, *J.C.S. Chem. Commun.*, 953 (1969).

¹⁷ D. Spinelli, V. Armanino, and A. Corrao, *J. Heterocycl. Chem.* **7**, 1441 (1970).

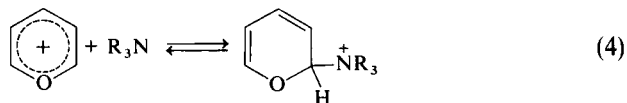
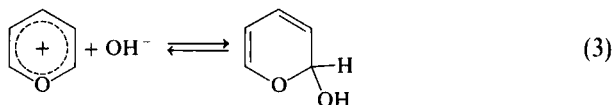
σ -bond by an "attachment reaction" (single covalent bond formation) of any type of entering groups (electrophilic, nucleophilic, or radical) with a ring carbon of the substrate whereby the ring aromaticity is disrupted.^{18,19} Thus σ -adduct formation is outside the definition of an "addition reaction," which is a more complex process, requiring two covalent bonds to be formed for its completion.¹⁸ As a matter of fact, σ -adduct formation is frequently assumed to be the first step in overall aromatic substitution or addition processes.

In heterocyclic chemistry it can be misleading to speak of "covalent addition" to mean both a product of an addition reaction, such as the hydration of a neutral substrate (i.e., transformation of pteridine to the 4-hydroxydihydro derivative),²⁰ and a product of an attachment reaction, such as the reaction of the hydroxide ion with the ring carbon of a heteroaromatic cation.²¹

No matter what the charge of the σ -adduct formed, we feel it is more essential to look at the charge type of the attachment reaction by which the adduct is formed. Thus σ -adduct formation using nucleophilic reagents usually belongs in the following charge types (Eqs. 1-4).



AG = activating groups



¹⁸ IUPAC "Glossary of Terms Used in Physical Organic Chemistry" (V. Gold, ed.), *Pure Appl. Chem.* **51**, 1725 (1979).

¹⁹ The definition of "attachment reaction" is included in the revised edition of Ref. 18 (to be published).

²⁰ A. Albert, "Heterocyclic Chemistry," 2nd ed., p. 129. Athlone Press, London, 1968.

²¹ J. W. Bunting, *Adv. Heterocycl. Chem.* **25**, 2 (1979).

Charge Type of Reaction	σ -Adduct
I. Molecule-anion	Anionic (Eq. 1)
II. Molecule-molecule	Zwitterionic (Eq. 2)
III. Cation-anion	Neutral (Eq. 3)
IV. Cation-molecule	Cationic (Eq. 4)

The reactions of heterocyclic cationic substrates such as quinolinium ions have been treated in an authoritative article by Bunting.²¹ In the present chapter we shall be concerned with the formation of σ -adducts as obtained from neutral heteroaromatic substrates and nucleophilic reagents of all types. This matter has never been reviewed before but is included in part in a comprehensive review article by Terrier.²²

In view of the role of σ -adducts as primary intermediates in the course of the reactions of heteroaromatic compounds with nucleophilic reagents, there is a large body of indirect evidence based on the nature of the reaction products, as resulting from overall substitutions, ring openings, and other reactions, as well as on kinetic behavior (base and bifunctional catalysis, leaving-group effects, etc.). We shall refer to such indirect evidence only occasionally and shall focus our attention on investigations enabling the detection or, even, isolation of the adducts and the determination of their structure, stability, and ease of formation.

According to a recent IUPAC resolution,¹⁸ we shall use the terms *Meisenheimer adduct*, or σ -*adduct*, rather than the widely used but less precise terms Meisenheimer complex or σ -complex.

This chapter covers the literature on the subject up to approximately the end of 1981.

The structural formulas are numbered in a single sequence even though they are occasionally cited only in tables, schemes, or equations.

II. Six-Membered Ring Adducts

A. REACTIONS WITH RO⁻ NUCLEOPHILES: CHARACTERIZATION STUDIES

1. *General Introductory Remarks*

The structure of anionic σ -adducts can be investigated with the aid of several spectral methods including UV-visible, IR,²³ ¹H-, ¹³C-, and ¹⁵N-NMR²⁴ spectroscopy, and X-ray crystallography. The latter is extremely

²² F. Terrier, *Chem. Rev.*, **82**, 77 (1982). We wish to thank Professor Terrier for sending a preprint of his article.

²³ L. K. Dyal, *J. Chem. Soc.*, 5160 (1960).

²⁴ V. Macháček, V. Sterba, A. Lycka, and D. Snobl, *J.C.S. Perkin II*, 355 (1982).

valuable but can only be applied under especially favorable conditions (isolation in crystal form, stability).^{25,26} Electronic and vibrational spectra can provide exceptionally important information. Although they may not lead to complete or unequivocal results, they are an essential complement to NMR studies.

The NMR spectra of the anionic σ -adducts are usually accompanied by upfield shifts relative to the starting aromatic or heteroaromatic substrate and can be rendered particularly valuable for identifying the point(s) of attachment of the nucleophilic reagent with the ring. The interpretation of the ^1H - and ^{13}C -NMR spectra of the anionic σ -adducts is a fascinating problem and is still a matter for further investigation. Although the electron density at any given position can be correlated to the chemical shift,²⁷⁻²⁹ disruption of ring current in going from aromatic substrate to adduct^{30,31} and strong delocalization toward electron-withdrawing groups,^{32,33} such as nitro and aza, are among other factors to be accounted for. Furthermore, the strong association of such metal ions as Li^+ with the nitrogen atom of the adducts generated from azines leads to a π -electron distribution that is very similar to a fixed double bond situation such as that found in dihydropyridines.³⁴ The diagnostic role of the NMR spectra with regard to the structure of the adducts will be indicated in this chapter in connection with typical examples. Finally, it may be worth mentioning that the $sp^2 \rightarrow sp^3$ change at a CH position is usually accompanied by a marked upfield shift in the ^1H -NMR spectrum.

In the following description of adduct formation reference is usually made to ^1H -NMR studies of which the essential data are collected in Table I. Additional data are also reported directly in the text. UV-Visible spectral data are reported in Table II and will be commented on only occasionally.

In the tables nonequivalent NMR positions are referred to with lowercase letters (a,b,c, etc.), which can be found in the related formulas reported in the text.

²⁵ R. Destro, C. Gramaccioli, and M. Simonetta, *Acta Crystallogr.* **24**, 1369 (1968).

²⁶ G. G. Messmer and G. J. Palenik, *Acta Crystallogr., Sect. B* **B27**, 314 (1971).

²⁷ G. Fraenkel, R. E. Carter, A. McLachlan, and J. R. Richards, *J. Am. Chem. Soc.* **82**, 5846 (1960).

²⁸ D. G. Farnum, *Adv. Phys. Org. Chem.* **11**, 123 (1975).

²⁹ W. E. Byrne, E. J. Fendler, J. H. Fendler, and C. E. Griffin, *J. Org. Chem.* **32**, 2506 (1967).

³⁰ P. Caveng, P. B. Fischer, E. Heilbronner, A. L. Miller, and H. Zollinger, *Helv. Chim. Acta* **50**, 848 (1967).

³¹ H. Kloosterziel and J. A. A. van Drunen, *Recl. Trav. Chim. Pays-Bas* **89**, 368 (1970).

³² G. A. Olah and H. Mayr, *J. Org. Chem.* **41**, 3448 (1976).

³³ E. Buncl, N. Chuaqui-Offermanns, R. Y. Moir, and A. R. Norris, *Can. J. Chem.* **57**, 494 (1979).

³⁴ R. E. van der Stoel and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas* **97**, 116 (1978).

TABLE I
¹H-NMR DATA FOR 6-MEMBERED HETEROAROMATIC PRECURSORS AND THE CORRESPONDING σ -ADDUCTS OBTAINED
 BY THE REACTION WITH RO⁻ IONS

Precursor ^a and adduct	Solvent	Chemical shift (δ)				Coupling constant (Hz)	References
		H-a	H-b	H-c	OMe and other groups ^b		
<i>Dinitropyridines</i>							
3,5-Dinitropyridine Adduct 1	DMSO- <i>d</i> ₆	9.73	9.13	9.73	— ^c	<i>J</i> _{ab} = 2.3	13, 35
	DMSO- <i>d</i> ₆	6.07–6.10	8.28–8.37	8.58–8.62	3.20	<i>J</i> _{ab} = 1.2 <i>J</i> _{ac} = 0.7 <i>J</i> _{bc} = 2.3	13, 35, 36
Adduct 2	DMSO- <i>d</i> ₆	8.33	5.97	8.33	3.13	<i>J</i> _{ab} = 1.3	35, 36
4-Methoxy-3,5- dinitropyridine	DMSO- <i>d</i> ₆	9.32	—	—	4.08	—	37, 38
Adduct 5	DMSO- <i>d</i> ₆	8.78	—	—	2.92	—	37
		8.44	—	—	2.95	—	38
Adduct 6	MeOH	8.60	—	—	—	—	37
	DMSO- <i>d</i> ₆	6.02	—	8.47	(a), 3.22 (b), 3.79	<i>J</i> _{ac} ≤ 0.5	37, 38
2-Methoxy-3,5- dinitropyridine	DMSO- <i>d</i> ₆	—	9.22	9.37	4.18	<i>J</i> _{bc} = 2.6	38
		—	(b + c), AB system at 9.24		4.24	<i>J</i> _{bc} = 3	39
Adduct 9	DMSO- <i>d</i> ₆	—	8.51	5.92	(a), 3.70 (c), 3.22	<i>J</i> _{bc} = 1.5	38
		—	8.59	5.99	(a), 3.77 (c), 3.26	<i>J</i> _{bc} ≈ 1	39

(continued)

³⁵ M. E. C. Biffin, J. Miller, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.* **23**, 963 (1970).

³⁶ R. Schaal, F. Terrier, J. C. Halle, and A. P. Chatrousse, *Tetrahedron Lett.*, 1393 (1970).

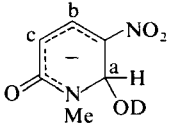
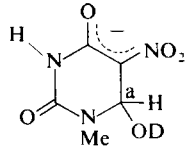
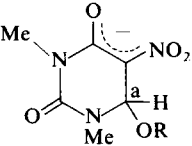
³⁷ P. Bemporad, G. Illuminati, and F. Stegel, *J. Am. Chem. Soc.* **91**, 6742 (1969).

³⁸ M. E. C. Biffin, J. Miller, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.* **23**, 957 (1970).

³⁹ C. Abbolito, C. Iavarone, G. Illuminati, F. Stegel, and A. Vazzoler, *J. Am. Chem. Soc.* **91**, 6746 (1969).

TABLE I (continued)

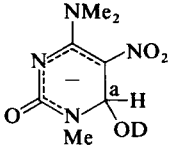
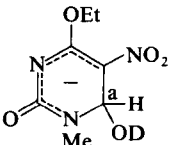
Precursor ^a and adduct	Solvent	Chemical shift (δ)				Coupling constant (Hz)	References
		H-a	H-b	H-c	OMe and other groups ^b		
2,6-Dimethoxy-3,5-dinitropyridine	DMSO- <i>d</i> ₆	—	9.09	—	4.19	—	40
Adduct 12	DMSO- <i>d</i> ₆	—	8.73	—	(a), 3.01 (c), 3.74	—	40
2-(2-Hydroxyethoxy)-3,5-dinitropyridine	—	—	(b + c), AB system at 9.10, 9.31	—	—	—	13
Adduct 14	—	—	(b + c), AB system at 8.35	OCH ₂ CH ₂ O, 4.12	—	—	13
<i>Nitropyrimidines</i>							
5-Nitropyrimidine	DMSO- <i>d</i> ₆	9.41	9.45	9.45	—	$J_{ab} \leq 0.1$	41
Adduct 15	DMSO- <i>d</i> ₆	5.53	8.18	8.18	3.20	$J_{ab} = 1.4$	41
2-Methoxy-5-nitropyrimidine	DMSO- <i>d</i> ₆	—	9.38	9.38	4.07	—	41
Adduct 16	DMSO- <i>d</i> ₆	—	5.84	8.35	—	—	14
		—	5.76	8.27	(a), 3.57; (b), 3.07	$J_{bc} = 1.6$	41
4-Methoxy-5-nitropyrimidine	DMSO- <i>d</i> ₆	9.05	—	9.25	4.12	—	41
Adduct 17	DMSO- <i>d</i> ₆	5.76	—	8.43	—	—	14
		5.74	—	8.40	(a), 3.20 (b), 3.63	$J_{ac} = 1.25$	41
<i>Nitropyridones and related substrates</i>							
1-Methyl-5-nitro-2-(1 <i>H</i>)-pyridinone	DMSO- <i>d</i> ₆	9.17	8.16	6.49	—	$J_{ab} < 3.2$ $J_{bc} = 10$	42

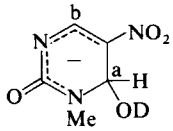
 18a 1-Methyl-5-nitro-2,4- (1<i>H</i>,3<i>H</i>)- pyrimidinedione	DMSO- <i>d</i> ₆	5.89	7.34	5.13	—	$J_{ab} = 2$ $J_{bc} = 9.5$	42
	DMSO- <i>d</i> ₆	9.24	—	—	—	—	42
	DMSO- <i>d</i> ₆	5.80	—	—	—	—	42
	DMSO- <i>d</i> ₆	9.28	—	—	—	—	42
	DMSO- <i>d</i> ₆	5.82	—	—	—	—	42
 18b 1,3-Dimethyl-5-nitro- 2,4(1<i>H</i>,3<i>H</i>)- pyrimidinedione	DMSO- <i>d</i> ₆	5.86	—	—	—	—	42
 18c: R = D 18d: R = OEt	DMSO- <i>d</i> ₆	9.25	—	—	—	—	42
4-Amino-1-methyl-5-nitro-2(1 <i>H</i>)- pyrimidinone	DMSO- <i>d</i> ₆						

(continued)

⁴⁰ A. P. Chatrousse, F. Terrier, and R. Schaal, *C.R. Acad. Sci., Ser. C* **271**, 1477 (1970).⁴¹ M. E. C. Biffin, J. Miller, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.* **22**, 2561 (1969).⁴² H. U. Blank, I. Wempen, and J. J. Fox, *J. Org. Chem.* **35**, 1131 (1970).

TABLE I (continued)

Precursor ^a and adduct	Solvent	Chemical shift (δ)			OMe and other groups ^b	Coupling constant (Hz)	References
		H-a	H-b	H-c			
 18e 4-Dimethylamino-1-methyl-5-nitro-2(1H)-pyrimidinone	DMSO- <i>d</i> ₆	5.69	—	—	—	—	42
 18f 4-Ethoxy-1-methyl-5-nitro-2(1H)-pyrimidinone	DMSO- <i>d</i> ₆	5.92	—	—	—	—	42
 18g	DMSO- <i>d</i> ₆	5.73	—	—	—	—	42

1-Methyl-5-nitro- 2(1 <i>H</i>)pyrimidinone	DMSO- <i>d</i> ₆	9.49	9.17	—	—	$J_{ab} = 3.5$	42
 18h	DMSO- <i>d</i> ₆	5.79	8.24	—	—	$J_{ab} = 1.3$	42
Polyazines							
6-(2-Hydroxyethoxy)- 9-methoxymethyl- purine	<i>t</i> -BuOH	8.62	8.42	—	OCH ₂ CH ₂ O, 4.80, 4.12 NCH ₂ O, 5.78	—	43
Adduct 19	<i>t</i> -BuOH	8.22	7.90	—	OCH ₂ CH ₂ O, 3.70 NCH ₂ O, 5.68	—	43
6-Methoxy-9-me- thoxymethylpurine	<i>t</i> -BuOH	8.60	8.44	—	4.25 NCH ₂ O, 5.72	—	43
Adduct 20	<i>t</i> -BuOH	8.20	7.88	—	3.90 NCH ₂ O, 5.62	—	43
2-Chloro-4,6- dimethoxy-1,3,5- triazine	DMSO- <i>d</i> ₆	—	—	—	4.07	—	44
Adduct 21	DMSO- <i>d</i> ₆	—	—	—	3.08	—	44

^a Precursors are assigned the same letters (a, b, and c) as the corresponding ring positions of the adducts.

^b Groups other than OMe are indicated near the δ value as appropriate.

^c — indicates data do not exist.

⁴³ C. L. Liotta and A. Abidaud, *J. Am. Chem. Soc.* **94**, 7927 (1972).

⁴⁴ P. Rys, A. Schmitz, and H. Zollinger, *Helv. Chim. Acta* **54**, 167 (1971).

TABLE II
 UV-VISIBLE SPECTRAL DATA FOR SOME 6-MEMBERED σ -ADDUCTS

Adduct	Solvent	$\lambda_{\max}$ (nm)	Log ϵ	References
1	MeOH	455	4.30	45
	MeOH-DMSO ^a	~ 480	—	36
2	MeOH-DMSO ^a	~ 492	—	36
3	H ₂ O	465	4.23	45
4	H ₂ O-DMSO ^b	~ 470	~ 4.4	45
5	MeOH	304-308,	3.69-3.74,	15, 37, 46
		455	4.15-4.25	
6	MeOH	435	4.37	46
9	MeOH	455	4.56	39
	DMSO	477.5	—	38
12	MeOH	450	4.48	47
13	MeOH-DMSO ^c	~ 420	~ 4.3	47
14	DMSO	462	—	13
15	DMSO	366	—	41
16	DMSO	403	—	41
	MeOH	394	~ 4	14
17	DMSO	365	—	41
	MeOH	352	~ 4	14
21	DMSO	320	—	44

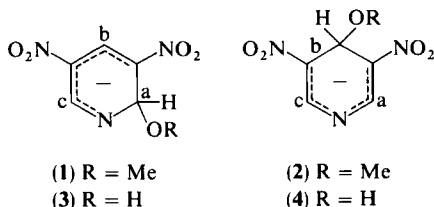
^a DMSO, 92.6% by weight.^b DMSO, 51.2% by weight.^c DMSO 80% by volume.

2. 3,5-Dinitropyridine

The adduct formation from the reaction of the 3,5-dinitropyridine with MeONa was first reported by Fyfe.¹³ In DMSO solution the reaction is accompanied by the disappearance of the NMR spectrum of the substrate and the appearance of three new signals of equal intensity. Furthermore, one of the three ring proton signals is much more shielded than in the substrate, due to the hybridization change from sp^2 to sp^3 . The observed pattern is in agreement with structure **1**. Subsequent NMR and spectrophotometric studies have shown that the isomeric adduct **2** competitively forms together with **1** and eventually turns into the latter, due to a substantial difference in stability.^{35,36,45} The conversion **2** $\rightarrow$ **1** is accelerated by methanol. The more

⁴⁵ A. P. Chatrousse and F. Terrier, *Bull. Soc. Chim. Fr.*, 4549 (1972).⁴⁶ F. Terrier, A. P. Chatrousse, and R. Schaal, *J. Org. Chem.* **37**, 3010 (1972).⁴⁷ A. P. Chatrousse, F. Terrier, and R. Schaal, *J. Chem. Res., Synop.*, 228 (1977).

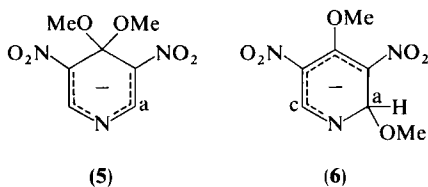
stable product **1** is the one resulting from attack at a position that is para to a nitro group and is flanked by an aza group and a nitro group.



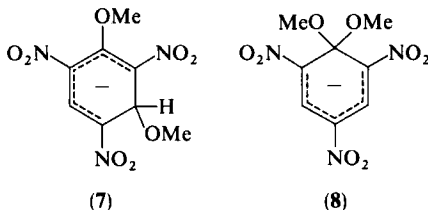
Evidence for the formation of adducts using OH^- as a nucleophile has been obtained by spectrophotometric studies in H_2O and H_2O -DMSO mixed solvents.⁴⁵ In H_2O and at low DMSO concentrations addition occurs at position 2 only, to yield adduct **3**. The characterization of the adduct is based on the similarity of the spectrum ($\lambda_{\text{max}} = 465\text{nm}$, $\epsilon = 1.7 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) with that of adduct **1**, as observed in methanol from the reaction with MeO^- ($\lambda_{\text{max}} = 455 \text{ nm}$, $\epsilon = 1.99 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). In DMSO-rich media the formation of **3** is preceded by the appearance of the less stable adduct **4**, which was identified mainly on the basis of the kinetic analogies with the reaction with MeO^- leading, under similar conditions, to adduct **2**. The formation of **2** and **4** has been shown to occur under kinetic control and to be followed by their extensive conversion to the more stable **1** and **3**, respectively.

3. 4-Methoxy-3,5-dinitropyridine

The reaction of 4-methoxy-3,5-dinitropyridine with the methoxide ion leads to one of the most easily formed adducts **5** as obtainable from pyridine derivatives and was investigated by several groups.^{14,37,38,46} In the early stages of the reaction adduct **6** can also be detected, provided that DMSO-rich media are used, because the addition of methanol to the DMSO solutions containing **6** causes the rapid disappearance of the related signals and a simultaneous intensity increase of the spectrum of **5**. The structure of **6** results from nucleophilic attack at one of the CH positions as in the case of adduct **1**. Adduct **5** is characterized by a symmetrical structure and the geminal methoxy substituents.



The behavior of 4-methoxy-3,5-dinitropyridine bears a substantial analogy with that of 2,4,6-trinitroanisole, which also yields two isomeric adducts (**7** and **8**) resulting from attack at the CH and COMe positions, respectively.⁴⁸



The presence of a 4-methoxy group in the heteroaromatic substrate upsets the dynamic pattern observed with 3,5-dinitropyridine. With the methoxy derivative the more stable adduct is the one resulting from attack of the MeO^- ion at a position that is flanked by two nitro groups and is para to an aza group, whereas in 3,5-dinitropyridine the favored reaction center is located between an aza and a nitro group and is para to a nitro group. Although a para nitro group brings about a stabilizing factor relative to a para aza group because of its higher capacity to accommodate the electronic charge, the behavior of the 4-methoxy derivative is determined by the greater stabilizing effect of other factors such as steric relief of the overcrowded surroundings about the methoxy group in the starting substrate and the geminal dimethoxy grouping in the corresponding adduct.

Adduct **5** has been isolated as the sodium salt in two different ways, i.e., either by solvent evaporation of the reaction mixture as obtained from equivalent amounts of the starting reagents in methanol solution,^{37,38} or by chilling a solution of 4-chloro-3,5-dinitropyridine and sodium methoxide.^{15,49} The IR spectrum of the solid thus obtained shows a series of strong bands between 1040 and 1225 cm^{-1} , which are typical of ketals, in agreement with the presence of a geminal dimethoxy grouping. The NMR spectrum

⁴⁸ K. L. Servis, *J. Am. Chem. Soc.* **87**, 5495 (1965).

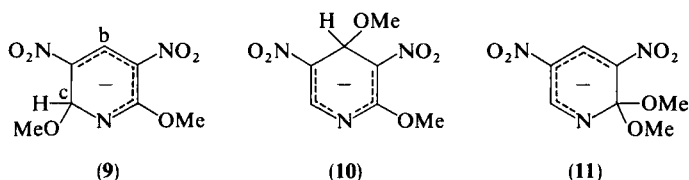
⁴⁹ For some reason, Dickeson *et al.*¹⁵ were unable to obtain 4-methoxy-3,5-dinitropyridine from the 4-chloro compound and obtained adduct **5** instead. This failure led them to suppose that adduct **5** would directly form from a C—Cl adduct, as derived from the 4-chloro compound on ipso attack of MeO^- to position 4, by solvolysis, according to a previous suggestion by Farmer.⁵⁰ Actually, 4-methoxy-3,5-dinitropyridine does form from the chloro compound, as described by us,³⁷ and can eventually be converted *in situ* to **5** in the presence of an excess of MeO^- . To date there is no evidence for the detection of the C—Cl adduct, even though its intermediacy in the formation of the 4-methoxy compound is expected.

⁵⁰ R. C. Farmer, *J. Chem. Soc.*, 3425 (1959).

of the adduct dissolved in either MeOH or DMSO is exactly the same as that recorded when the adduct is formed *in situ*. Interestingly, the adduct remains unchanged in the solid state without special precautions, whereas 4-methoxy-3,5-dinitropyridine tends to decompose easily.

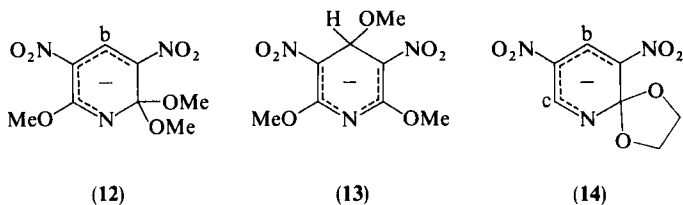
4. 2-Methoxy-3,5-dinitropyridine and Related Substrates

The reaction of 2-methoxy-3,5-dinitropyridine has been investigated in methanol, DMSO, and mixed solvents therefrom.^{38,39} In DMSO and DMSO-rich mixtures an adduct is formed rapidly and quantitatively upon addition of one equivalent of methoxide ion. Its NMR spectrum is characterized by the presence of two nonequivalent nuclear protons and two sets of non-equivalent methoxyl protons. One of the ring protons is strongly shielded with respect to those in the substrate. These features suggest that the attack on the substrate occurs at a CH position. When the starting compound is deuterated at position 6, the resulting adduct is accompanied by only a small upfield shift of the proton at position 4. Therefore, addition is assumed to occur at the 6-position, i.e., between a nitro group and the heteroatom, yielding adduct **9**. Spectrophotometric studies using the stopped-flow technique have confirmed the NMR results and have provided no evidence for the formation of more than one adduct. In particular, neither **10** nor **11** was detected.⁴⁷ Unlike the adducts resulting from attack at a CH position of 4-methoxy-3,5-dinitropyridine or 2,4,6-trinitroanisole, no isomerization of **9** to a geminal dimethoxy adduct is observed. This behavior is thus similar to that of 3,5-dinitropyridine where attack also occurs at a position α to the heteroatom. The above results were confirmed by Miller *et al.*³⁸



When methanol is added to the DMSO solution of the adduct, dealkylation occurs irreversibly to lead to the conjugate base of 2-hydroxy-3,5-dinitropyridine. The latter is characterized by an AB system centered at δ 8.9 and presumably results from a nucleophilic substitution at the methoxyl saturated carbon by MeO^- rather than through attack by traces of OH^- on the heteroaryl carbon 2.^{39,47}

The presence of a second methoxy group α to nitrogen, as in 2,6-dimethoxy-3,5-dinitropyridine, causes a decrease in the tendency to undergo addition with MeO^- .⁴⁷ An adduct can be detected only in DMSO or DMSO–MeOH mixtures containing at least 40% (by volume) of DMSO and is shown to have structure **12**, as supported by the small upfield shift of the ring protons and by the presence of two sets of methoxyl protons at δ 3.74 and 3.01; the latter signal is two times as intense as the former and originates from the two geminal methoxy groups bound to the sp^3 carbon atom.⁴⁰



When DMSO is the predominant component of the medium, the formation of **12** is preceded by the formation of the less stable adduct **13**. Because the rate of interconversion $\mathbf{13} \rightarrow \mathbf{12}$ is quite fast, kinetic evidence for **13** is obtained by the stopped-flow method, but its structure has not been proved by NMR. As already observed in the reaction of 2-methoxy-3,5-dinitropyridine, a demethylation reaction eventually takes place, yielding the conjugate base of 2-hydroxy-6-methoxy-3,5-dinitropyridine.

In the case of 2-dimethylamino-3,5-dinitropyridine the reaction with MeO^- in DMSO solution gives rise to two NMR signals at δ 6.05 and 8.20 as the spectrum of the substrate fades out.¹³ The former signal indicates an attack of the nucleophile at a CH position, either 4 or 6. The exact site of addition has not been established.

Fyfe also showed that a 2-hydroxyethoxy group gives rise to ring closure via intramolecular attack of the nucleophilic β oxygen as promoted by the methoxide ion in DMSO solution. The resulting spiro adduct **14** is characterized by a strongly coupled AB system centered at δ 8.65 and a singlet at δ 4.12, with an intensity ratio of 1:2.¹³ The ease of formation of a 5-membered ring provides the driving force for the formation of a geminal dialkoxy-substituted adduct at a carbon atom ortho to an aza group.⁵¹⁻⁵³ In the absence of such a driving force, the attack on position 2 would have not been especially favored, as suggested by the behavior of 2-methoxy-3,5-dinitropyridine.

⁵¹ M. R. Crampton and M. J. Willison, *J.C.S. Perkin II*, 155 (1976).

⁵² C. F. Bernasconi and J. R. Gandler, *J. Org. Chem.* **42**, 3387 (1977).

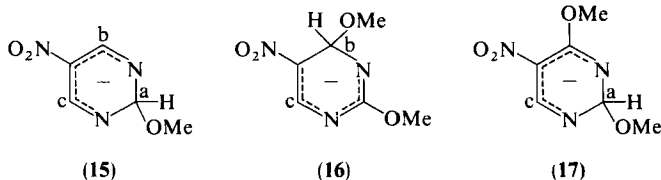
⁵³ G. Illuminati and L. Mandolini, *Acc. Chem. Res.* **14**, 95 (1981).

5. 3,5-Dinitropyridine 1-Oxide

Even though no NMR evidence is as yet available for the formation of adducts from *N*-oxides, 3,5-dinitropyridine 1-oxide was shown by Ochiai and Kaneko to display a strong tendency to react with weakly basic aqueous solutions (K_2CO_3), which develop a red color ($\lambda_{\max} \approx 500$ nm).⁵⁴ On treatment with strong bases (KOH in H_2O), the color becomes yellow whereas partial neutralization restores the red color. Because 3,5-dinitropyridine itself is quite reactive toward nucleophilic addition, the corresponding *N*-oxide is expected to be even more so because of the increased electron-withdrawing power of the *N*-oxide group relative to the aza group. It has indeed been noted that ethanol alone can bring about a slow appearance of the red color and that the crystallization of the substrate can only be performed in the presence of a trace of HCl. This behavior is similar to that of 2-methoxy-3,5-dinitrothiophene for which a very high equilibrium constant was obtained (see Section III,C).^{55,56} Stepwise uptake of two equivalents of reagent to yield mono- and dianionic adducts, respectively, has been suggested in order to explain the observed phenomena.

6. 5-Nitropyrimidine

The adduct obtained from 5-nitropyrimidine in DMSO- d_6 solution was assigned structure **15**.⁴¹ The NMR spectrum displays an AB₂ pattern that cannot be firmly distinguished from a deceptively simple ABX system corresponding to an attack at the 4-position. The ambiguity is eliminated, however, by carrying out the reaction with the 4-deutero derivative. The spectrum under the latter conditions shows two doublets of equal intensity at δ 5.53 and 8.18, thus confirming the above assignment. The observed adduct is thus the one resulting from attack at the position located para rather than ortho to the nitro group.



⁵⁴ E. Ochiai and C. Kaneko, *Chem. Pharm. Bull.* **8**, 28 (1960).

⁵⁵ G. Doddi, G. Illuminati, and F. Stegel, *J. Org. Chem.* **36**, 1918 (1971).

⁵⁶ F. Terrier, A. P. Chatrousse, C. Paulmier, and R. Schaal, *J. Org. Chem.* **40**, 2911 (1975).

7. Methoxynitropyrimidines

In the case of 2-methoxy-5-nitropyrimidine, the adduct that forms predominantly in DMSO solution has been shown to have the structure of **16**, as characterized by two doublets of equal intensities in the NMR spectrum.^{14,41} The presence of a weak singlet has been indicated as evidence for the formation of minor amounts of the *gem*-dimethoxy isomer,⁴¹ although no further confirmation is available. Thus the preferred attack occurs at a position adjacent to the nitro group, located para to an aza group and other than the methoxyl-bearing position.

4-Methoxy-5-nitropyrimidine is also attacked at a CH position, as indicated by the relatively high upfield shift of one of the ring protons.^{14,41} The formation of the *gem*-dimethoxy adduct is thus ruled out. Of the two possible isomeric adducts only the one resulting from attack at the 2-position (**17**) is formed, as unequivocally shown by the singlet at δ 5.75, which is observed starting from 4-methoxy-5-nitropyrimidine-6-*d*.⁴¹

The NMR and UV spectra of the aforementioned adducts in DMSO solution decay after some time and are eventually replaced by the spectra of the conjugate bases of the corresponding hydroxypyrimidines. The lower the stability of the adduct, the more effectively the demethylation reaction appears to compete with adduct formation.

No evidence was found of isomerization of the CH to the COMe adduct on addition of methanol to the DMSO solution,⁴¹ although a solvent effect of this kind was observed in carbocyclic series.⁴⁸ However, methanol seems to have a depressing effect on the stability of the CH adduct and to promote its decomposition. Slow ring opening has been suggested to occur in MeOH-DMSO (1:9) starting from the 4-methoxy isomer.⁴¹

In summary, both 2- and 4-methoxy-5-nitropyrimidines undergo attack at a CH position rather than at the COMe position. A major factor for this behavior is believed to be the COMe bond-strengthening effect of the conjugation of the methoxy substituent with the ring. This is especially evident in the formation of adduct **16** resulting from attack of the reagent at the more hindered position 4 relative to position 2.⁴¹

8. Nitropyridones and Related Compounds

In the presence of RO⁻ ions several oxo derivatives related to 5-nitrouracil undergo the attachment reaction at position 6.^{42,57} The formation of adducts **18a-18h** is favored by the presence of the nitro group. As usual, the forma-

⁵⁷ I. H. Pitman, M. J. Cho, and G. S. Rork, *J. Am. Chem. Soc.* **96**, 1840 (1974).

tion of adducts is characterized by an upfield shift with respect to the starting substrate in the $^1\text{H-NMR}$ spectrum ($\Delta\delta \approx 3.6$ ppm). The conversion of the substrates to the corresponding adducts is not always complete.

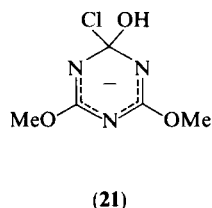
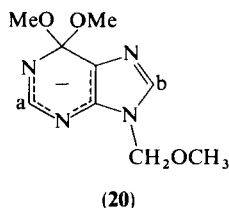
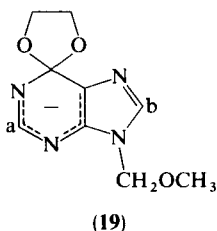
In earlier work,⁵⁸ 1,3-dimethyl-5-nitrouracil had been reported to react with sodium ethoxide to yield a crystalline, stable sodium salt, whose anion had been suggested to possess structure **18d**. Such structure was confirmed more recently by NMR evidence.⁴²

In the reaction of 1,3-dimethyl-5-nitrouracil, the formation of the adduct is accompanied by a small bathochromic shift, which is also generally observed in the reaction of the same substrate with other nucleophiles⁵⁷ (see Section II,E).

9. Purine Substrates

Evidence for the formation of Meisenheimer-type adducts from a purine system has been obtained by Liotta in two cases.⁴³ The addition of $t\text{-BuO}^-$ to 6-(2-hydroxyethoxy)-9-methoxymethylpurine in $t\text{-BuOH}$, as monitored by $^1\text{H-NMR}$ spectroscopy, causes an upfield shift of both pyrimidine and imidazole ring protons and the conversion of two absorptions of the methylene protons of the $\text{CH}_2\text{CH}_2\text{OH}$ group to a broad absorption of the dioxolane ring, in agreement with the formation of the spiro adduct **19**. Similarly, adduct **20** was formed from 6-methoxy-9-methoxymethylpurine by slow reaction with MeO^- in $t\text{-BuOH}$.

The absence of nitro groups in these substrates is noteworthy. The observed adducts are exclusively stabilized by the electron-withdrawing capacity of the aza groups present in the fused ring system of purine. Accordingly, all ring protons in the adducts are more shielded than the corresponding protons in the substrates. Adducts **19** and **20** can be taken as models for intermediates in nucleophilic aromatic substitution at the C-6 position of purine. Moreover, their formation support the view that a tetrahedral carbon at C-6 is involved in the mechanism of the adenosine deaminase-catalyzed hydrolysis of 6-substituted purine ribonucleosides.⁴³



⁵⁸ W. Pfeleiderer and H. Mosthaf, *Chem. Ber.* **90**, 728 (1957).

10. Triazine Derivatives

Evidence for the formation of an adduct in the *s*-triazine series has been obtained by Rys *et al.*⁴⁴ in connection with the hydrolysis of 1,3-dimethoxy-5-chloro-*s*-triazine in DMSO. The substrate alone in DMSO shows a singlet for the methoxy groups at δ 4.07. Upon addition of H₂O, a signal is detected at δ 3.08, whose intensity increases at first and subsequently decreases gradually. At the end of the reaction, only the signal of the substitution product (δ 3.26) is obtained. The signal at δ 3.08 is attributed to the methoxy groups of adduct **21**, which would form upon interaction of the substrate with the OH⁻ ion or H₂O and equilibrate with a neutral covalent adduct on protonation of any of the ring nitrogens.

Further information on the structure of the intermediate is given by the UV spectra. The reaction of the substrate with water in aqueous DMSO gives rise to a transient absorption at 320 nm. In analogy with the NMR spectral behavior (signal at δ 3.08), the intensity of the 320-nm band increases first, then it decreases slowly. Because triazines have an absorption maximum at nearly 260 nm, it is unlikely that the 320-nm maximum corresponds to a triazine derivative. An extrapolation of the absorption maxima values as a function of the number of aza groups in the ring of aza-nitro adducts indicates that the position of the maximum at 320 nm is consistent with the formation of an adduct. In view of the peculiarity of the detection of a Meisenheimer intermediate involving attack of the nucleophile at a Cl-bearing position, further, more direct evidence of structure **21** may be desirable.

B. RATES AND EQUILIBRIA FOR THE REACTIONS WITH RO⁻ NUCLEOPHILES

1. Determination of Equilibrium Constants

Because the Meisenheimer adducts are usually characterized by intense UV-visible absorption bands, the equilibrium constants for their formation (*K*) can be determined spectrophotometrically by standard methods, whether complete conversion to the adduct can be attained⁵⁹ or not,⁶⁰ depending on the equilibrium constant value ($K \gtrless \sim 10$).

In a few cases the equilibrium constants were estimated by NMR, by evaluating the relative concentrations of reactants at equilibrium.⁴¹ This

⁵⁹ V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1687 (1964).

⁶⁰ H. A. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.* **71**, 2703 (1949).

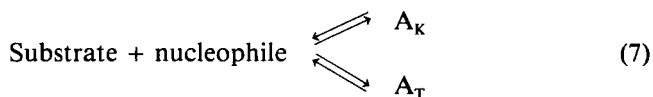
method is suitable only for reactions characterized by relatively low equilibrium constants, i.e., of the order of $10^2 M^{-1}$.

2. Concurrent Formation of Isomeric Adducts

Several pyridine substrates can yield two isomeric adducts.^{45,46} It has often been found that one of them (A_K) is kinetically favored, whereas the other (A_T) is thermodynamically favored. The independent rates of attainment of the equilibrium (k_{eq}) for the formation of A_K and A_T , respectively, are expressed by Eqs. (5) and (6). The reaction scheme is illustrated by Eq. (7).

$$k_{eq}^K = k_f^K [Nu] + k_r^K \quad (5)$$

$$k_{eq}^T = k_f^T [Nu] + k_r^T \quad (6)$$



At high concentrations of nucleophile the second term on the right side of these equations becomes negligible, so that the initial rate for the formation of A_K , relative to that for A_T , approaches the k_f^K/k_f^T ratio. If the equilibria are strongly shifted toward the adducts, the less stable adduct A_K can be detected as a transient species before its conversion to the more stable adduct A_T .

Solvents may have a role in the aforementioned behavior. If DMSO is a major component of the medium, forward rates increase and reverse rates decrease. Thus in mixed DMSO-protic solvents the detectability of A_K improves at greater DMSO contents, whereas in methanol or H_2O the equilibrium constants K^K are relatively small and only the more stable adducts A_T are detected.

3. Kinetic Form

The reactions of adduct formation have generally been followed spectrophotometrically. Due to the high reactivity of the substrates or to the use of DMSO-rich media, many reactions are very fast and must be followed by the stopped-flow technique. The reactions are generally carried out under pseudo first-order conditions, using an excess of the nucleophile.

The kinetic form depends upon the complexity of the reaction. Whenever only one adduct is formed from a given substrate, the observed pseudo first-order rate constant k_{obs} is given by Eq. (8), where k_f is the second-order rate

constant for the formation of the adduct, and k_r is the first-order rate constant for return to the reactants.

$$k_{\text{obs}} = k_f [\text{Nu}] + k_r \quad (8)$$

The slope of the plot of k_{obs} against the concentration of the nucleophile yields k_f , k_r being the intercept. The determination of k_r by extrapolation may be seriously affected by experimental errors when k_r is very small. Alternatively, k_r can be measured directly by following the rate of return to the reactants starting from the isolated adduct.

The equilibrium constant K can be evaluated from the rate data and is given by the k_f/k_r ratio. For a more reliable answer, it is safe to check the K value, as obtained by the kinetic method, by comparison with the one obtainable from equilibrium studies, as referred to previously.

More complex reaction patterns are observed for the reversible formation of two isomeric adducts from the same substrate (Eq. 7). In such cases the kinetic form takes into account the formation of the A_K and A_T species as discussed above (see Section II,B,2). Thus the interaction leads to two distinguishable processes, the first of which consists of the formation of a mixture in which A_K is predominant. The related observed rate constant for this process is expressed according to Eq. (9).

$$k_{\text{obs}} = k_{\text{eq}}^K = k_f^K [\text{Nu}] + k_r^K \quad (9)$$

In the subsequent, thermodynamically controlled process the more stable adduct A_T becomes predominant through a reequilibration via the starting substrate. The observed pseudo first-order rate constant is given by Eq. (10).⁴⁶

$$k_{\text{obs}} = k_r^T (1 + K^K [\text{Nu}] + K^T [\text{Nu}]) / (1 + K^K [\text{Nu}]) \quad (10)$$

If $K^T \gg K^K$, Eq. (10) is reduced to Eqs. (11) and (12).

$$k_{\text{obs}} = k_r^T (1 + K^T [\text{Nu}]) / (1 + K^K [\text{Nu}]) = (k_r^T + k_f^T [\text{Nu}]) / (1 + K^K [\text{Nu}]) \quad (11)$$

$$k_{\text{obs}} (1 + K^K [\text{Nu}]) = k_r^T + k_f^T [\text{Nu}] \quad (12)$$

When the left member of Eq. (12), as calculated from the observed rate constant and K^K values, is plotted against $[\text{Nu}]$, it is possible to determine the rate constant for the formation and decomposition of adduct A_T and to evaluate the equilibrium constant K^T . The preceding treatment can be safely used if the second step is sufficiently slow with respect to the first one. When such a condition is not fulfilled, a more elaborate treatment of the kinetic data is required.⁶¹

⁶¹ R. Gaboriaud and R. Schaal, *Bull. Soc. Chim. Fr.*, 2683 (1969).

Whenever both $K^T[\text{Nu}]$ and $K^K[\text{Nu}]$ are much larger than 1, Eq. (11) becomes Eq. (13).

$$k_{\text{obs}} = k_r^T K^T / K^K = k_f^T / K^K \quad (13)$$

The required conditions may either be fulfilled at the highest concentration of the nucleophile or in DMSO-rich media, where the equilibria are strongly shifted toward the adducts. It is then found that a plot of k_{obs} against the concentration of the nucleophile, after showing an initial increase, reaches a plateau, corresponding to the maximum allowed value, for k_{obs} .⁴⁶ If the K^K value can be independently measured, Eq. (13) affords the rate constant for the formation of the more stable adduct (k_f^T). Alternatively, Eq. (11) may be written

$$1/k_{\text{obs}} = (1 + K^K [\text{Nu}]) / (k_r^T + k_f^T [\text{Nu}]) \quad (14)$$

If k_r^T can be neglected with respect to the $k_f^T [\text{Nu}]$ term, Eq. (15) is obtained.

$$1/k_{\text{obs}} = (1/k_f^T [\text{Nu}]) + K^K/k_f^T \quad (15)$$

A plot of $1/k_{\text{obs}}$ versus $1/[\text{Nu}]$ gives a straight line, the slope of which gives the reciprocal of k_f^T , and the intercept of which gives the K^K/k_f^T ratio.⁴⁷

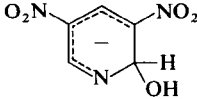
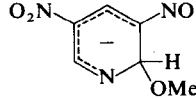
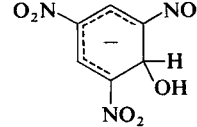
4. 3,5-Dinitropyridine Derivatives

a. *3,5-Dinitropyridine*. In water the formation of adduct **3**, which occurs by attachment of OH^- to position 2, follows Eq. (8).⁴⁵ The reaction is followed spectrophotometrically at the λ_{max} value of **3** (465 nm) with the stopped-flow technique. The kinetics and equilibrium data are reported in Table III, together with similar data for the formation of the corresponding adduct (**22**) from trinitrobenzene. In DMSO- H_2O mixtures, the kinetics become more complicated as the DMSO content increases, because the formation of **3** is preceded by the faster formation of the less stable adduct **4**, resulting from attachment of the reagent to position 4. The kinetic pattern is described by Eqs. (9) and (10), and the data are reported in Section II,B,7.

In methanol the reaction with MeO^- is analogous to that observed with OH^- in H_2O and yields only adduct **1** (Table III), whereas in DMSO-rich mixtures the formation of **1** is preceded by that of the less stable **2**.

As is usually observed in nucleophilic reactions, the reactivity of the substrate is higher in the MeO^- -MeOH than in the OH^- - H_2O nucleophile-solvent system. The $k_{\text{MeO}}/k_{\text{OH}}$ rate ratio for the attachment to position 2 of 3,5-dinitropyridine is nearly 72 at 25°C. The reverse rate is higher, by a

TABLE III
SELECTED KINETIC AND EQUILIBRIUM DATA FOR ADDUCT FORMATION^a AT 25°C BY THE
REACTION OF 3,5-DINITROPYRIDINE AND 1,3,5-TRINITROBENZENE WITH OH⁻ (IN H₂O) AND MeO⁻ (IN MeOH)^b

				
	3	1	22	23
k_f ($M^{-1} \text{ sec}^{-1}$)	34	2460	37.5	7050
k_r (sec^{-1})	2.82	35.5	9.8	305
K (M^{-1})	12	69.5	3.73	23.1
$\Delta H_f^\ddagger$	57.1	52.3	65.3	42.7
$\Delta H_r^\ddagger$	49.8	43.5	30.6	38.5
ΔH°	7.3	8.8	34.7	4.2
$\Delta S_f^\ddagger$	- 23.4	- 4.2	4.6	- 28.0
$\Delta S_r^\ddagger$	- 66.9	- 71.1	- 123.0	- 68.2
ΔS°	43.5	66.9	127.6	40.2

^a ΔH (kJ/mol); ΔS ($\text{J mol}^{-1} \text{ K}^{-1}$).

^b References: 45 for 1 and 3, 62 for 22 and 23.

⁶² V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1692 (1964).

factor of nearly 13, for the reaction with MeO^- than for that with OH^- . As a result, the methoxy adduct is six times more stable than the corresponding hydroxy adduct, each being considered in the respective solvent. The reaction of both nucleophiles is accelerated when DMSO is added; however, whereas the reaction of OH^- at position 4 can still be followed by the stopped-flow technique even at high DMSO content, that of MeO^- at the same position becomes too fast for measurement.

The difference in stability noted above is of the same order of magnitude as that found for the formation of adducts **22** and **23** for the reaction of 1,3,5-trinitrobenzene with the OH^- and MeO^- ions, respectively. Examination of the activation parameters shows some relevant differences between the heterocyclic and the homocyclic systems, however. The higher reverse rate for the methoxy adduct of trinitrobenzene **23** relative to the corresponding hydroxy adduct **22** is controlled by the higher activation entropy, whereas the higher reverse rate for the methoxy adduct of the dinitropyridine **1** relative to **3** is determined by the activation enthalpy. The entropy effect has been related to the different role of intramolecular interactions of the hydroxy adducts in the benzene and pyridine series. The reason for this difference is still unclear, however.⁴⁵

The adducts formed by attack of RO^- at position 2 of 3,5-dinitropyridine are more stable than those formed at position 4. In DMSO-rich media the stability difference results from a markedly lower return rate for the former as compared with the latter (see data in Section II,B,7). The overall result is in agreement with the well established fact that the presence of a stronger electron-withdrawing group (NO_2) has a larger stabilizing effect at a para position than at an ortho position with respect to the reaction center.^{63,64}

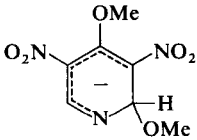
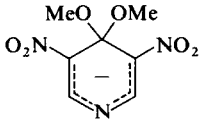
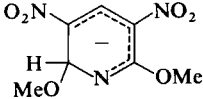
b. *4-Methoxy-3,5-dinitropyridine*. When the hydroxide ion is used as a nucleophile in the reaction of alkoxynitro derivatives, complications may arise from the competition between adduct formation and dealkylation processes yielding the conjugate bases of hydroxynitro derivatives. Therefore, the available data for the reactions of such substrates concern alkoxide ions only as nucleophiles.

In methanol, when the MeO^- concentration is lower than $10^{-2} M$, the reaction of 4-methoxy-3,5-dinitropyridine yields the more stable adduct **5** only, which results from attack at position 4.^{37,46} At higher MeO^- concentrations, the formation of **5** is preceded by the faster formation of the less stable isomer **6**.⁴⁶ In fact, only the latter adduct is detected at the beginning of

⁶³ J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.* **34**, 689 (1969).

⁶⁴ E. J. Fendler, J. H. Fendler, C. E. Griffin, and J. W. Larsen, *J. Org. Chem.* **35**, 287 (1970).

TABLE IV
SELECTED KINETIC AND EQUILIBRIUM DATA^a FOR ADDUCT FORMATION BY THE REACTION OF METHOXYDINITROPYRIDINES^b WITH MeO⁻

	 6			 5			 9	
	MeOH		DMSO-MeOH ^c	MeOH		DMSO-MeOH ^c	MeOH	DMSO-MeOH ^c
	20°C	25°C	25°C	20°C	25°C	25°C	20°C	25°C
k_f ($M^{-1} \text{ sec}^{-1}$)	275	390	1640	16.5	23	136	415	3600
k_r (sec^{-1})	25	33.2	4.4	5.8×10^{-3}	8.6×10^{-3}	—	125	40
K (M^{-1})	11	11.7	372	2870	2680	—	3.32	90
							1.91 ^d	
$\Delta H_f^\ddagger$	—	43.1	44.4	—	47.7	48.3	—	38.1
$\Delta H_r^\ddagger$	—	38.9	39.8	—	58.2	—	—	44.4
ΔH°	—	4.2	4.6	—	— 10.5	—	—	— 6.3
$\Delta S_f^\ddagger$	—	— 50.6	— 35.6	—	— 58.6	— 41.8	—	— 49.4
$\Delta S_r^\ddagger$	—	— 85.3	— 99.6	—	— 90.0	—	—	— 66.1
ΔS°	—	34.7	64.0	—	31.4	—	—	16.7
ΔG°	—	— 6.1	— 14.5	—	— 19.9	—	—	— 11.3

^a ΔH (kJ/mol); ΔG (kJ/mol); ΔS ($\text{J mol}^{-1} \text{ K}^{-1}$).

^b References: 46 for 6; 37 and 46 for 5; 47 for 9.

^c 30% DMSO by volume.

^d Reference 39.

the reaction if the concentration of MeO^- is higher than 0.5 M . The appearance of the less stable adduct can also be observed at lower MeO^- concentrations in the presence of increasing amounts of DMSO in the medium. When a single adduct is observed, the kinetics fit Eq. (8). Because of the low value of the intercept, reliable values of k_r are obtained either from the K value or by measuring the rate of return of the isolated adduct to the reactants. The kinetic pattern of the reaction involving the competitive formation of the two isomeric adducts is described by Eqs. (9) and (10). Kinetic and equilibrium data are reported in Table IV.⁴⁶ It is worth comparing the preceding data with those of related substrates. In the case of 4-methoxy-3,5-dinitropyridine the kinetically controlled reaction occurs at the 2-position, followed by the formation of the thermodynamically controlled product resulting from attack at the 4-position. This is just the opposite to what is observed in the case of 3,5-dinitropyridine (Table III).

The rate of formation of **6** is nearly 17 times as high as the rate of formation of **5**. Therefore, the higher stability of the latter adduct is a consequence of a lower reverse rate. Accordingly, the enthalpy of activation for the return of **5** to the reactants is larger by nearly 19 kJ/mol than that for return of the less stable **6**.

c. *2-Methoxy-3,5-dinitropyridine*. 2-Methoxy-3,5-dinitropyridine reacts with MeO^- to yield **9** as the only adduct.^{39,47} No evidence has been obtained using DMSO-rich media for the formation of either adduct **10**, which would result from the reaction at the CH position 4, or the geminal dimethoxy adduct **11**. Because the equilibrium constant for the formation of **9** in MeOH is low, the detection of the adduct is possible only at MeO^- concentrations higher than $10^{-2} M$. Kinetic measurements have been made by the stopped-flow technique.⁴⁷ Although the reaction is accompanied by demethylation, yielding the conjugate base of 2-hydroxy-3,5-dinitropyridine, the latter is a relatively slow process and does not affect the measurements.

The equilibrium constant in methanol was evaluated in two independent ways, i.e., by direct determination ($K = 1.9 M^{-1}$ at 25°C)³⁹ and by the kinetic method in DMSO–MeOH and extrapolation to zero DMSO concentration ($K = 3.3 M^{-1}$ at 20°C; see also Table IV).⁴⁷ The two results are in satisfactory agreement with each other.

The reactivity data and the equilibrium constant for the formation of **9** are similar to those observed for the formation of the kinetically controlled adduct **6** (Table IV), which can be explained by the structural analogies of these adducts. In both cases the equilibrium constants are higher than the value reported for the formation of adduct **7** from 2,4,6-trinitroanisole (Table V).

TABLE V
KINETIC AND EQUILIBRIUM DATA^a FOR ADDUCT
FORMATION BY THE REACTION OF
2,4,6-TRINITROANISOLE AND MeO⁻ IN MeOH AT 25°C^b

	7	8
k_f (M ⁻¹ sec ⁻¹)	950	17.3
k_r (sec ⁻¹)	350	1.04×10^{-3}
K (M ⁻¹)	2.7	1.7×10^4
$\Delta H_f^\ddagger$	43.5	54.0
$\Delta H_r^\ddagger$	34.3	77.0
ΔH°	9.2	- 23.0
$\Delta S_f^\ddagger$	- 45.2	- 39.3
$\Delta S_r^\ddagger$	- 80.8	- 20.0
ΔS°	35.6	- 19.2
ΔG° (kJ/mol)	- 1.4	- 28.7

^a ΔH (kJ/mol); ΔS (J mol⁻¹ K⁻¹).

^b References: 65 for 7, 66 for 8.

d. *2,6-Dimethoxy-3,5-dinitropyridine*. The interreaction of 2,6-dimethoxy-3,5-dinitropyridine with MeO⁻ ion has been studied only in DMSO-rich mixtures because of the relatively small equilibrium constant for adduct formation.^{40,47} Under these conditions, however, the reaction is very fast and must be followed by the stopped-flow technique. In MeOH-DMSO mixtures with DMSO contents lower than 60% (v/v), only the formation of adduct **12** is observed ($\lambda_{\max} = 450$ nm) and the reaction can be described kinetically by Eq. (8). At high MeO⁻ concentration or DMSO content, the formation of the more stable adduct **12** is preceded by the appearance of the 4-adduct **13** ($\lambda_{\max} = 420$ nm). Under these conditions the kinetic scheme fits Eqs. (9) and (10). Forward and reverse rate constants for the formation of **12** can be determined in MeOH-rich DMSO-MeOH mixtures but cannot be obtained in DMSO-rich mixtures because forward rates, and consequently the equilibrium constants, would be too high for a reliable determination. The equilibrium constant for the formation of **12** in MeOH has been calculated by extrapolation of the kinetic data obtained in DMSO-MeOH mixtures, because the adduct itself is not detected in MeOH alone. In DMSO-rich mixtures the kinetics allow the determination of the equilibrium constant for the formation of adduct **13** as well as the rate constant for the formation of adduct **12** (Eq. 15).

In 2,6-dimethoxy-3,5-dinitropyridine the site of attachment correspond-

⁶⁵ Data reported in Ref. 22 as unpublished work by F. Terrier and A. P. Chatrousse.

⁶⁶ J. W. Larsen, J. H. Fendler, and E. J. Fendler, *J. Am. Chem. Soc.* **91**, 5903 (1969).

ing to the more stable adduct is an α position. This behavior, whereby kinetic control affords a 4-adduct and thermodynamic control a 2-adduct, is similar to that of 3,5-dinitropyridine.

Adduct **12** turns out to be nearly 30 times less stable than adduct **9**, which is formed on attack at position 6 of 2-methoxy-3,5-dinitropyridine. If allowance is made for the destabilizing effect of a meta methoxy group (by a factor of nearly 10) in an azine system⁶⁷ and for the statistical factor, adduct **12** can be considered as an approximate model for the hypothetical geminal dimethoxy adduct **11**, which would be formed on attack of 2-methoxy-3,5-dinitropyridine at position 2. Therefore, the equilibrium constant for **11** is not expected to be high enough to make the formation of **11** competitive with that of **9**. Also, the formation of **11** is presumably slower than that of adduct **9**, as is generally observed for the attachment to a COMe position relative to a CH position. The preceding considerations explain why the formation of **11** is not observed, particularly in view of the limited sensitivity of the ¹H-NMR technique.

Finally, it should be noted that while 2-methoxy-3,5-dinitropyridine yields **9**, rather than **10**, by undergoing attack at the CH position 6, the CH position 4 is attacked by CH₃O⁻ when both positions 2 and 6 are occupied by a methoxy group to yield **13**. Of course, adduct **10** may be formed in DMSO-rich media and escape detection because its conversion to **9** is very fast.

5. Role of the Heteroatom

Although the information concerning the influence of structural changes in azine substrates on the formation of Meisenheimer adducts is still rather limited, there are enough quantitative data for the reactions with MeO⁻ to permit some general features to be fairly well established and to illustrate the importance of such data as a valuable complement for a better understanding of the dynamics of adduct formation in homocyclic series. The aim of this section is to utilize such data, which have been presented in the preceding sections, in order to interpret them from the point of view of structural effects.

a. *The Electron-Withdrawing Capacity of the Aza Group.* The ability of the aza group, relative to the nitro group, to accommodate the electronic charge of the adduct can be observed best at a position para to the reaction center, away from complications of a different kind that may occur at the ortho position.

The replacement of a para nitro group with an aza group involves a loss in stability of the adduct (Table VI) by one order of magnitude or so, in agree-

⁶⁷ M. Forchiassin, G. Illuminati, and G. Sleiter, *J. Heterocycl. Chem.* **6**, 879 (1969).

TABLE VI
REACTIONS OF AZINE DERIVATIVES WITH RO^- -ROH SYSTEMS. KINETIC AND EQUILIBRIUM
CONSTANTS FOR ADDUCT FORMATION: COMPARISON WITH RELATED TRINITROBENZENE
DERIVATIVES

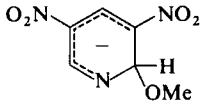
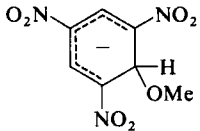
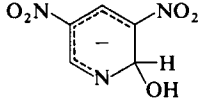
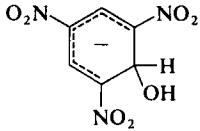
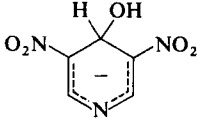
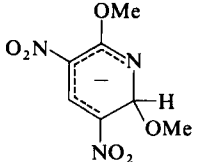
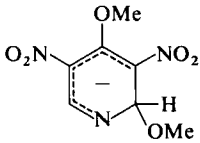
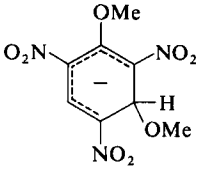
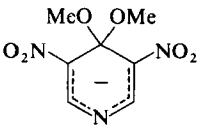
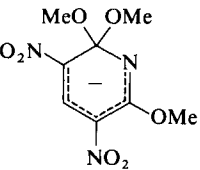
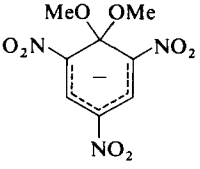
Adduct	$k_f (M^{-1} \text{ sec}^{-1})$	$k_r (\text{sec}^{-1})$	$K (M^{-1})$
3,5-Dinitropyridine (CH attack) ^{a,b} MeO ⁻ -MeOH, at 20°C			
 1	1740	24	72.5
 23	5250	232	22.6
OH ⁻ -H ₂ O, at 25°C			
 3	34	2.82	12
 22	37.5	9.8	3.7
OH ⁻ -H ₂ O-DMSO, at 20°C ^c			
 4	1025	3.5	293
22	547	0.15	3770
Methoxy-3,5-dinitropyridines (CH attack), MeO ⁻ -MeOH, at 20°C ^{a,b}			
 9	415	125	3.3

TABLE VI (continued)

Adduct	$k_f (M^{-1} \text{ sec}^{-1})$	$k_r (\text{sec}^{-1})$	$K (M^{-1})$
 6	275	25	11
 7	690	270	2.6
4-Methoxy- and 2,6-dimethoxy-3,5-dinitropyridine (COME attack), MeO ⁻ -MeOH, at 20°C ^{a,b}			
 5	16.5	5.75×10^{-3}	2.87×10^3
 12	10.5	180	5.8×10^{-2}
 8	11.8	6.05×10^{-4}	1.95×10^4

^a References: 45 for 1, 3, 4, 22; 46 for 5, 6; 47 for 9, 12; 40 for 7; 63 for 8; 68 for 23; 69 for 22.

^b The values for 7, 8, and 23 were calculated from the activation parameters, those for 12 were extrapolated from the data in DMSO-MeOH mixtures.

^c 51.2% DMSO by weight.

⁶⁸ C. F. Bernasconi, *J. Am. Chem. Soc.* **93**, 6975 (1971).

⁶⁹ C. F. Bernasconi, *J. Am. Chem. Soc.* **92**, 4682 (1970).

ment with a less effective delocalization of the negative charge of the adduct by the aza group (compare **4** with **22**; **5** with **8**). However, because the change in stability is small, the electronic effect may be partly offset by the stronger solvation of the aza group by the protic solvent. This effect is expected to be stronger with the aza^{70,71} than with the nitro group because the delocalized fractional charge is concentrated on a single heteroatom in the former and dispersed over three centers in the latter. The observed overall loss in stability occurs whether the site of addition is CH or COMe.

The decrease in stability of aza adducts is peculiarly accompanied by an increase in the forward rate and, therefore, by a relatively strong increase in the reverse rate.

b. Attachment at a CH Position. If a CH position undergoing attack by the RO⁻ reagent is flanked by an aza and a nitro group, a slight increase in stability is noted as compared with the situation in which there are two flanking nitro groups in the corresponding homocyclic adducts. This effect has been observed for the reaction with OH⁻ ($K_{\text{aza}}/K_{\text{NO}_2} = 3.2$) and with MeO⁻ ($K_{\text{aza}}/K_{\text{NO}_2} = 3.0$) at position 2 of 3,5-dinitropyridine, for the reaction with MeO⁻ at position 2 of 4-methoxy-3,5-dinitropyridine ($K_{\text{aza}}/K_{\text{NO}_2} = 4.3$), and for the reaction at position 6 of 2-methoxy-3,5-dinitropyridine ($K_{\text{aza}}/K_{\text{NO}_2} = 1.3$), as shown in Table VI (adducts **1**, **3**, **6**, and **9**).

The rates of adduct formation follow an inverted trend with respect to that found to the related stabilities. For example, the reaction of MeO⁻ with 3,5-dinitropyridine is slightly slower than that with 1,3,5-trinitrobenzene. The higher stability of the heterocyclic adduct **1** results in this case from a relatively low reverse rate.

The equilibrium and kinetic patterns change when the steric environment at the CH reaction center consists of two flanking nitro groups for both the heterocyclic and homocyclic adducts. In such a case the difference in the substrate tendency toward adduct formation is dominated by the different electronic effect of an aza group and of a nitro group at the para position (see Section II,B,5,a).

c. Attachment at a COMe Position. The ipso attack by MeO⁻ at a COMe position flanked by an aza group and a nitro group is markedly less favored than the attack at a similarly situated CH position. Thus adduct **12** is less stable than **9** by a factor of the order of 10². Also, in the reactions of 2-methoxy-3,5-dinitropyridine, 2-methoxy-, and 4-methoxy-5-nitropyrimidine, attachment of the MeO⁻ ion occurs at a CH position, and yields **9**, **16**, and **17**, respectively. Equilibrium constants are reported for the

⁷⁰ G. Illuminati, G. Marino, and G. Sleiter, *J. Am. Chem. Soc.* **89**, 3510 (1967).

⁷¹ M. Calligaris, G. Illuminati, and G. Marino, *J. Am. Chem. Soc.* **89**, 3518 (1967).

formation of adducts from methoxynitropyrimidines and MeO^- (MeOH -DMSO mixtures) by attachment to CH positions, occurring with little or no subsequent isomerization to the geminal dimethoxy adducts.^{41,65}

The reluctance of the ipso attack is also reflected in the reaction rates (compare **9** and **12**) and can be mainly attributed to the required disruption of OMe ring conjugation on going from the heteroaromatic substrate to the transition state and to the adduct.

The importance of the conjugative effect of the methoxy group can be further illustrated by noting that 2-methoxy-5-nitropyrimidine is attacked at the presumably more hindered 4-position rather than at the 2-position, thus avoiding disruption of conjugation.⁴¹ In contrast, position 2 is attacked (adduct **17**) when the methoxy substituent is moved to position 4 of the 5-nitropyrimidine system.

When the COMe position is flanked by two nitro groups and the aza group is thus moved away from the environment at the reaction center, as in 4-methoxy-3,5-dinitropyridine, a very stable geminal dimethoxy adduct (**5**) is formed. That both features, i.e., a COMe grouping and two nitro groups adjacent to it, give rise to a stabilizing effect on the adduct is shown by the inability to detect the isomeric adducts **10** and **11**. Similarly, the COMe adducts obtained from 2,6-dinitro-4-X-anisoles are generally much more stable than the corresponding CH adducts.^{22,37,59,68,72} For comparison, the kinetic and equilibrium data for **5** and **8** are reported on Table VI.

Several factors have been considered to play a role in determining the stability of a geminally substituted dimethoxy adduct and/or its rate of formation by ipso attack on a methoxy substituted substrate provided with two nitro groups flanking the methoxy group. Such factors include

i. Steric strain at the overcrowded reaction center. The steric interaction between the methoxy group and the two nitro groups forces these groups out of the ring plane by twisting around the $\text{C}_{\text{Ar}}\text{-N}$ and $\text{C}_{\text{Ar}}\text{-O}$ bonds. This is a well documented effect as shown by X-ray crystallographic investigations.^{7,25,73} It is expected to destabilize the ground state with respect to the maximum conjugation obtainable by a hypothetical situation whereby the nitro groups are coplanar with the ring and no bond bendings occur. Adduct formation at the COMe position will give rise to a substantial relief of steric strain by change of the sp^2 carbon at the reaction center to a tetrahedral carbon.⁶²

ii. Conjugation of the MeO group with the ring. Because this is a bond-strengthening effect, energy is required on the ipso attack by the reagent to

⁷² F. Terrier, F. Millot, and J. Morel, *J. Org. Chem.* **41**, 3892 (1976).

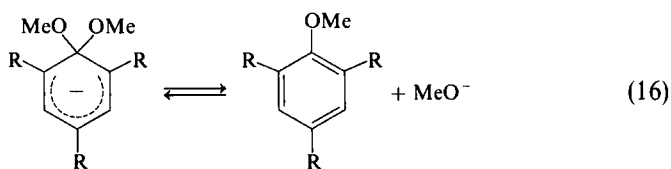
⁷³ H. Ueda, N. Sakabe, J. Tanaka, and A. Furusaki, *Bull. Chem. Soc. Jpn.* **41**, 2866 (1968).

disrupt conjugation on going from the initial to the transition state and to the adduct.⁶⁹ Although ring-OMe conjugation is not maximal because of the steric compression (1), a certain degree of it is still present in the substrate.⁷⁴

iii. *Electron-withdrawing inductive effect of the MeO group.* It is expected to contribute to lower the electron density at the reacting carbon in the substrate.⁶²

iv. *F-Strain on the approach of the reagent.* This effect develops in the transition state of the bimolecular adduct formation as the reagent approaches the substrate at a bonding distance and the reacting site is still partly overcrowded.^{35,75}

v. *Geminal dimethoxy-substituted tetrahedral carbon.* Carbon-fluorine and carbon-oxygen bonds are markedly strengthened by substitution of two or more fluorine or oxygen atoms at the same carbon. Stabilization by as much as 29 kJ/mol is calculated for simple (cyclic) ketals with respect to ethers.⁷⁶ This effect can be explained in terms of double bond-no bond resonance and has been proposed by Bernasconi to contribute to the stability of Meisenheimer adducts.⁶⁹ However, the influence of structural changes on the importance of double bond-no bond resonance has never been considered in this connection. Thus in the equilibrium reported in Eq. (16) the shift toward the aromatic form is likely to be assisted by the double bond-no bond resonance effect of the adduct as suggested by the contributing amphi-ionic resonance structure involved and by the strong driving force of rearomatization. Therefore, not only should the geminal dimethoxy effect on the stabilization of Meisenheimer adducts be much weaker than in simple ketals, but it should also be dependent on the stability of the polysubstituted aromatic substrate.



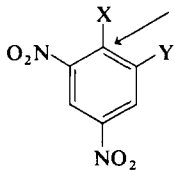
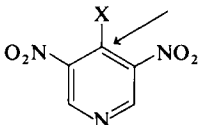
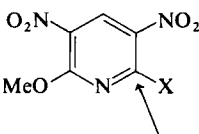
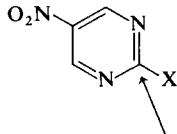
A number of available data having a bearing on the problem concerning the great stability of **5** and **8** is assembled in Table VII. The data compare the stabilities as well as the rate constants for the formation of the adducts by the ratios $K_{\text{H}}/K_{\text{OMe}}$ and $k_{\text{H}}/k_{\text{OMe}}$ at the CH and COMe reaction centers, respectively. They show that whenever the reaction center is flanked by a nitro and an aza group or by two aza groups, it is the CH adduct that is more stable

⁷⁴ G. Illuminati, *J. Am. Chem. Soc.* **80**, 4941 (1958).

⁷⁵ M. R. Crampton, *J.C.S. Perkin II*, 1442 (1977).

⁷⁶ J. Hine, *J. Am. Chem. Soc.* **85**, 3239 (1963).

TABLE VII
COMPARISON OF RATE CONSTANTS AND OF EQUILIBRIUM CONSTANTS
FOR ADDUCT FORMATION ON ATTACK OF MeO^- ION IN
MeOH AT CH AND COMe POSITIONS AS EXPRESSED BY $k_{\text{H}}/k_{\text{OMe}}$
AND $K_{\text{H}}/K_{\text{OMe}}$ RATIOS, RESPECTIVELY^a

Substrate	Y	$k_{\text{H}}/k_{\text{OMe}}$	$K_{\text{H}}/K_{\text{OMe}}$	References
	NO_2	410	1.4×10^{-3}	63, 68
	CN	—	$\sim 10^{-3}$	6, 63, 77
	H	—	2.2×10^{-2}	78, 79
		—	$< 10^{-2,b}$	45, 46
		39.6	57	39, 47
		—	$> 1^c$	22, 41

^a X = H, OMe; data at 20° or 25°C.

^b Limit deduced by considering the K value for CH attack at position 2 ($69.5 M^{-1}$); because no CH attack at position 4 is observed, K_{H} in the $K_{\text{H}}/K_{\text{OMe}}$ ratio must be markedly less than such value.

^c Limit deduced by considering the K value at position 4 in MeOH-DMSO, 1:1, ($54.2 M^{-1}$); because no COMe attack at position 2 is observed and DMSO has a strong stabilizing effect, K_{OMe} in the $K_{\text{H}}/K_{\text{OMe}}$ ratio as referred to MeOH solution must be markedly less than such value.

than the COMe adduct. The only factor that is effectively reduced (or eliminated) in the latter structures is steric strain (*i*) whereas factors (*iii*) and (*v*) do not seem to play an important role. Replacement of an ortho nitro group by hydrogen leads to a $K_{\text{H}}/K_{\text{OMe}}$ ratio of 2.2×10^{-2} , which is

⁷⁷ E. J. Fendler, J. H. Fendler, N. L. Arthur, and C. E. Griffin, *J. Org. Chem.* **37**, 812 (1972).

⁷⁸ M. R. Crampton, M. A. El Ghariani, and H. A. Khan, *J.C.S. Perkin II*, 1178 (1972).

⁷⁹ M. R. Crampton, *J.C.S. Perkin II*, 710 (1973).

intermediate between that found for two flanking nitro groups (1.4×10^{-3}) and that for one nitro and aza groups (57). It would seem that factor (i) is still appreciable when an ortho nitro group is replaced by hydrogen and, therefore, is responsible for the low value ($\sim 10^{-3}$) that is found in the presence of one nitro and one cyano group.

The k_H/k_{OMe} reactivity ratios do not parallel the stability ratios. The low rates of formation of **5** and **8** can neither be attributed to factor (i), which seems to stabilize the final product, nor to factor (iii), which would also facilitate the reaction. Because factor (v) appears to be weak in the product, it should be even weaker in the transition state.

Such low reactivity may then be reasonably well explained by a combination of F-strain (factor 4)³⁵ and ring-OMe conjugation (factor 2)⁶⁸ in the transition state.

d. *Other Structural Effects.* Structural modifications may change the orders of reactivity and/or stability. Thus 2-(2-hydroxyethoxy)-3,5-dinitropyridine reacts intramolecularly in the presence of bases to yield the spiro adduct **14**, which is a *gem*-dialkoxy product, as assisted by the ease of formation of a 5-membered ring.¹³

Another example is the attachment reaction of a purine substrate as a result of the electronic effect of the imidazole fused ring and of the absence of steric effects (adduct **20**).⁴³

6. Effect of the Methoxy Group

In Table VI are listed data related to the effect of a methoxy group on the forward and reverse rate constants and equilibrium constants. The presence of a methoxy group at a position meta to the reaction center brings about a decrease in stability of the adducts, which is mainly caused by a decrease in forward rate (compare **1** with **9** and **6**, and **23** with **7**). The decrease in rate is comparable to the deactivating effect of a meta methoxy group in nucleophilic substitution.^{66,80} This effect is explained in terms of conjugation of the alkoxy group with the azine system and of the resulting decrease in electron-withdrawing effectiveness of the activating groups. Similar effects, for which similar explanations can be proposed, are found for σ -adduct formation in the homocyclic series especially when the methoxy group is

⁸⁰ M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron* **19**, 345 (1963).

adjacent to a strong electron-withdrawing group, such as a nitro^{68,81,82} or cyano group located para with respect to the reaction site.

Differences in steric hindrance due to overcrowding, in conjugation of the substituents, and in solvation play a subtle role in determining the kinetic and equilibrium differences between **6** and **9**.

7. Effect of DMSO

The addition of DMSO to protic solvents brings about a strong increase in K values, by a factor of $\sim 10^8$, going from pure ROH to pure DMSO (Table VIII). Both an increase in forward rates and a decrease in reverse rates contribute equally well to such effects. DMSO-ROH mixed solvents have been used to adjust the appropriate conditions whereby the adducts can be detected.

The increase in stability with the DMSO content is a general feature for Meisenheimer adduct formation and is observed to similar extents for pyridine as well as benzene adducts. It is mainly caused by the enhanced nucleophilicity of the RO^- ion, resulting from a decreased specific solvation of the charged reagent as the concentration of the protic solvent is decreased and dispersion interactions between the large, polarizable adduct and the dipolar aprotic solvent.^{36,83}

Linear correlations are observed between both $\log k_f$ and $\log k_r$ and the molar fraction of DMSO in DMSO-MeOH mixed solvents. As a consequence, the $\log K$ too is linearly correlated with the DMSO content. These correlations can be useful for predicting rate and equilibrium constant values in methanol by extrapolation whenever such values are too low for measurement in this solvent.

Even if the addition of DMSO to protic solvents has a dramatic effect on the rate and equilibrium constants for adduct formation, to a first approximation it does not affect the relative stability of adducts formed from the same substrate. As already observed in the chemistry of Meisenheimer adducts in the benzene series, the ratios K^K/K^T , k_f^K/k_f^T , and k_r^K/k_r^T are practically independent of the composition of the medium.⁴⁶ Under such circumstances it is possible to obtain approximate kinetic or thermodynamic data for a given adduct in a particular medium whenever kinetic and

⁸¹ A. R. Norris and L. H. Gan, *Can. J. Chem.* **49**, 2490 (1971).

⁸² F. Millot and F. Terrier, *Bull. Soc. Chem. Fr.*, 1823 (1974).

⁸³ G. Illuminati, in "Solutions and Solubilities" (M. R. J. Dack, ed.), Part 2, p. 159. Wiley, New York, 1976.

TABLE VIII
EFFECT OF DMSO CONTENT ON RATE AND EQUILIBRIUM CONSTANTS FOR ADDUCT
FORMATION IN DMSO-ROH MIXTURES AT 20°C^a

Adduct	Cosolvent	DMSO ^b (%)	k_f (M ⁻¹ sec ⁻¹)	k_r (sec ⁻¹)	K (M ⁻¹)
3	H ₂ O	0	23.5	2	11.75
		10.8	33	1.1	30
		21.3	51.5	0.65	79.5
		31.7	81	0.32	253
		41.4	138	0.12	1150
		51.2	412	—	—
4	H ₂ O	41.4	345	9	38.4
		51.2	1025	3.5	293
6	MeOH	0	275	25	11
		10	398	17.3	23
		20	630	6.95	91
		30	1175	3.25	361
		40	2000	1.6	1250
		50	3710	0.7	5300
		60	6900	—	—
		70	22000	—	—
5	MeOH	0	16.5	5.2×10^{-3}	3180
		10	25.7	3.56×10^{-3}	7230
		20	48	2.37×10^{-3}	20200
		30	90	—	—
		40	180	—	—
		50	330	—	—
12	MeOH	0	10.5 ^c	180 ^c	$5.8 \times 10^{-2,c}$
		30	101	19.8	5.1
		40	178.5	12	14.8
		50	300	5.75	52
		60	960	2.45	390
		70	2500	0.91	2750
		80	7950	0.28	28400
13	MeOH	60	—	—	6.6
		70	—	—	45
		80	—	—	660

^a References: 45 for 3, 4; 46 for 5, 6; 47 for 12, 13.

^b % DMSO by weight for 3 and 4; by volume for 5, 6, 12, and 13.

^c Extrapolated from data at higher DMSO concentration.

thermodynamic data are measured for an isomeric adduct and a complete set of similar data is available for both adducts in a different medium.

C. REACTIONS WITH THE AMIDE ION

1. *Introductory Remarks and Detection Techniques*

Many anionic σ -adducts have been described as obtained from the interaction of N-heteroaromatic compounds with the amide ion in liquid ammonia. The reaction is often followed by decomposition leading to overall substitution (amination). This field has been intensively investigated by van der Plas, Zoltewicz, and co-workers.

A variety of amination mechanisms have been recognized, some of which imply the formation of σ -adducts as reaction intermediates.^{10,84}

The $S_N(AE)$ mechanism consists of the initial addition (A) of the nucleophile (attachment) to the carbon atom bearing the potential leaving group, followed by the elimination (E) of the latter.⁸⁵ It is analogous to the one usually occurring in the nucleophilic substitution of nitro-activated aromatic substrates.

The $S_N(EA)$ mechanism involves a preliminary base-promoted elimination to yield a heteroaryne intermediate and the subsequent addition of, e.g., NH_3 to yield the substitution product(s).⁸⁵

The $S_N(ANRORC)$ mechanism⁸⁶ involves the addition (A) of a nucleophile (N), a ring opening (RO) reaction of the adduct, and finally, a ring closure (RC) reaction leading to the final product.⁸⁵ The mechanism has frequently been observed in the reactions of polyaza aromatic compounds with the NH_2^- ion. Its occurrence has been demonstrated by ^{15}N labeling whereby a labeled nitrogen atom initially placed in the ring will be found in the exocyclic amino group of the final product. The extent of ring rearrangement can be determined quantitatively by following the fate of the labeled atoms by chemical degradation methods and mass spectrometry. Interestingly, the ANRORC mechanism does not necessarily lead to a different ring and may preserve the original ring type (degenerate ring transformation).

The $S_{RN}1$ mechanism is initiated by the donation of an electron to the substrate ArX from a suitable donor.⁸⁷ The radical anion $ArX^\cdot$ thus formed may be converted to $Ar^\cdot$ by X^- loss. Combination of $Ar^\cdot$ with a nucleophile

⁸⁴ J. A. Zoltewicz, *Top. Curr. Chem.* **59**, 33 (1975).

⁸⁵ The terms *addition* and *elimination* are used to explain the mechanistic symbols AE, EA, etc. They actually refer to attachment and detachment reactions.¹⁹

⁸⁶ H. C. van der Plas, *Acc. Chem. Res.* **11**, 462 (1978).

⁸⁷ J. F. Bunnett, *Acc. Chem. Res.* **11**, 413 (1978).

and electron donation to maintain a chain process will finally yield the substitution product.

Only $S_N(AE)$ and $S_N(ANRORC)$ mechanisms require the formation of anionic σ -adducts. A great deal of attention has been paid to the correlation of the formation of these adducts with the mechanism of amination. However, inasmuch as a detailed account of the latter reaction is outside the scope of this chapter, we report only a few typical sequences proposed in the literature and suggest that the reader gain more information on this point from the outstanding work by van der Plas and his group.

Detection of the adducts in the $NH_2^- - NH_3$ system has involved both ^1H -NMR and ^{13}C -NMR techniques. The reference spectra can be obtained in $CDCl_3$ and other nonprotic solvents because changes in chemical shifts with respect to liquid NH_3 are generally small.⁸⁸

The ring protons of the adducts are shielded with respect to those of the substrates.^{88,89} The upfield shift is 1.8–2.9 ppm for hydrogens at positions other than the reaction center, and 3.4–4.3 ppm for hydrogens bound to the reaction center. The stronger shielding in the latter case is the result of the $sp^2 \rightarrow sp^3$ change in hybridization. When NH_2^- becomes bound to a CH position, the nuclear hydrogen is often detected as a triplet ($J = 7.5$ Hz) because of the coupling with the hydrogens of the NH_2 group. However, the triplet may collapse into a singlet, e.g., in the presence of an excess of the NH_2^- ion, due to hydrogen exchange.

The carbon atoms of the adducts are generally shielded with respect to those in the substrates.⁹⁰ As observed with ^1H -NMR spectra, the difference in shielding is particularly high at the reaction center undergoing the $sp^2 \rightarrow sp^3$ hybridization change ($\Delta\delta \approx 90$ ppm). Selective CH decoupling and change in CH coupling in going from the substrate to the corresponding adduct also contribute to a definite determination of the site of attachment of the nucleophile.⁹⁰

2. Pyridine and Benzopyridines

No definite evidence is available for the formation of an adduct between pyridine and the amide ion in ammonia, even though some interaction does occur, because the reaction mixture slowly discolors.⁸⁹ Some evidence for the formation of adducts from benzopyridines was reported in an early study by

⁸⁸ P. G. Lont, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **92**, 708 (1973).

⁸⁹ J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.* **94**, 682 (1972).

⁹⁰ J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *Org. Magn. Reson.* **7**, 86 (1975).

TABLE IX
 ^1H -NMR DATA FOR σ -ADDUCTS AS FORMED FROM BENZOPYRIDINES AND THE AMIDE ION^a

Precursor and adduct ^b	Chemical shift (δ)				Coupling constant (Hz)
	H-a	H-b	H-c	H-d to H-g	
Isoquinoline ^{c,d}	9.15	8.45	7.50	7.5–7.8	$J_{bc} = 6.0$
24	5.34	—	4.87	(+H-b), 6.4–7.3	$J_{bc} = 5.5$
Quinoline ^{c,e}	8.81	7.27	8.00	7.4–8.1	$J_{ab} = 4.1$
					$J_{ac} = 1.7$
					$J_{bc} = 8.2$
26	5.1	5.2	— ^f	H-e, 5.6 others, 6.0–7.1	$J_{ab} = 4.3$
					$J_{ac} = -1$
					$J_{bc} = 9.0$
27	— ^f	4.2	4.7	6.0–7.1	$J_{ab} = 6.5$
					$J_{bc} = 4.3$

^a Data for adducts in liquid NH_3 from Reference 92.

^b Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^c Data in CCl_4 .

^d Data from Reference 93.

^e Data from Reference 94.

^f Signal concealed by benzenoid ring multiplets.

Bergstrom.⁹¹ Such adducts were firmly detected first by Zoltewicz *et al.*⁹² The reactions were carried out in liquid ammonia, in the presence of an excess of KNH_2 . They were rapid and complete, but sufficiently slow on the NMR scale to allow the detection of both free substrate and the corresponding adduct when an excess of the substrate was employed (Table IX).

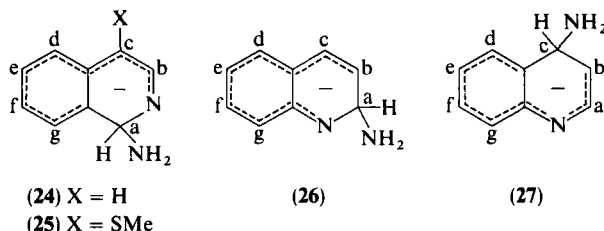
The amide ion attacks position 1 of isoquinoline, yielding adduct **24**. The observed upfield shifts are 4.1 ppm at the reaction center and nearly 3 ppm at position 4. The latter is likely to indicate an increased electron density at the ring position; it is detected as a doublet ($J = 5.5$ Hz) because of the coupling with H-3. The signal of the latter is not distinguishable from the protons of the benzenoid ring, which resonate at δ 6.35–7.3, as a broad multiplet. The upfield shift can be estimated to be of nearly 0.65 ppm for the H-3 proton and is even lower for the protons of the benzenoid ring.

⁹¹ F. W. Bergstrom, *J. Org. Chem.* **2**, 411 (1937).

⁹² J. A. Zoltewicz, L. S. Helmick, T. M. Oestreich, R. W. King, and P. E. Kandetzki, *J. Org. Chem.* **38**, 1947 (1973).

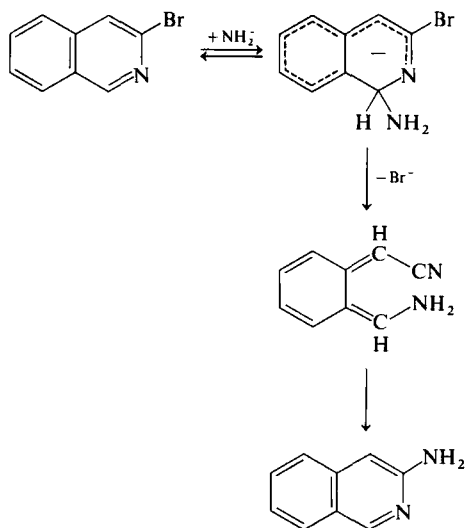
⁹³ P. J. Black and M. L. Heffernan, *Aust. J. Chem.* **19**, 1287 (1966).

⁹⁴ P. J. Black and M. L. Heffernan, *Aust. J. Chem.* **17**, 558 (1964).



The assignment of the H-3 and H-4 proton signals of adduct **24** is easily made by comparison with the spectrum of adduct **25**, formed under the same conditions from 4-methylthioisoquinoline, because the methylthio group is known to affect the chemical shift but slightly.

The reaction of quinoline with the amide ion yields both isomeric adducts **26** and **27**. Attack at position 2, leading to **26**, is a kinetically favored process, whereas the one at position 4 is under thermodynamic control. The less stable adduct **26** can indeed be detected for a short time, at -45°C , immediately after the beginning of the reaction. It displays several signals in the δ 4–6 region including the signal at δ 5.1, corresponding to the proton bound to the sp^3 carbon atom. The isomeric adduct **27** shows the signal of the proton at the attacked position at δ 4.7. The unequivocal assignment of the signals of adducts **26** and **27** was secured by conducting the NMR analysis with the corresponding adducts formed from quinoline-2-*d*. In particular, the CH signals bound to the carbon atom undergoing the hybridization change are the ones showing an upfield chemical shift of nearly 3.8 ppm.



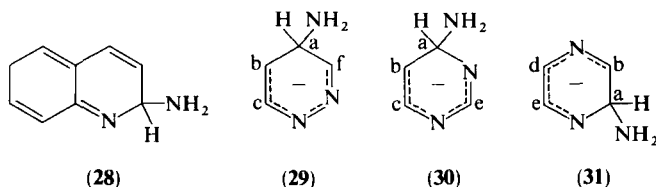
SCHEME 1

A considerable fraction of charge in adduct **26** seems to be delocalized into the benzenoid ring, as indicated by the shielding of the 6-position to which the charge can be effectively relayed from the reaction center (resonance formula **28**).

The aforementioned behavior of isoquinoline has a bearing on the mechanism of the aminodebromination of 3-bromoisoquinoline to 3-aminoisoquinoline. Labeling experiments show that this reaction partially occurs by an ANRORC mechanism,⁹⁵ which can be explained by the formation of a C-1 adduct as a primary step (Scheme 1), in agreement with the finding that attachment of NH_2^- does occur at position 1 of isoquinoline.

3. Diazines

Adducts of diazines were obtained by Zoltewicz as deeply colored solutions upon addition to KNH_2 or NaNH_2 in liquid ammonia.⁸⁹ The ^1H -NMR spectra (Table X) show that in the presence of an excess of amide ion diazines are completely converted to adducts, whereas with less than the equimolecular amount of the nucleophile, signals of both free diazines and the corresponding adducts, but no signal averaging, are observed. The adduct solutions are stable for days at -70°C , but the spectra change irreversibly at room temperature. No isolation of the diazine adducts has been reported.



Pyridazine, pyrimidine, and pyrazine yield adducts **29**, **30**, and **31**, respectively (Table X). In the first case, the structural assignment of the ^1H -NMR spectrum of the adduct has been made unequivocal by starting from pyridazine-3,6- d_2 . Minor amounts of the isomeric adduct **32** resulting from attack at the C-3 position are presumably formed, as suggested by the presence of weak doublets at δ 4.51 and 5.80 ($J = 8.0$ Hz). Starting from pyrazine and pyrimidine, the assignment is straightforward. In particular, the adduct formed from pyrimidine is characterized by four signals as required by structure **30**. It will be noted that with pyridazine and pyrimidine

⁹⁵ G. M. Sanders, M. van Dijk, and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas* **93**, 198 (1974).

TABLE X
¹H- AND ¹³C-NMR DATA FOR σ-ADDUCTS AS FORMED FROM DIAZINES AND THE AMIDE ION^a

Precursor and adduct ^b	Chemical shift (δ)						Coupling constant (Hz)
	H-a	H-b	H-c	H-d	H-e	H-f	
Pyridazine ^{c,d}	7.55	7.55	9.24	— ^e	—	9.24	$J_{ab} = 8.4; J_{ac} = 2.0;$ $J_{af} = 4.9; J_{cf} = 3.0;$
29	3.73	4.27	6.70	—	—	6.55	$J_{ab} = 4.5; J_{af} = 3.5;$ $J_{bc} = 7.0; J_{bf} = 3.0;$ $J_{cf} = 0.5$
Pyrimidine ^{c,f}	8.78	7.36	8.78	—	9.26	—	$J_{ab} = J_{bc} = 5.0;$ $J_{ac} = 2.5; J_{bc} = 1.5$
30	4.63	4.32	6.27	—	7.07	—	$J_{ab} = 3.5; J_{ac} = J_{ce} = 0.5;$ $J_{bc} = 6.5; J_{be} = 1.5$
Pyrazine ^{d,g}	8.63	8.63	—	8.63	8.63	—	—
31	4.22	5.61	—	5.82	6.60	—	$J_{ab} = 3.0; J_{be} = 0.5;$ $J_{de} = 3.0$
	C-a	C-b	C-c	C-e			
Pyrimidine	157.6	122.5	157.6	159.6			
30	62.5	98.0	140.5	156.7			
33	62.9	108.2	134.8	150.3			

^a ¹H-NMR data for adducts from Reference 89, and ¹³C-NMR data from Reference 90.

^b Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^c In CDCl₃.

^d Reference 96.

^e — indicates data do not exist.

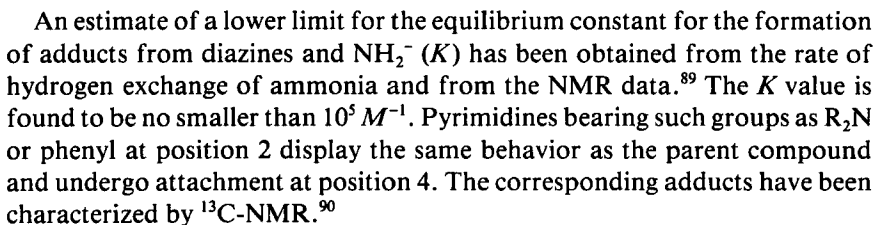
^f Reference 97.

^g Neat.

⁹⁶ G. S. Reddy, R. T. Hobgood, and J. H. Goldstein, *J. Am. Chem. Soc.* **84**, 336 (1962).

⁹⁷ C. Tori and M. Ogata, *Chem. Pharm. Bull.* **12**, 272 (1964).

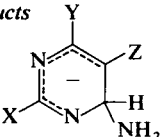
The characterization of adduct **30** has also been made via ^{13}C -NMR.⁹⁰ The ^{13}C chemical shifts of the anionic adduct **30** have been compared with those of the neutral adduct **33**, formed from NH_2^- and 1-methylpyrimidinium cation. Only a small difference (0.4 ppm) is found for the C-a atoms, reflecting a remarkable similarity of the sp^3 carbons in the two adducts.



4. Substituted Diazines

⁹⁹ A. P. Kroon, H. C. van der Plas, and G. van Garderen, *Recl. Trav. Chim. Pays-Bas* **93**, 325 (1974).

TABLE XI
SELECTED ^1H - AND ^{13}C -NMR DATA FOR σ -ADDUCTS AS FORMED FROM SUBSTITUTED PYRIMIDINES AND THE AMIDE ION

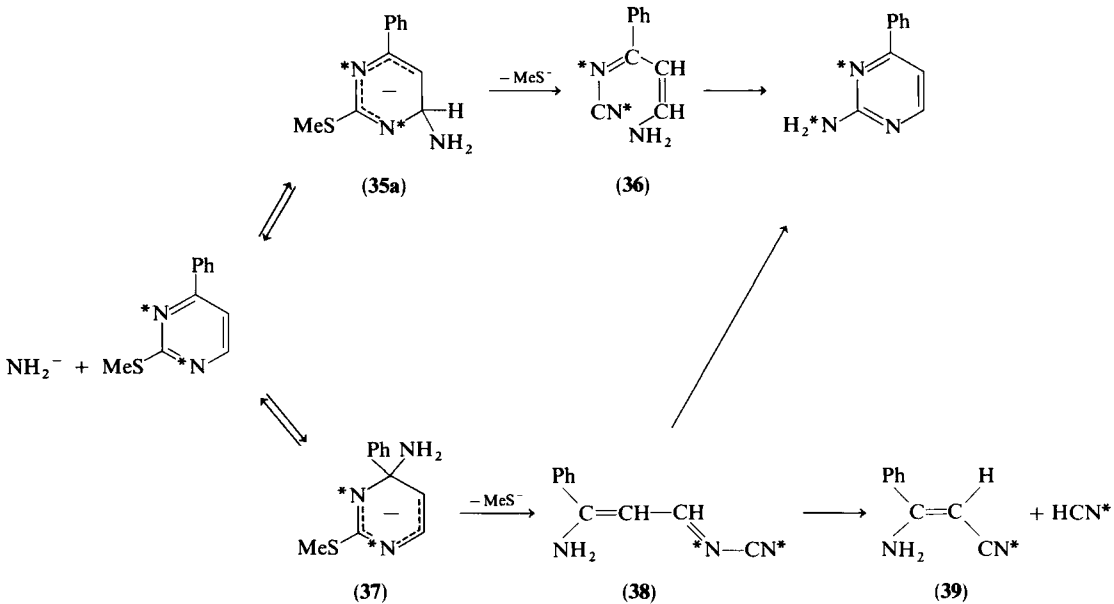
Precursor and adduct ^a	X	Y	Z	Chemical shift (δ)				Coupling constant (Hz)	References
				H-a	H-b				
2-Adducts									
4,6-Diphenylpyrimidine ^b	— ^c	—	—	9.33	8.08			—	98
34	—	—	—	4.68	6.10			—	98
4(6)-Adducts									
									
2-Methylthio-4-phenylpyrimidine ^b				8.50	7.30			$J_{ab} = 5$	99
35	MeS	C ₆ H ₅	H	4.71	4.84			$J_{ab} = 4$	99
4-Chloro-2-phenylpyrimidine ^d				8.55	7.19				103
40 (R = Ph)	C ₆ H ₅	Cl	H	4.90	4.30			$J_{ab} = 5.5$	103
5-Bromo-4-phenylpyrimidine ^b				8.98	9.23				105
41 (R = Ph)	H	C ₆ H ₅	Br	4.79	6.96			—	105
5-Bromo-4- <i>tert</i> -butylpyrimidine ^b				8.95	9.25				105
41 (R = <i>t</i> -Bu)	H	<i>t</i> -Bu	Br	4.67	6.87			—	105
5-Bromo-2,4-di- <i>tert</i> -butylpyrimidine ^b				8.59					98
44	<i>t</i> -Bu	<i>t</i> -Bu	Br	4.90	—			—	98
				C-a	C-b	C-c	C-d		
4-Chloro-2-phenylpyrimidine ^b				158.3	119.3	161.6	165.6		90
40 (R = Ph)	C ₆ H ₅	Cl	H	66.8	88.9	147.4	158.2		90
2-Dimethylamino-4-chloropyrimidine ^b				158.7	108.3	161.1	162.3		90
40 (R = Me ₂ N)	Me ₂ N	Cl	H	67.3	86.2	147.8	161.2		90

^a Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^b In CDCl₃.

^c — indicates data do not exist.

^d In CCl₄.



SCHEME 2

for the sp^3 CH as large as 3.79 ppm. The assignment of the signals was made possible by recording the ^1H -NMR spectrum of 2-methylthio-4-phenylpyrimidine-5- d , which on addition of the reagent shows only one singlet at 4.74.

The final product of this reaction is 2-amino-4-phenylpyrimidine. ^{15}N -Labeling showed that the net substitution takes place by the ANRORC mechanism rather than by an AE process. The related sequence is shown in Scheme 2. Isolation of 3-amino-3-phenylacrylonitrile (**39**) in low yields at -75°C suggests that a parallel pathway via adduct **37** is also possible. However, the latter has not been detected in the reaction mixture.

The ANRORC mechanism is also responsible for the amination of 2-halogeno-4-phenylpyrimidines to 2-amino-4-phenylpyrimidine.¹⁰⁰ The overall reaction is likely to follow a pattern similar to that illustrated for the reaction of the 2-methylthio derivative, involving a preliminary attachment of the nucleophile to position 6. In contrast, some strongly electron-withdrawing groups at position 2 (Me_3N^+ and PhSO_2 but not MeSO_2) favor displacement by an addition-elimination mechanism.⁹⁹ In the latter cases the reaction is thought to occur via adduct formation resulting from attachment of the reagent to position 2. There is some but not definite NMR evidence for the formation of adduct **35b** from 2-methanesulfonyl-4-phenylpyrimidine and KNH_2 .⁹⁹ Inasmuch as no methyl resonance is detected, probably due to deprotonation of the acidic CH_3SO_2 group in the basic medium, attachment of the reagent to position 2 is thought to be made difficult by the resulting negatively charged $^-\text{CH}_2\text{SO}_2$ group. This may be the reason why the conversion of the 2-methanesulfonyl derivative to the 2-amino derivative appears to prefer an ANRORC mechanism unlike the benzenesulfonyl analog.

The ANRORC mechanism is also supported by the isolation of a small amount of the open-chain 3-amino-1-phenylallylidene cyanamide (**36**) (Scheme 2) from the products of the reaction of 2-bromo-4-phenylpyrimidine as formed from an adduct structurally related to **35a**.¹⁰⁰

4-Chloro-2-R-pyrimidines ($\text{R} = \text{Me}, \text{Et}, \text{Ph}, \text{NMePh}, \text{NMe}_2, \text{morpholino}, \text{piperidino}$) have been shown to undergo a complex reaction with $\text{KNH}_2\text{-NH}_3$ leading to 2-R-4-methyltriazine derivatives whereas the products of aminodechlorination are only formed in limited amounts.^{101,102} ^1H -NMR spectroscopy at -38°C revealed the formation of adducts **40**, involving attachment of the reagent at position 6 (Table XI).¹⁰³

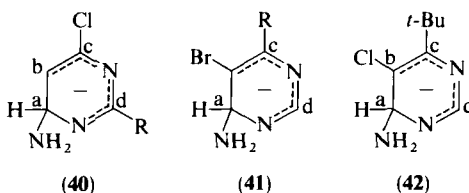
¹⁰⁰ A. P. Kroon and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas* **93**, 111 (1974).

¹⁰¹ H. C. van der Plas and B. Zuurdeeg, *Recl. Trav. Chim. Pays-Bas* **88**, 426 (1969).

¹⁰² J. P. Geerts and H. C. van der Plas, *J. Org. Chem.* **43**, 2682 (1978).

¹⁰³ J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **92**, 1232 (1973).

A different course is followed by a substrate in the above series when the R substituents are sufficiently acidic ($R = \text{NHMe}, \text{NHPh}, \text{CH}_2\text{Ph}$). Formation of the monoanionic conjugate base by proton abstraction from the substituent reduces the tendency toward adduct formation. However, with the latter group of substrates the final product is a 4-amino-2-R-pyrimidine, which presumably is derived from the conjugate base by the intermediacy of a (nondetected) dianionic 1:1 σ -adduct.¹⁰³



The structural assignments of **40**, as based on ^1H -NMR spectra, have been confirmed by ^{13}C -NMR spectroscopy.⁹⁰ In the formation of adducts the carbon atoms undergo upfield shifts in the order $\text{C}_6 \gg \text{C}_5 > \text{C}_4 > \text{C}_2$. In accordance with this behavior, indicating a change in hybridization of C-6 from sp^2 to sp^3 , the $J(\text{C}_6\text{-H})$ value decreases from 180 Hz of the initial substrate to 150 Hz of the adduct. In decoupling experiments, selective irradiation at νH_6 and νH_5 causes the C-6 and C-5 doublets, respectively, to collapse into singlets.

The formation of adduct **40** appears to be favored with respect to attack at the halogen-bearing carbon atom. By a further detailed ^{13}C -NMR study, the adducts of this type, as derived from 4-chloro-2-dimethylaminopyrimidine and its 5-phenyl derivative, are reported to be the primary intermediates of a process leading to the final triazines via a number of identified ring-opening intermediates.¹⁰¹

4-Chloro-2-phenyl-5-R-pyrimidines ($R = \text{MeO}, \text{EtO}, \text{MeS}, \text{C}_6\text{H}_5$) undergo conversion to 4-amino-2-phenyl-5-R-pyrimidines.¹⁰⁴ Here, attachment at position 6 also occurs as a first step of this seemingly simple reaction. It has, in fact, been shown that the replacement of chlorine is not direct but consists of a tele amination reaction.

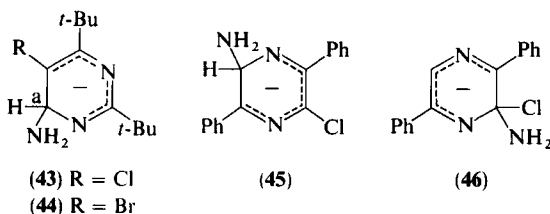
5-Bromo-4-R-pyrimidines ($R = \text{Ph}, t\text{-Bu}, \text{OMe}, \text{and PhMeN}$) react quite rapidly with an excess of KNH_2 in liquid ammonia and are converted completely to C-6 adducts **41**.¹⁰⁵ The ^1H -NMR data are reported in Table XI for $R = \text{Ph}$ and $t\text{-Bu}$. The structure assignment was further confirmed by deuterium labeling experiments. When 4-substituents bearing acidic α hydrogens (Me, NHMe) are present, the formation of the conjugate base of

¹⁰⁴ H. W. van Meeteren and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas* **90**, 105 (1971).

¹⁰⁵ J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **93**, 231 (1974).

the substrate competes with the formation of the adduct. The ring protons of the conjugate base are shielded with respect to the substrates ($\Delta\delta = 0.9$ ppm), but to a lesser extent than in the σ -adducts. In the reaction of the methyl derivative, the concentration ratio of conjugate base to the σ -adduct decreases from 3:1 to 2:1 on going to the trideuteromethyl group, indicating a kinetic hydrogen isotope effect in the hydrogen abstraction process. For $X = \text{NHCH}_3$, only the conjugate base is detected.

Although the final products of the amination of 5-bromo-4-R-pyrimidines are the 6-amino-4-R-pyrimidines,^{106,107} two mechanisms, by which these same products are formed, have been recognized. The substrate is converted in part to the product via C-6 adduct **41**, whereas the remaining part follows an ANRORC mechanism requiring attack of the reagent at C-2.¹⁰⁵ Evidence for the existence of C-2 adducts as intermediates in nucleophilic substitutions is hard to obtain. However, the formation of an adduct of this kind (**34**) from 4,6-diphenylpyrimidine was definitely proved by ¹H-NMR measurements (Table XI).⁹⁸ C-6 adducts such as **42–44** have also been described (see also Table XI) and shown to be the sole intermediates in the amination of 5-chloro-4-*tert*-butylpyrimidine and 5-X-2,4-di-*tert*-butylpyrimidines ($X = \text{Cl}, \text{Br}$), the ANRORC mechanism remaining excluded with the latter substrates.⁹⁸



b. Substituted Pyrazines. The reaction of 2-chloro-3,6-diphenylpyrazine with $\text{KNH}_2\text{--NH}_3$ leads to adduct **45** by attachment at CH, as shown by the ¹H-NMR spectrum.⁸⁸ The reaction can be reverted nearly quantitatively back to the starting material on neutralization with NH_4Cl . However, on prolonged standing the reacting mixture eventually yields the product of displacement, 2-amino-3,6-diphenylpyrazine. Because 2-chloro-5-deutero-3,6-diphenylpyrazine is transformed into the amino derivative without H-D exchange, the most likely substitution mechanism is suggested to involve rearrangement of **45** to **46** in a slow step followed by rapid loss of Cl^- . Thus the formation of **45** would be a kinetically controlled process: difference in crowding at the 2 and 5 ring positions are held responsible for the different rates of attachment.⁸⁸ No evidence is found for the formation of **46**.

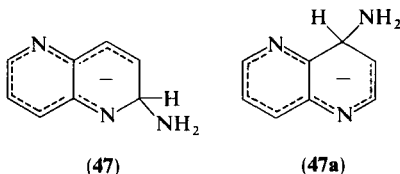
¹⁰⁶ H. C. van der Plas and G. Geurtsen, *Tetrahedron Lett.*, 2093 (1964).

¹⁰⁷ H. C. van der Plas, P. Smit, and A. Koudijs, *Tetrahedron Lett.*, 9 (1968).

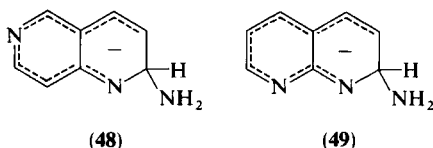
5. Naphthyridines

1,X-Naphthyridines react with NH_2^- - NH_3 to give anionic σ -adducts. At low temperatures (-35 to -40°C) the initial attachment of the nucleophile occurs at the site with the lowest electron density. At higher temperatures in some instances, the kinetically controlled adducts change to the more stable isomers.

Thus 1,5-naphthyridine at low temperature undergoes attack at position 2, to yield adduct **47**.¹⁰⁸ When the temperature is raised to 10°C , this adduct is replaced by the more stable **47a**, resulting from attachment at position 4.¹⁰⁹ In the latter case C-3 displays a relatively high upfield shift compared with the substrate, indicating the presence of a significant fraction of the negative charge at that carbon atom. Essential NMR data are reported in Table XII. Interestingly, the Chichibabin amination of 1,5-naphthyridine occurs at position 2 at -33°C and at room temperature, but yields 4-amino-1,5-naphthyridine at 50°C . These findings show that the formation of the σ -adducts and the substitution reaction display a similar dependence on temperature.



In contrast, the reaction of 1,6- and 1,8-naphthyridines with NH_2^- - NH_3 leads to adducts **48** and **49**, respectively, resulting from attachment to position 2, whether the temperature is kept at -40°C or raised to 10°C .^{108,109} As usual, the adducts are characterized by an increased shielding of H and C



at position 2, where the hybridization change takes place (Table XII) and, to a lesser extent, at positions 8 and 6 for adducts **48** and **49**, respectively, as a consequence of the contribution of relevant para quinoid resonance

¹⁰⁸ H. C. van der Plas, A. van Veldhuizen, M. Woźniak, and P. Smit, *J. Org. Chem.* **43**, 1673 (1978).

¹⁰⁹ H. J. W. van den Haak, H. C. van der Plas, and B. van Veldhuizen, *J. Org. Chem.* **46**, 2134 (1981).

TABLE XII
¹H- AND ¹³C-NMR DATA FOR σ-ADDUCTS FORMED FROM NAPHTHYRIDINES AND AMIDE ION^a

Precursor and adduct	H-2	H-3	H-4	H-5	H-6	H-7	H-8		
1,5-Naphthyridine ^b	8.96	7.55	8.37	— ^c	8.96	7.55	8.37		
47	4.97	5.38	—	—	6.80	^d	^d		
47a	^d	4.18	4.59	—	7.31	^d	^d		
1,6-Naphthyridine ^b	9.03	7.43	8.20	9.22	—	8.75	7.87		
48	5.05	5.19	6.23	7.15	—	7.20	5.82		
1,7-Naphthyridine ^b	9.01	7.48	8.14	7.64	8.60	—	9.50		
50	5.02	5.31	6.28	6.35	6.76	—	7.52		
52	7.65	6.77	6.77	4.52	7.01	—	5.13		
1,8-Naphthyridine ^b	9.15	7.51	8.21	8.21	7.51	9.15	—		
49	5.21	5.42	6.32	6.65	5.62	7.60	—		
	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1,5-Naphthyridine ^b	151.0	124.1	137.2	—	151.0	124.1	137.2	144.0	144.0
47	65.8	121.3	127.4 ^e	—	125.1	122.7	121.6 ^e	151.2	137.3
47a	141.8	92.2	50.9	—	134.6	121.2	125.1	145.8 ^e	145.3 ^e
1,6-Naphthyridine ^b	154.9	122.7	135.8	153.0	—	146.9	122.2	150.5	123.8
48	66.1	120.0	124.6	146.1	—	146.6	112.2	156.2	114.0
1,7-Naphthyridine ^b	152.1	125.2	134.7	119.9	144.0	—	154.5	143.7	131.3
50	65.9	120.2	124.3	120.2	123.8	—	142.6	—	—
52	138.2	121.9 ^d	122.5 ^d	80.2	151.8	—	71.0	—	—
1,8-Naphthyridine ^b	153.8	122.3	137.3	137.3	122.3	153.8	—	156.6	123.1
49	67.0	122.1	126.0	131.5	100.8	149.3	—	162.6	112.9

^a Data from References 108 and 109.

^b In CDCl₃.

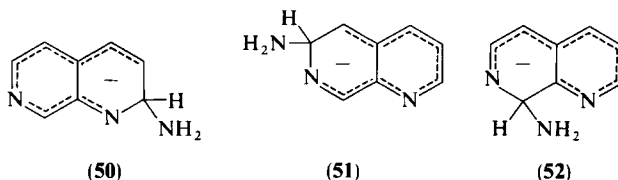
^c — indicates data do not exist.

^d These signals were not assigned.

^e Assignment may be interchanged.

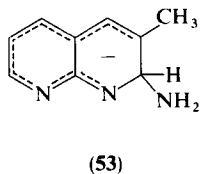
structures. The structure of these adducts is in line with the fact that 1,6- and 1,8-naphthyridines undergo the amination reaction at the same position.

At low temperature, 1,7-naphthyridine is converted to a mixture of adducts **50** and **52**; the formation of the formerly proposed **51** was definitely ruled out. Positions 2 and 8 have the lowest electron densities. However, on warming the reaction mixture to 10°C, only **52** is detected as the apparently more stable adduct. When the solution of **50** and **52** in $\text{NH}_2\text{-NH}_3$ was treated with potassium permanganate not only were the 2-amino- and 8-amino-1,7-naphthyridines formed but also the 4-amino isomer, indicating the possible intermediacy of the undetected 4- σ -adduct.



2,6-Naphthyridine undergoes NH_2^- attachment at position 1 at -30°C . The NMR spectrum of the resulting adduct does not change at 20°C . Accordingly, the amination of the same substrate yields 1-amino-2,6-naphthyridine.¹¹⁰ A similar behavior is displayed by 2,7-naphthyridine, attachment of the reagent occurring at position 1.¹¹⁰ Also in this case the Chichibabin amination occurs at room temperature at the same position.

Of the isomeric X-methyl-1,8-naphthyridines, only the 3-methyl derivative yields an adduct (**53**) resulting from attack at position 2. In contrast, when the methyl group is at position 2 or 4, the nucleophilic attack is prevented by extensive proton loss from the acidic methyl group.¹⁰⁸

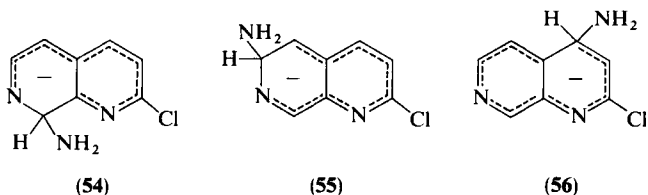


6. Halogenonaphthyridines

a. *Halogeno-1,7-naphthyridines.* 2-Chloro-1,7-naphthyridine is converted at -50°C by $\text{KNH}_2\text{-NH}_3$ to a mixture of adducts **54**, **55**, and **56** in the ratio 1.75:1.0:4.25, which are formed by attachment of NH_2^- ion to

¹¹⁰ H. J. W. van den Haak, H. C. van der Plas, and B. van Veldhuizen, *J. Heterocycl. Chem.* **18**, 1349 (1981).

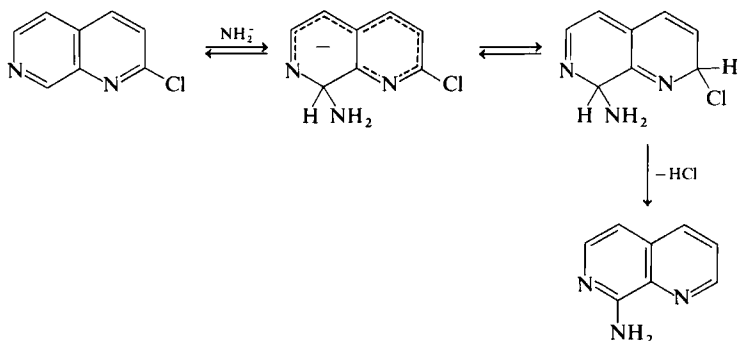
positions 8, 6, and 4, respectively.¹¹¹ The identification of the structure of the adducts was carried out on examination of the NMR behavior of the



8-deutero and 6,8-dideutero derivatives. The hydrogen atoms of the adducts bound to the tetrahedral ring carbon atoms are shielded upfield by nearly 4 ppm with respect to the corresponding positions of the starting substrate. In the C-4 adduct **56** the coupling constant between positions 3 and 4 ($J = 4.5$ Hz) is similar to that observed in other adducts having adjacent HC (sp^2), HC (sp^3) groupings. Ipso attack at C-2 is not observed.

The amination reaction carried out at -33°C gives a mixture consisting of 4-amino-, 8-amino-, and 2-amino-1,7-naphthyridine, 4-amino-2-methyl-1,3,7-triazanaphthalene, and some unsubstituted 1,7-naphthyridine. The composition of this mixture is not related to that of the adducts described above in any simple way. Adducts **54** and **56** are suggested to be involved in the formation of the 8-amino and 4-amino derivatives, respectively, by a tele-amination mechanism.¹¹¹ Scheme 3 illustrates one of these proposed paths.

3-Bromo- and 3-chloro-1,7-naphthyridine take up NH_2^- at position 2. Interestingly, the formation of σ -adducts precedes the appearance of



SCHEME 3

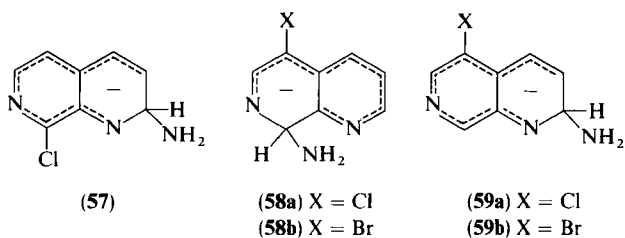
¹¹¹ H. C. van der Plas, M. Woźniak, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **96**, 151 (1977).

3-amino- and 4-amino-1,7-naphthyridine, which are formed according to an elimination-addition process.^{111a}

The reaction of 8-chloro-1,7-naphthyridine with KNH_2 in liquid NH_3 brings about the formation of adduct **57** by addition of the nucleophile to position 2.^{111,112} The pair of doublets due to H-2 centered at δ 9.16 in the substrate are replaced by a new doublet at δ 5.16. The higher shielding of H-2 and the new multiplicity pattern substantiate the structure of the adduct.

Under these conditions the amination reaction yields a mixture of 2-amino- and 8-amino-1,7-naphthyridines in a nearly 1:1 ratio. Here again the observed σ -adduct is responsible for the formation of only one of the products, the 2-amino compound, which arises by a tele amination mechanism. The other amine requires some other as yet undetected σ -adduct.¹¹¹

Of the 5-halogeno-1,7-naphthyridines, the bromo derivative reacts with $\text{KNH}_2\text{-NH}_3$ to yield **58b** by attachment to position 8, whereas the chloro compound yields a 3:1 mixture of **58a** and **59a** by attachment to positions 8 and 2, respectively.¹¹³ Adducts **58** are characterized by the presence of a singlet at δ 5.1 for the hydrogen at position 8. The upfield shift with respect to the starting substrate is nearly 4.2 ppm, in agreement with the structure of the adducts. Adduct **59a** shows a pair of doublets at δ 5.45 ascribed to H-3. Because the H-2 signal of the latter adduct happens to overlap with that of the H-8 singlet of adduct **58a**, a definite assignment of the structure of **59a** is provided by deuterating the 8-position. As with the other halogeno-1,7-naphthyridines, the site of attachment, as detected by NMR, is found to be a position other than the one bearing the halogeno substituent.



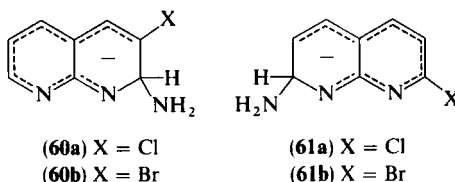
The amination products from 5-halogeno-1,7-naphthyridines include the 8-amino and the 5-halogeno-8-amino derivatives. The 2-aminodiazine is also obtained from the bromo compound.

^{111a} H. C. van der Plas, M. Woźniak, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **95**, 233 (1975).

¹¹² H. C. van der Plas, M. Woźniak, and A. van Veldhuizen, *Tetrahedron Lett.*, 2087 (1976).

¹¹³ M. Woźniak and H. C. van der Plas, *J. Heterocycl. Chem.* **15**, 731 (1978).

b. *Halogeno-1,8-naphthyridines*. 3-Chloro-1,8-naphthyridine reacts with $\text{KNH}_2\text{-NH}_3$ at -50°C to yield a new species characterized by a sharp singlet in the NMR spectrum at δ 5.2, indicating the presence of a hydrogen atom bound to an sp^3 carbon atom. Experiments with 3-chloro-2-deutero-1,8-naphthyridine show that attachment occurs at C-2, yielding adduct **60a**.¹¹⁴ The 3-bromo derivative behaves similarly (adduct **60b**). These adducts do not appear to have a role in the amination reaction that leads to a mixture of the 3- and 4-amino derivatives. The substitution would consist of an elimination-addition reaction via 3,4-didehydro-1,8-naphthyridine. Part of adduct **60** decomposes to yield 2-amino-3-ethynylpyridine (10%) and 3-ethynyl-2-(formylamino)pyridine (6%) by ring-opening processes.



2-Chloro- and 2-bromo-1,8-naphthyridine react with $\text{KNH}_2\text{-NH}_3$ to yield adducts **61a** and **61b**, respectively, as formed by addition to position 7.^{112,114} Evidence for the structure of adducts **61** was based upon the chemical shift and multiplicity pattern of H-7, which undergoes a strong upfield chemical shift as substrate (δ 9.10 in CDCl_3) gives rise to adduct (δ 5.10) and appears as a doublet, being coupled to H-6 ($J = 4.0$ Hz). The final product is 2-amino-1,8-naphthyridine. By using a substrate deuterated at position 7 and by examining the deuterium content both in the amino product and in the unreacted substrate, it was deduced that amination occurs in part by a tele-substitution process and by an AE mechanism involving attack of the amide ion at position 2.¹¹⁴

7. Triazines and Tetrazines

a. *1,3,5-Triazines*. ^1H -NMR evidence has been obtained for the formation of adduct **62** by the reaction of 2-phenyl-1,3,5-triazine with $\text{KNH}_2\text{-NH}_3$.¹¹⁵ The formation of this adduct occurs immediately upon dissolving the substrate in the presence of 2–3 equivalents of the nucleophile (Table XIII). In contrast, amination to 2-amino-4-phenyl-1,3,5-triazine is a very slow reaction. After 40 hours at -33°C , the substrate can be recovered

¹¹⁴ H. C. van der Plas, M. Woźniak, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **97**, 130 (1978).

¹¹⁵ G. Simig and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas* **95**, 125 (1976).

TABLE XIII
SELECTED ^1H -NMR DATA FOR σ -ADDUCTS AS FORMED
FROM TRIAZINES AND THE AMIDE ION

Precursor and adduct ^a	Chemical shift (δ)	
	H-a	H-b
2-Phenyl-1,3,5-triazine ^b	9.25	9.25
62	5.33	7.31
2,4-Diphenyl-1,3,5-triazine ^b	9.25	—
63	5.58	—

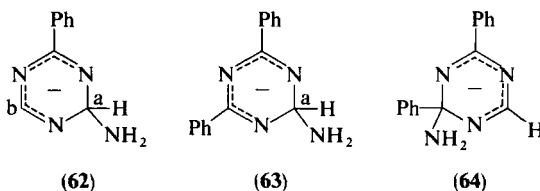
^a Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^b In CDCl_3 .

^c Data from Reference 115.

^d Data from Reference 116.

almost unchanged from the reaction mixture. However, the recovery of the starting material from a solution of K^{15}NH_2 in $^{15}\text{NH}_3$ yields a ^{15}N -labeled species. The incorporation of ^{15}N , the low rate of amination, and the lack of a promoting effect by KNO_3 , which is observed in the Chichibabin reaction,⁹¹ show that adduct **62** is not necessarily a direct precursor of the amino derivative. In fact, the observed results indicate the incursion of an ANRORC-type mechanism.



Starting with 2,4-diphenyl-1,3,5-triazine and $\text{KNH}_2\text{-NH}_3$, adduct **63** (Table XIII) is formed.¹¹⁶ The reaction mixture slowly leads to 2-amino-4,6-diphenyl-1,3,5-triazine by a mechanism that is shown by ^{15}N labeling to consist of an addition-elimination process. Therefore, adduct **63** is likely to be a true reaction intermediate for the Chichibabin reaction. Although a related substrate, 2-methylthio-4,6-diphenyl-1,3,5-triazine, gives the 2-amino derivative exclusively by the ANRORC mechanism, which is likely to involve the addition of NH_2^- to a phenyl-bearing position in the initial step, the formation of such adducts as **64** has not been reported.¹¹⁶

¹¹⁶ G. Simig, H. C. van der Plas, and C. A. Landheer, *Recl. Trav. Chim. Pays-Bas* **95**, 113 (1976).

It is noteworthy that on going from the monophenyl to the diphenyl derivative of triazine the chemical process changes from an NH_2^- -promoted degenerate transformation of the substrate¹¹⁵ to an addition-elimination displacement of hydride ion.¹¹⁶ Because both triazines undergo initial σ -adduct formation of the amide ion at a hydrogen-bearing position, the nature of the prevailing process is likely to depend upon the competition between the irreversible loss of hydride ion from the adduct and the reversible ring-opening reaction initially yielding an open-chain conjugated system.

b. *1,2,4-Triazines*. The high reactivity of 1,2,4-triazine and some of its derivatives allows the formation of adducts in liquid ammonia in the absence of potassium amide and related salts. The unsubstituted ring undergoes attack of the nucleophile at the C-5 position, as shown by ^1H - and ^{13}C -NMR spectroscopy.¹¹⁷ Electron-Releasing substituents such as 3-amino do not allow adduct formation under the same conditions, but 3-methylthio, 3-methoxy, and 3-amino-6-bromo do. Apparently a strong π -electron deficiency at position 5 must be preserved to enable a weak nucleophile to be effective. Alkyl and phenyl substituents located at C-5 prevent adduct formation.

The NMR spectra recorded in liquid ammonia are attributed to the products of addition of ammonia across the C-5-N-4 bond (covalent addition) rather than to the products of attachment at C-5 (anionic σ -adducts). Actually the present data do not seem to be able to distinguish between the two species.

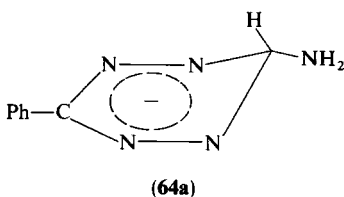
An interesting result achieved by ^{15}N labeling experiments is that liquid ammonia reacts with 1,2,4-triazine without causing ring opening, inasmuch as the compound can be recovered unlabeled after treatment with ^{15}N -ammonia in spite of the substrate-nucleophile equilibration ensuing from the interaction.

c. *Tetrazines*. There is ^1H - and ^{13}C -NMR evidence for the formation of an anionic adduct (**64a**) as derived from the reaction of 3-phenyl-1,2,4,5-tetrazine with liquid ammonia in the absence of the amide ion followed by deprotonation of the resulting addition product.^{117a} The most significant feature of the spectrum of the adduct is the signal for the tetrazine proton at an exceptionally high field (δ 1.51), whereas in methanol, where the interaction of the starting substrate with the solvent is weak, the cor-

¹¹⁷ A. Rykowski, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **97**, 273 (1978).

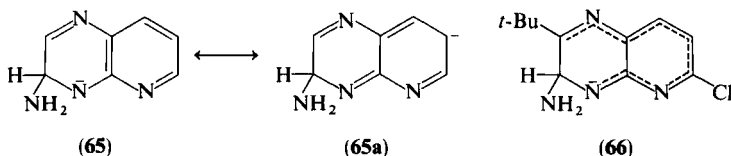
^{117a} A. Counotte-Potman, H. C. van der Plas, and B. van Veldhuizen, *J. Org. Chem.* **46**, 2138, 3805 (1981).

responding ring proton is detected at δ 10.35. This large upfield shift is caused by a tetrazole-like homoaromatic structure of the adduct. The tetrahedral carbon lies out of the plane of the other five ring atoms, and the hydrogen atom bound to it points toward the π -electron system. The homoaromatic character of adducts such as **64a** is found in the parent, neutral 1,6-dihydro-1,2,4,5-tetrazine. Adduct **64a** appears to be the only example of a homoaromatic σ -adduct reported so far.



8. *Pyrido*[2,3-*b*]pyrazine

Nucleophilic attack of pyrido[2,3-*b*]pyrazine (3-deazapteridine) by the $\text{KNH}_2\text{-NH}_3$ system occurs at position 3 and leads to the formation of adduct **65**, which has been characterized by its ^{13}C -NMR spectrum.¹¹⁸ Large upfield shifts are observed at C-3, which experiences hybridization change, and at C-7, where much of the electronic charge is accommodated by delocalization (resonance structure **65a**). Analogous spectral changes are observed in the reaction with 2-*tert*-butyl-6-chloropyrido[2,3-*b*]pyrazine, yielding adduct **66**.¹¹⁹

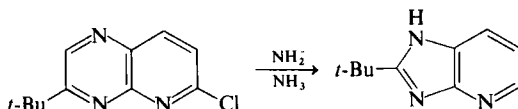


In contrast, 3-*tert*-butyl-6-chloropyrido[2,3-*b*]pyrazine rapidly reacts with $\text{KNH}_2\text{-NH}_3$ to yield a ring contraction product, 2-*tert*-butyl-1*H*-imidazo[4,5-*b*]pyridine (Scheme 4). The transformation is reminiscent of the ring contraction undergone by 2-methylthio-4,6,7-triphenylpteridine to yield 6,8-diphenyl-2-methylthiopurine.¹²⁰ Although no σ -adduct could

¹¹⁸ A. Nagel, H. C. van der Plas, G. Geurtsen, and A. van Veldhuizen, *J. Heterocycl. Chem.* **16**, 301 (1979).

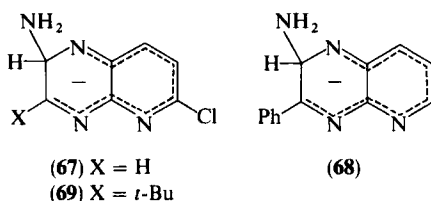
¹¹⁹ A. Nagel, H. C. van der Plas, G. Geurtsen, and A. van der Kuilen, *J. Heterocycl. Chem.* **16**, 305 (1979).

¹²⁰ A. Nagel and H. C. van der Plas, *Heterocycles* **7**, 205 (1977).



SCHEME 4

be detected, experiments with ¹⁵N- and ¹³C-labeled 6-chloropyrido[2,3-*b*]-pyrazine suggest that ring contraction takes place via formation of adduct **67** by initial attachment of the nucleophile to C-2. An adduct of this kind (**68**) is indeed detected in the reaction of 3-phenylpyrido[2,3-*b*]pyrazine.¹¹⁸ This gives some support to the hypothesis that adduct **69** may be involved as a labile species in the ring contraction reaction.



The investigations on the pyrido[2,3-*b*]pyrazine ring were inspired by the related pteridine ring, of importance in natural products. Pteridines are very reactive systems with both liquid ammonia and KNH₂ in liquid ammonia, but in neither medium have anionic σ -adducts ever been detected. Such adducts presumably form initially and rapidly evolve toward covalent amination and ring contraction products.^{119,121}

9. Concluding Remarks

Aza and polyaza heteroaromatic compounds generally undergo C-attachment of the amide ion in KNH₂-NH₃. The structure of the resulting σ -adducts has been firmly established in a large number of instances.

The presence of only one aza group in pyridine is not sufficient to drive the equilibrium toward an extensive formation of the σ -adduct. Benzoannulation promotes a substantial shift of such an equilibrium because of a more extensive delocalization of the negative charge. It is worth noting that the higher tendency of benzopyridines relative to pyridine to undergo nucleophilic attachment corresponds to milder reaction conditions in the amination reaction¹²² and indicates that the two effects are related to each other.

¹²¹ A. Nagel and H. C. van der Plas, *Chem. Pharm. Bull.* **23**, 2678 (1975).

¹²² M. T. Leffler, *Org. React.* **1**, 95 (1942).

In going to polyaza derivatives, the tendency to form adducts decidedly increases. Very reactive compounds, such as 1,2,4-triazines and pteridines, undergo covalent addition in liquid ammonia alone, i.e., without any added amide salts, presumably by a two-stage process via anionic σ -adduct formation.

Unfortunately, equilibrium and rate data in this area are practically non-existent. However, sometimes it has been possible to obtain evidence for kinetically and thermodynamically controlled processes.

A well understood case is that of quinoline; reaction at position 2 is kinetically favored as compared with reaction at position 4, but the adduct from the latter is thermodynamically more stable. This situation, where the site of attack leading to the more stable adduct is the γ position, is analogous with those regarding the formation of Meisenheimer adducts from benzene and pyridine derivatives and RO^- nucleophiles. Presumably, with quinoline kinetic control favors the position that is more strongly influenced by the inductive effect of the heteroatom. The fact that position 2 of quinoline is the most reactive toward nucleophilic reagents is probably related to the lower π -electron density at that position.¹²³ However, the predominance of the C-4 adduct at equilibrium can be better justified by the atom localization energies for nucleophilic attachment at the different positions of quinoline. Moreover, both π -electron densities and atom localization energies indicate position 1 of isoquinoline to be the most favored one for nucleophilic addition.

Kinetic control leads to σ -adducts other than the more stable ones in the reactions of 1,5- and 1,7-naphthyridines.

The stronger stabilizing effect of a γ -aza relative to an α -aza atom is confirmed by the behavior of pyridazine and pyrimidine, which preferably form adducts **29** and **30**, respectively. Phenyl substituents discourage ipso attack by NH_2^- , as shown by the observation that in the reactions with 4,6-diphenylpyrimidine, 2-phenyl-1,3,5-triazine, or 2,4-diphenyl-1,3,5-triazine only CH adducts are detected. However, indirect evidence for adducts resulting from attack at CPh positions is provided by a study of the reaction products from diphenyltriazine and related substrates, unequivocally showing that such adducts are transiently formed along an S_N (ANRORC) pathway.

When such substituents as halogen atoms and, less commonly, alkoxy, thioalkoxy, and amino groups are present, the most significant observed feature is that addition easily occurs at activated positions other than those occupied by the substituents, i.e., at CH positions. This is true even when the substituents, such as halogeno, are good leaving groups. For some reason,

¹²³ R. Zahradník and J. Koutecký, *Adv. Heterocycl. Chem.* **5**, 69 (1965).

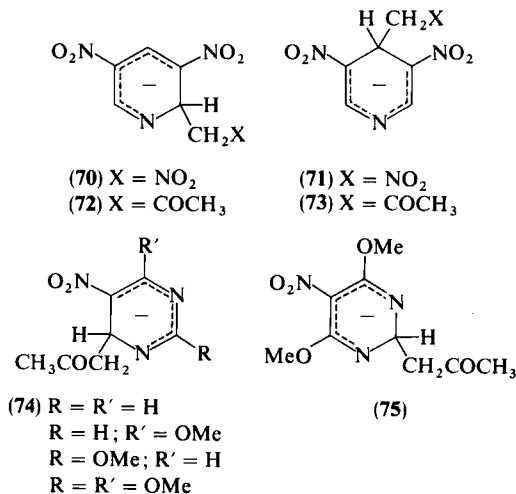
the attack at certain CH positions seems to be kinetically favored with respect to others that are similarly activated by the ring substituents.

The role of steric hindrance and of conjugation of the substituent with the ring in connection with the ease of ipso attack is still an open question. Conjugation may be quite effective with electron-releasing substituents located α or γ to the aza group.

D. ADDUCTS FROM INTERACTION WITH NUCLEOPHILIC CARBON

1. Reactions with Carbanions

3,5-Dinitropyridine reacts with the conjugate base of nitromethane, formed upon interaction of nitromethane with triethylamine, to yield a red-purple color and two new sets of $^1\text{H-NMR}$ signals, corresponding to adducts **70** and **71**.¹²⁴ Adduct **70** shows a pair of doublets at δ 5.85 ($J = 5$ Hz, $J = 7$ Hz), and two doublets ($J = 2$ Hz), one at 8.34 and the other at 8.52. The signal at 5.85 is split into 4 lines because of the nonequivalence in the methylene induced by asymmetry in the ring system.

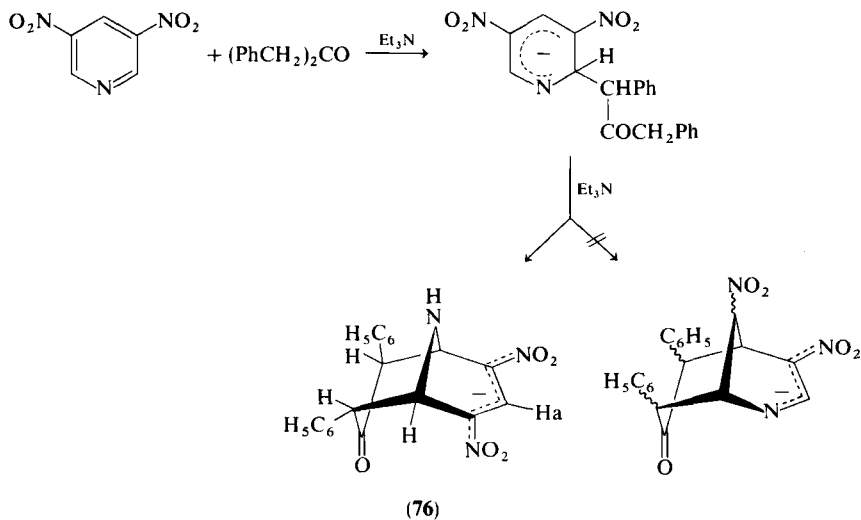


Adduct **71** is characterized by a triplet at 5.30 and a doublet at 8.2 ($J = 3.5$ Hz). Adducts structurally related to **70** and **71** are formed in a DMSO-acetone mixture when the DMSO solution of adduct **1** is diluted with acetone.¹³ Adducts **72** (δ 5.50, 8.22, and 8.32) and **73** (δ 4.88 and 8.15) are formed in the ratio of 3:1.

¹²⁴ C. A. Fyfe, *Can. J. Chem.* **46**, 3047 (1968).

5-Nitropyrimidine, its 2- and 4-methoxy, and 2,4- and 4,6-dimethoxy derivatives react with acetone in the presence of potassium hydroxide to yield the potassium salts of the anionic adducts **74** and **75**, with structures elucidated by spectral ($^1\text{H-NMR}$, IR, and UV-visible) methods. The nucleophilic attachment was found to occur only at CH positions, and when there was a choice between 2- and 4(6)-positions, the latter was preferred.^{125,126} An adduct of the kind corresponding to structure **75** was also obtained by using the conjugate base of acetophenone. The adducts can be converted to the corresponding CH_3COCH_2 - or PhCOCH_2 -substituted pyrimidines by oxidation, either directly or via the related dihydropyrimidine derivatives.¹²⁷

Some interesting synthetic applications have been found by Strauss for the interactions of 3,5-dinitropyridine with carbanions, as generated *in situ* by base-promoted CH ionization, to yield bicyclic systems by meta bridging,¹²⁸ under conditions favoring a similar reaction with 1,3,5-trinitrobenzene.⁹ 3,5-Dinitropyridine reacts with 1,3-diphenyl-2-propanone and triethylamine to give the bridged ion **76**, according to Scheme 5. The reaction consists



SCHEME 5

¹²⁵ V. M. Cherkasov, G. Ya. Remennikov, and E. A. Romanenko, *Khim. Geterotsikl. Soedin.*, 1389 (1978).

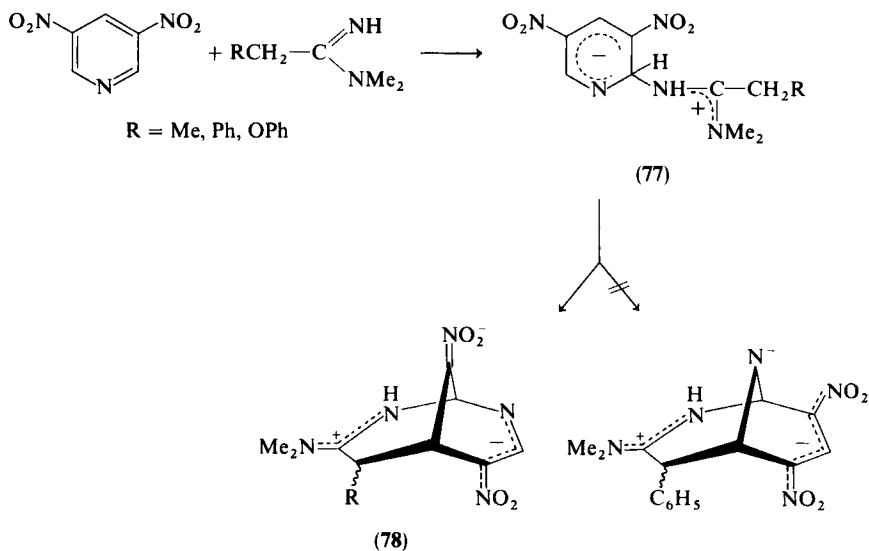
¹²⁶ V. M. Cherkasov, G. Ya. Remennikov, and E. A. Romanenko, *Khim. Geterotsikl. Soedin.*, 239 (1980).

¹²⁷ V. M. Cherkasov, G. Ya. Remennikov, and E. A. Romanenko, *Khim. Geterotsikl. Soedin.*, 823 (1981).

¹²⁸ R. Bard, M. J. Strauss, and S. A. Topolosky, *J. Org. Chem.* **42**, 2589 (1977).

of two consecutive nucleophilic attachment reactions at the available α positions of the pyridine ring, leading to a Meisenheimer adduct first and then to a dianionic adduct by intramolecular ring closure. The 1,3-dinitropropenide anion **76** ($\lambda_{\max} = 517$ nm) results from protonation of the dianion at the ring nitrogen and is characterized by having two phenyl groups *trans* to each other.¹²⁸

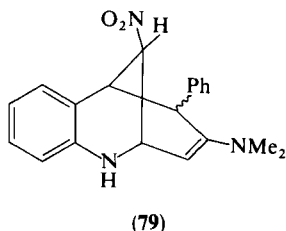
When α -substituted *N,N*-dimethylacetamidines are used as the bidentate nucleophiles, the reaction proceeds according to Scheme 6. The primary attack occurs at an α position by the nucleophilic nitrogen to yield the zwitterionic adduct **77** ($\lambda_{\max} = 506$ nm) and is followed by intramolecular ring closure at the γ position leading to a bicyclic adduct (**78**). In contrast, with the *N*-oxide of 3,5-dinitropyridine the points of attachment of the reagent are both α to the aza group.



SCHEME 6

The regioselectivity in the cyclization process of unsymmetrical adducts is controlled by the ability of the ortho substituent to accommodate the developing negative charge in the transition state.¹²⁸ However, the observed orientation of the reagent may also depend on other factors and still is not well understood.

3-Nitroquinoline is activated enough to yield bicyclic products in a similar way; thus it reacts with α -phenyl-*N,N*-dimethylacetamidine, yielding the bridged compound **79**, which implies primary attachment of the nucleophilic nitrogen at C-2.¹²⁸



2. Reactions with Organometallic Compounds

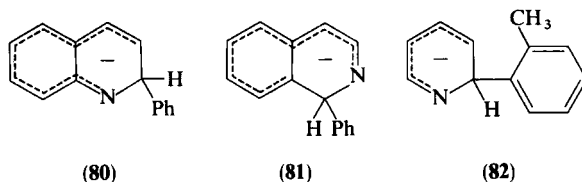
a. *Monoazines*. The adducts that form by interaction of azaheterocyclic substrates and organometallic compounds, usually in solvents of low polarity, are often depicted as covalent addition compounds. However, there is evidence that the bonding of nitrogen in the anionic σ -adducts with the metal counterions such as lithium, sodium, and magnesium is largely ionic and may range from that of an ion-pair association to a polar covalent one. There is also evidence that delocalization of the anionic charge from nitrogen into the ring carbons occurs to varying extents depending on the systems. In several instances we shall use the covalent structures of the metal derivatives as crude approximations unless we specifically refer to some experimental evidence favoring one structure or the other. Alternatively, we shall simply use the free anions in a delocalized form.

The interaction between pyridine and organolithium compounds in benzene was first reported by Ziegler and Zeiser¹²⁹ and was attributed to the formation of 1:1 adducts. Indirect evidence for intermediates of this kind was based on the formation of dihydropyridines by treatment of the reaction mixture with water. More definite evidence was obtained with quinoline, isoquinoline, and acridine.¹³⁰ Phenyllithium reacts quantitatively with quinoline in ether to yield an adduct as a yellow powder that can be recrystallized. In order to define the site of attachment, the adducts were hydrolyzed to dihydro derivatives and the latter dehydrogenated. Because this treatment leads mainly to 2-phenylquinoline and 1-phenylisoquinoline from quinoline and isoquinoline, respectively, the related adducts can be assumed to have structures **80** and **81**. Isolation and characterization of the dihydro derivatives have been carried out, as well as in the case of the reaction of acridine with phenyllithium.

Evidence for the formation of an adduct in the reaction of pyridine derivatives with organolithium compounds was also reported by Abramovitch and

¹²⁹ K. Ziegler and H. Zeiser, *Chem. Ber.* **63**, 1847 (1930).

¹³⁰ K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.* **485**, 174 (1931).



Poulton.¹³¹ By treating 3-picoline with *o*-tolyllithium, these authors obtained 1,2,5,6-tetrahydro-3-methyl-2-*o*-tolylpyridine together with 3-methyl-2-*o*-tolylpyridine and 5-methyl-2-*o*-tolylpyridine and interpreted the formation of the tetrahydro derivative as resulting from the disproportionation of the 1,2-dihydro derivative formed on protonation of the expected adduct **82**.

The first direct, conclusive evidence for the formation and structure of butyllithium-pyridine adducts was given by Fraenkel and Cooper and was based upon ¹H-NMR data (Table XIV). After mixing equimolar amounts of

TABLE XIV
¹H-NMR DATA FOR ORGANOLITHIUM-PYRIDINE ADDUCTS AND SOME OF THEIR
1-DEUTERO-1,2-DIHYDROPYRIDINE DERIVATIVES^a

Adduct	Chemical shift (δ)					Coupling constants (Hz)
	H-a	H-b	H-c	H-d	H-e	
85	3.64	4.34	5.93	4.62	6.68	$J_{ab} = 4.2$; $J_{ac} = 0.5$; $J_{bc} = 8.2$; $J_{bd} = 0.8$; $J_{be} = J_{ce} = 0$; $J_{cd} = 5.4$; $J_{de} = 5.8$
83	3.84	4.77	5.61	4.35	5.94	$J_{ab} = 4.2$; $J_{ac} = 1.1$; $J_{bc} = 9.8$; $J_{bd} = 1.3$; $J_{be} = 0.9$; $J_{cd} = 5.4$; $J_{ce} = 1.4$; $J_{de} = 7.1$
83a	<i>b</i>	3.87	— ^c	4.62	6.01	$J_{ab} = 3.2$; $J_{bd} = 2.0$; $J_{de} = 6.0$
85a	<i>b</i>	4.11	—	4.72	6.52	$J_{de} = 8.3$; no other coupling constants were assigned
85b	<i>b</i>	4.32	5.96	5.09	—	$J_{bc} = 8.2$; $J_{cd} = 5.9$
85c	<i>b</i>	—	5.73	4.56	6.62	$J_{cd} = 6.5$; $J_{ce} = 2.5$; $J_{de} = 6.0$
86	4.78	4.43	6.01	4.68	6.79	$J_{ab} = 4.4$; $J_{bc} = 8.0$; $J_{cd} = 5.8$; $J_{de} = 5.8$
87	4.78	4.43	—	4.68	6.67	$J_{ab} = 4.1$; $J_{de} = 6.5$
88	4.77	—	5.63	4.31	6.52	$J_{cd} = 5.5$; $J_{de} = 6.0$
89	4.73	—	5.58	—	6.31	

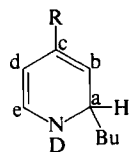
^a Data from Reference 132 (60 MHz) for butyllithium-pyridine adducts (in Et₂O) and Reference 134 (100 MHz) for phenyllithium-pyridine adducts (in TMEDA).

^b Very broad signal.

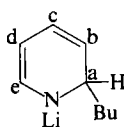
^c — indicates data do not exist.

¹³¹ R. A. Abramovitch and G. A. Poulton, *Chem. Commun.*, 274 (1967).

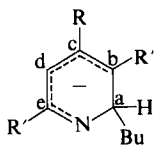
butyllithium and pyridine in diethyl ether at -78°C and warming the solution to 0°C , a deep red color develops within one hour.¹³² ^1H -NMR analysis of this solution shows that nearly 80% of the pyridine has been converted to a new species, involving attack of the reagent at the α position. Hydrolysis with D_2O of the adduct thus obtained leads to 1-deutero-2-hydro-2-butylpyridine (**83**). The spectrum of the butyllithium-pyridine adduct is similar to that of **83**, the ring hydrogens being shielded by 2–3 ppm with respect to those in pyridine. Furthermore, comparison with the spectrum of 1,3-cyclohexadiene indicates that the effect of the nitrogen atom in both the adduct and **83** is to shield the protons at C-3 and C-5, leaving those at C-4 and C-6 essentially unchanged. The structure of the adduct has been suggested to be closer to **84** than to **85**, 80% of the negative charge being associated with the nitrogen-lithium bond. Similar findings were observed for the butyllithium-pyridine adducts starting with 4-*tert*-butylpyridine, 2-*tert*-butylpyridine, or 3-picoline. In all cases the structure of the adducts resembled that of the corresponding 1,2-dihydro derivatives. Foster and Fyfe¹³³ arrived at similar conclusions by carrying out the reaction of pyridine with butyllithium in hexane solution, thus obtaining an NMR pattern in general accordance with that described by Fraenkel and Cooper. They also favor the covalent structure **84** rather than **85**.



(83) $\text{R} = \text{H}$
(83a) $\text{R} = t\text{-Bu}$



(84)



(85) $\text{R} = \text{R}' = \text{R}'' = \text{H}$
(85a) $\text{R} = t\text{-Bu}$; $\text{R}' = \text{R}'' = \text{H}$
(85b) $\text{R} = \text{R}'' = \text{H}$; $\text{R}' = t\text{-Bu}$
(85c) $\text{R} = \text{R}' = \text{H}$; $\text{R}'' = \text{Me}$

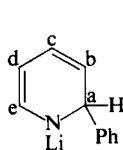
In 1969 Giam and Stout reported the first isolation of solid organolithium adducts of pyridine.¹³⁴ In a typical experiment pyridine was added to a cold LiBr-free ether solution of phenyllithium. The resulting yellow solid was collected and investigated by 100 Hz ^1H -NMR spectroscopy (Table XIV) in N,N,N',N' -tetramethyl-1,2-diaminoethane (TMEDA) solution. It was assigned structure **86**. The solid was sensitive to moisture, oxygen, and heat, and when dissolved in diethyl ether it was oxidized by oxygen to afford 2-phenylpyridine. Other adducts were similarly isolated from 4-*tert*-butyl-, 3-methyl-, and 3,5-dimethylpyridine (Table XIV). Their NMR patterns

¹³² G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, 1825 (1968).

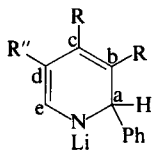
¹³³ R. Foster and C. A. Fyfe, *Tetrahedron* **25**, 1489 (1969).

¹³⁴ C. S. Giam and J. L. Stout, *J.C.S. Chem. Commun.*, 142 (1969).

supported the structures **87**, **88**, and **89**, respectively, corresponding to nucleophilic attack at an α position.



(86)

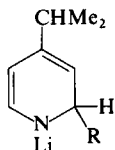
(87) R = H; R' = *t*-Bu; R'' = H

(88) R = Me; R' = H; R'' = H

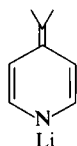
(89) R = R'' = Me; R' = H

The slight discrepancies between the spectra of adducts **84** and **86** formed from pyridine with phenyllithium and butyllithium, particularly with respect to the proton at the tetrahedral carbon, were attributed to diamagnetic shielding by the phenyl group.

In a reactivity study conducted by competitive methods, the influence of 3-alkyl groups (Me and Et) has been found to be rather peculiar.¹³⁵ 3-Alkylpyridines are attacked at the adjacent 2-position more easily than pyridine itself in spite of the weak adverse electronic effect of the substituent. However, at the 6-position the attack occurs more slowly, as expected. Of the several possible reasons for this behavior, probably the most likely is the establishment of a weak attractive interaction between the α carbon of the 3-alkyl group and phenyllithium, which would favor orientation for attack at the 2- rather than the 6-position and overcome the small electronic effect of the group.



(90) R = Ph

(92) R = Me, Bu, *t*-Bu

(91)

The acidic hydrogen atoms in the side chain of alkylpyridines may interfere with the formation of σ -adducts. Thus 4-isopropylpyridine reacts with phenyllithium in THF to yield a mixture of the 2-adduct **90** and 1-lithio-4-(2-propyliden)-1,4-dihydropyridine (**91**). However, alkylolithiums, such as BuLi, *t*-BuLi, and MeLi, mainly yield the related 2-adducts **92**.¹³⁶

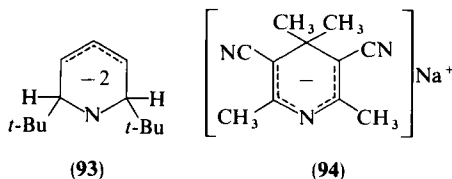
The organolithium-pyridine adduct has been reported to react further with the organometallic reagent.¹³⁷ When pyridine is treated for 3 days,

¹³⁵ R. A. Abramovitch and C. S. Giam, *Can. J. Chem.* **42**, 1627 (1964).

¹³⁶ C. S. Giam, T. E. Goodwin, K. F. Rion, and S. D. Abbott, *J.C.S. Perkin I*, 3082 (1979).

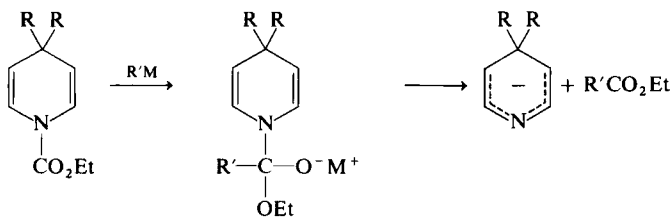
¹³⁷ R. F. Francis, W. Davis, and J. T. Wisener, *J. Org. Chem.* **39**, 59 (1974).

at -70°C , with an excess of *tert*-butyllithium, hydrolysis with MeOH affords 2,6-di-*tert*-butyl-1,2,3,6-tetrahydropyridine, which suggests the formation of the diadduct intermediate **93**.



Adducts have also been obtained by the reaction of methylmagnesium iodide with 3,5-dicyanopyridine and related substrates.¹³⁸ Their formation involves a shift in the IR spectrum from $1563\text{--}1575\text{ cm}^{-1}$ to $1612\text{--}1645\text{ cm}^{-1}$, for C=C bonds, and from $2230\text{--}2248\text{ cm}^{-1}$ to $2125\text{--}2225\text{ cm}^{-1}$, for the C $\equiv$ N bond, the final values being near the absorbance of the dihydro derivatives. Hydrolysis yields the expected dihydro derivatives. In connection with the nature of metal–nitrogen bond, it is of interest that in the sodium adduct **94** the IR spectrum indicates appreciable electron delocalization relative to the corresponding dihydro derivative (shift toward lower frequency), which suggests a substantial ionic character of the bond due to the low electronegativity of sodium.

It is worth noting that in some cases adducts may be prepared by routes other than those leading directly to adduct formation. Thus Fraenkel and his co-workers^{139,140} obtained 4,4-dialkyl-substituted adducts from 1-ethoxycarbonyl-4,4-dialkyl-1,4-dihydropyridines by reaction with organo-metallic compounds, R'M (M = Li, Na, K, MgX), according to Scheme 7. The NMR spectra of these adducts consisted of an AB system ($J = 6.5\text{--}8.0\text{ Hz}$). The chemical shift values were similar (Table XV) to those reported



M = Li, K, Na, MgX

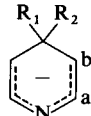
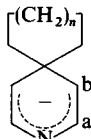
SCHEME 7

¹³⁸ J. Kuthan, A. Kohoutová, and L. Helesic, *Collect. Czech. Chem. Commun.* **35**, 2776 (1970).

¹³⁹ G. Fraenkel, C. Chung Ho, Y. Liang, and S. Yu, *J. Am. Chem. Soc.* **94**, 4732 (1972).

¹⁴⁰ S. Q. A. Rizvi, J. Foos, F. Steel, and G. Fraenkel, *J. Am. Chem. Soc.* **101**, 4488 (1979).

TABLE XV
¹H-NMR DATA FOR "4-ADDUCTS" OBTAINED BY DECOMPOSITION OF
 1-ETHOXYCARBONYL-4,4-DIALKYL-1,4-DIHYDROPYRIDINES^a

Adduct	R ₁ ,R ₂	Solvent	Metal ion	Chemical shift (δ)			
				H-a	H-b	J _{ab} (Hz)	
 95	95	Me,Me	Hexane	Li ⁺	6.25	4.30	6.5
			Hexane-TMEDA	Li ⁺	5.96	3.90	7.2
			THF	MgBr ⁺	6.00	<i>b</i>	7.4
			Hexane-crown ^c	K ⁺	5.90	<i>b</i>	7.2
 95a	95a: n = 3	(CH ₂) ₃	THF	Mg ²⁺	5.90	4.20	6.5
	95a: n = 4	(CH ₂) ₄	THF	Mg ²⁺	6.30	4.28	7.6
			Hexane	Li ⁺	6.25	4.38	7.6
			Hexane-TMEDA	Li ⁺	6.03	3.98	7.6
	95a: n = 6	(CH ₂) ₆	THF	MgBr ⁺	5.99	<i>b</i>	8.0
			Hexane-TMEDA	Li ⁺	5.99	4.00	8.0

^a Data from References 139 and 140.

^b Concealed signal.

^c Dicyclohexyl-18-crown-6.

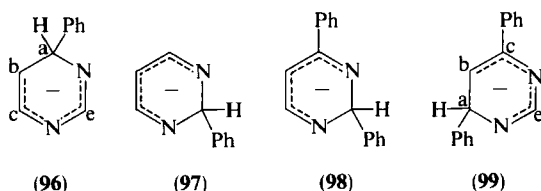
for the adducts formed by addition at position 2.¹³² Such adducts possess a remarkable thermal stability and can be kept unchanged for months at room temperature or heated for some hours. Because of the poor leaving-group ability of the alkyl groups as carbanions, no aromatization was observed. The above synthesis was especially devised to prepare spiro σ -adducts **95a**.

The negative charge distribution in the adducts was evaluated on the basis of the chemical shift values and found to be nearly 75% concentrated on the nitrogen atom. In the reactions of 1-ethoxycarbonyl-1,4-dihydropyridines with organosodium and organopotassium compounds, the resulting metal-associated σ -adducts were not soluble in aliphatic hydrocarbons alone but were made so by addition of 18-crown-6. This behavior would support ionic structures for the potassium and sodium adducts.

b. *Diazines*. The structures of the adducts from diazines and phenyllithium were determined by ¹H- and ¹³C-NMR spectroscopy (Table XVI).³⁴ In the latter case the spectra were obtained in the proton-decoupled mode and selective decoupling experiments. Essential IR data complemented such studies.

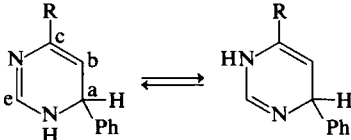
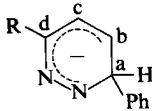
Pyrimidine reacts quantitatively with one equivalent of phenyllithium to yield adduct **96**, which is formed by attachment of the phenyl group to position 4(6). This mode of attachment is well supported by the markedly different shifts between positions 4 and 6, by the high field absorption of C-4, and by the magnitude of the hydrogen-carbon coupling constant of C-4 [¹J(CH) = 140 Hz].

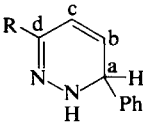
No evidence has been found for the presence of the isomeric adduct **97** in spite of the presence of a small amount of 2-phenylpyrimidine (nearly 4%) in the reaction mixture as obtained after hydrolysis of the adduct to dihydropyrimidine and subsequent oxidation. The composition of the reaction mixture is not affected if TMEDA is added.



Phenyl attachment at position 2 becomes more important when position 4(6) is substituted. The reaction of 4-phenylpyrimidine yields adducts **98** and **99**, in a 1:7.2 ratio. This ratio is significantly altered by complexing agents; in the presence of TMEDA it becomes 1:1.8. Apparently, the phenyl group has a relatively rate-depressing effect toward ipso attack, so that the reactions at positions 2 and 6 become more favored. This behavior is similar to that

TABLE XVI
¹H- AND ¹³C-NMR DATA OF PHENYLITHIUM-DIAZINE ADDUCTS, AND SOME OF THE CORRESPONDING DIHYDRO DIAZINES
 AND HETEROAROMATIC PRECURSORS^a

Adduct	Chemical shift (δ)						Coupling constant (Hz)
	H-a	H-b	H-c	H-d	H-e	Ar	
96^b	5.21	4.32	6.07	— ^d	7.74	7.1–7.3	$J_{ab} = 2.3$; $J_{bc} = 7.5$
99^c	5.19	4.66	—	—	7.69	7.0–7.6	$J_{ab} = 3.8$; $J_{bc} = 1.0$
							
103: R = H	5.02	4.58	5.96	—	6.70	7.35	$J_{ab} = 3.5$; $J_{bc} = 7.5$; $J_{bc} = 1.1$
103a: R = Ph	5.19	5.19	—	—	6.95	7.30	—
							
100: R = H^b	4.23	4.74	5.73	6.83	—	7.1–7.6	$J_{ab} = 3.7$; $J_{bc} = 8.0$; $J_{bd} = 1.9$; $J_{cd} = 5.3$

100a: R = Ph ^c	4.43	4.93	6.35	—	—	7.1–7.7	$J_{ab} = 3.8; J_{bc} = 8.0$
							
100b: R = H	4.82	5.75	5.75	6.73	—	7.24	$J_{bd} + J_{cd} = 5.0;$ $J_{ab} + J_{ac} = 2.8$
100c: R = Ph	4.91	6.01	6.50	—	—	7.2–7.8	$J_{ab} = 4.3; J_{ac} = 1.5;$ $J_{bc} = 9.8$
102^d	4.08	5.25	—	5.84	6.60	7.1–7.3	—
	C-a	C-b	C-c	C-d	C-e		
96^b	58.4	103.4	135.5	—	161.7		
103	55.9	104.6	128.8	—	145.9		
Pyrimidine	157.5	122.1	157.5	—	159.5		
100^b	61.1	105.8	118.4	131.7	—		
100b	55.0	128.1	118.2	134.6	—		
Pyridazine	151.9	126.6	126.6	151.9	—		
102^e	61.7	116.0 ^f	—	110.8 ^f	144.6		
Pyrazine	146.1	146.1	—	146.1	146.1		

^a Data from Reference 34.

^b In ether.

^c In benzene-*d*₆-ether.

^d — indicates data do not exist.

^e In TMEDA-ether.

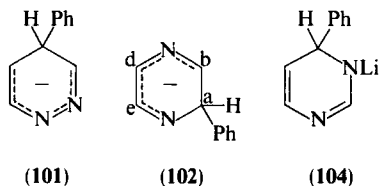
^f Uncertain assignment.

observed for the reaction of 4,6-diphenylpyrimidine with NH_2^- involving attack exclusively at position 2, which is the only available activated CH position (see Section II,C,3).

By the action of phenyllithium, pyridazine is converted to adduct **100** (Table XVI), resulting from nucleophilic attack at position 3.³⁴ The structural assignment is based upon ^1H - and ^{13}C -NMR, starting with pyridazine and its 4,5-dideutero derivative. The site of attachment of the phenyl group is other than that observed with the amide ion in ammonia (C-4). Analysis of the products obtained after hydrolysis and oxidation indicates the presence of nearly 5–6% of 4-phenylpyridazine. Although this finding implies the formation of a small amount of the isomeric adduct **101**, there is no NMR evidence for it. However, both isomeric adducts can be detected when the reaction is carried out in the presence of TMEDA or tetrahydrofuran at a lower temperature. The chemical shift values of adduct **101** are closely similar to those of the amino analog **29**.

Quantitative studies of these reactions would be desirable in order to understand the factors controlling the regioselectivity of nucleophilic attachment.

The reaction of pyrazine with phenyllithium in THF or TMEDA at -45°C leads quantitatively to **102**, as shown by the ^1H -NMR spectrum. The assignment of the structure is made possible by comparison with the amino analog **31**. Both ^1H - and ^{13}C -NMR spectra of **102** are rather poorly diagnostic because they consist of broad signals.



c. The Distribution of the Electronic Charge in the Phenyllithium-Diazine Adducts. The ^{13}C -NMR spectra of adducts formed from diazines and phenyllithium have been the basis for an estimation of the electron distribution at varying positions of the adducts.³⁴ The change in electron density is an important factor in determining a change in chemical shift at any given position in going from substrate to adduct.²⁸ However, more significant conclusions can be reached by comparing the NMR spectra of the adducts with those of the corresponding dihydroazines, as first suggested by Olah and Mayr for similar homocyclic systems.³²

For example, the C-5 position of pyrimidine undergoes an upfield chemical shift of 18.7 ppm in the conversion to adduct **96**. However, because the shift is only 1.2 ppm when compared with dihydropyrimidine **103** (Table

XVI), most of the aforementioned change does not appear to be caused by an electron density increase at C-5 but by the change to a dihydropyrimidine structure. This is conceivable if the adduct is not a free anion but is strongly associated with lithium. Further information about the structure of adduct **96** comes from a comparison between the anionic adduct **30** with the neutral adduct **33**, formed from pyrimidine and 1-methylpyrimidinium cation, respectively, by reaction with NH_2^- . Here the C-5 position of the anionic adduct is found to be 10.2 ppm upfield with respect to the neutral adduct. If it is assumed that in ammonia the anionic adduct is not associated with the positive counterion, the aforementioned phenyllithium adduct is more likely to possess a slightly delocalized electronic structure (**104**) resembling that of a dihydropyrimidine. This fact is not surprising, also in view of the low polarity of the solvent.

In adduct **100**, formed from pyridazine, the C-4 and C-6 positions are upfield with respect to the substrate by 20.8 and 20.2 ppm, respectively. When compared with the corresponding 2,3-dihydropyridazine, the upfield shifts are 22.3 and 2.9 ppm, respectively. Thus the electron density at C-4 seems to be higher than that at C-6, whereas the upfield shift at C-6 is mainly caused by change from the heteroaromatic to the dihydropyridazine structure.

Similar conclusions are reached for the distribution of electron density in the isomeric adduct **101**, where the carbon atoms adjacent to the reaction center are shifted upfield with respect to the corresponding 1,4-dihydropyridazine. Somewhat higher shielding is found for the C-5 atom (8.0 ppm) than for C-3 (3.7 ppm), but in either position the electron density appears to be appreciably lower than for C-4 in adduct **100**. Such differences are presumably to be related to the nature of the lithium–nitrogen bond, but clearly to a first approximation all the adducts from diazines and phenyllithium can be described as undissociated species, whether that bond is ionized or strongly polar covalent.

d. *Reactions of Organolithium–Azine Adducts.* Organolithium–pyridine adducts, such as 1-lithio-2-R-1,2-dihydropyridines, especially when used in isolated form rather than formed *in situ* as reaction intermediates, have proved to be interesting reagents possessing unique properties with regard to regioselectivity as well as other synthetic aspects.¹⁴¹

They have been recognized as hydride donors for effectively reducing, as in the case of 1-lithio-2-butyl-1,2-dihydropyridine, benzophenone and other aryl ketones to the corresponding alcohols.¹⁴²

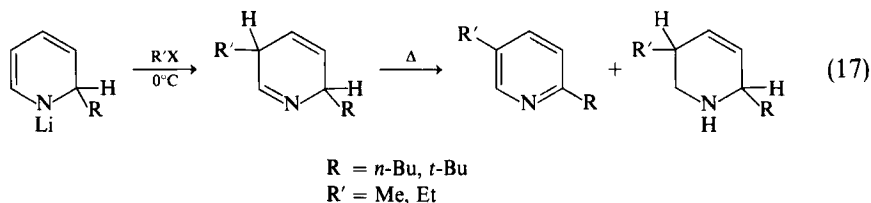
¹⁴¹ C. S. Giam and J. L. Stout, *J.C.S. Chem. Commun.*, 478 (1970).

¹⁴² R. Levine and W. M. Kadunce, *J.C.S. Chem. Commun.*, 921 (1970).

The most intensively investigated behavior of these adducts concerns their tendency to react with electrophilic reagents, indicating their ability to easily supply electronic charge on the nitrogen atom and on the C-5 position and, therefore, to retain an ionic character at least to some extent.

1-Lithio-2-phenyl- and 1-lithio-2-butyl-1,2-dihydropyridines react with several reagents (Br_2 , AlkX , or PhI) to yield 2,5-disubstituted pyridines.^{136,141}

A proton is also transferred easily to C-5. Thus by the action of methanol on 1-lithio-2-*tert*-butyl-1,2-dihydropyridine at -70°C , a mixture of 2-*tert*-butylpyridine and 2-*tert*-butyl-1,2,5,6-tetrahydropyridine was formed through the intermediacy of 2-*tert*-butyl-1,2-dihydro- and 2-*tert*-butyl-2,5-dihydropyridines.¹³⁷ The latter types of intermediates have been actually isolated in a number of instances to provide some general validity to the sequence shown in Eq. (17).¹⁴³



2-*tert*-Butylpyridine is the overall alkylation product starting with pyridine and *tert*-butyllithium. Using an excess of *tert*-butyllithium, 2,6-dialkylation is achieved.¹³⁷ In analogy with the preceding reactions, here the intermediacy of a diadduct, 1,3-dilithio-2,6-di-*tert*-butyl-1,2,3,6-tetrahydropyridine, though only indirectly proved, is probable.

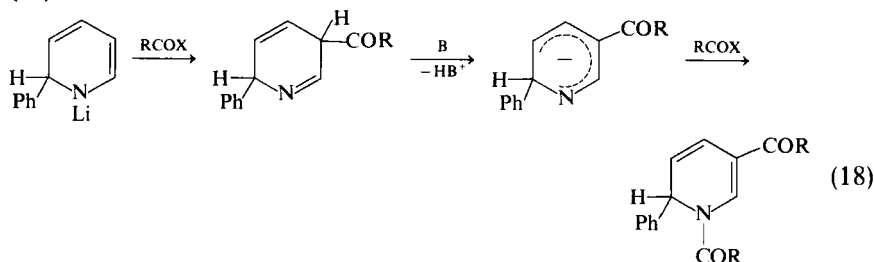
Several extensions of these reactions are possible with respect to the electrophilic reagent as well as to the structure of the adduct. Thus functionalized alkyl groups, such as 2-hydroxyethyl and 2-hydroxy-2-phenylethyl, can be introduced into the pyridine ring at the β position by treating 1-lithio-2-phenyl-1,2-dihydropyridine with ethylene epoxide and styrene epoxide, respectively.¹⁴⁴ When polyhalides such as CF_3I are used, bis-(substituted-pyridyl)methanes and the dimeric substituted dipyridyls are obtained along with other products.¹⁴⁴

1-Lithio-2-phenyl-1,2-dihydropyridine reacts with a variety of acylating agents as an ambident nucleophile. The N/C ratio of the products is found to depend on the electrophilicity of the reagent. Thus while acetyl chloride leads predominantly to the N-acetylated product (*N*-acetyl-2-phenyl-1,2-dihydropyridine), nearly exclusive C-alkylation is observed with trifluoroacetyl

¹⁴³ R. F. Francis, C. D. Crews, and B. S. Scott, *J. Org. Chem.* **43**, 3227 (1978).

¹⁴⁴ C. S. Giam, E. E. Knaus, R. A. Lockhart, and I. G. Keener, *Can. J. Chem.* **53**, 2305 (1975).

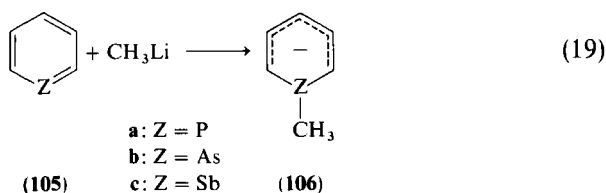
chloride.^{145,146} In some cases the reaction may proceed to yield N,C-disubstituted products.¹⁴⁶ A possible path for the latter process is shown by Eq. (18).



The reactions with 1-lithio-2-butyl- and 1-lithio-2-phenyl-1,2-dihydropyridines have been described with several other reagents including isocyanates, esters, and diethyl chlorophosphate.¹⁴⁷ A less familiar adduct from 10-methyl-10*H*-pyrido[3,2-*b*][1,4]benzothiazine and butyllithium has also been tested for reaction with water, deuterium oxide, and diethyl chlorophosphate.¹⁴⁸

The behavior of organolithium-diazine adducts toward electrophilic reagents, such as methyl iodide, methyl chloroformate, and tosyl chloride, has also been investigated.¹⁴⁹

e. Group V Heteroaromatic Compounds. Phosphabenzene (**105a**) and its higher heteroatomic homologs arsabenzene, and stibabenzene (**105b,c**) display a behavior decidedly different from that of pyridine in that their reaction with organolithium compounds consists of an attack of the carbanion at the heteroatom.^{150,151} The reaction of the parent compounds with methyllithium in ether-THF solution is described by Eq. (19).¹⁵¹



¹⁴⁵ C. S. Giam and E. E. Knaus, *Tetrahedron Lett.*, 4961 (1971).

¹⁴⁶ C. S. Giam, E. E. Knaus, and F. M. Pasutto, *J. Org. Chem.* **39**, 3565 (1974).

¹⁴⁷ T. A. Ondrus, F. M. Pasutto, E. E. Knaus, and C. S. Giam, *Can. J. Chem.* **56**, 1913 (1978).

¹⁴⁸ F. M. Pasutto and E. E. Knaus, *Can. J. Chem.* **56**, 2365 (1978).

¹⁴⁹ R. E. van der Stoep, H. C. van der Plas, H. Jongejan, and L. Hoeve, *Recl. Trav. Chim. Pays-Bas* **99**, 234 (1980).

¹⁵⁰ G. Märkl, F. Lieb, and A. Merz, *Angew. Chem., Int. Ed. Engl.* **6**, 87 (1967).

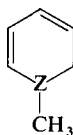
¹⁵¹ A. J. Ashe, III and T. W. Smith, *Tetrahedron Lett.*, 407 (1977).

TABLE XVII
¹H- AND ¹³C-NMR CHEMICAL SHIFTS (δ) OF THE
 HETEROCYCLOHEXADIENIDE ANIONS^a

Anion	H-2(6)	H-3(5)	H-4	C-2(6)	C-3(5)	C-4
106a	3.3	6.1	4.3	71.8	133.0	96.5
106b	3.6	6.1	4.0	72.9	132.1	92.6
106c	4.0	6.2	4.0	69.8	134.2	95.3

^a Data from Reference 151 (in DMSO).

The ¹H- and ¹³C-NMR spectra of the anions **106a-c**, which are reported in Table XVII, show a marked shielding of the protons and carbon atoms at C-2, C-4, and C-6 relative to those at C-3 and C-5, suggesting that the negative charge is largely localized in the former group of positions.¹⁵¹ The spectra are similar to those of the carbocyclic analog lithium 1,1-dimethyl-2,5-cyclohexadienide. The anions do not seem to show a paramagnetic ring current, which would be expected from an 8π-electron antiaromatic system, because the protons at C-3 and C-5 have chemical shift values nearly identical to those of their conjugate acids **107**. Adducts **106** are easily converted to their conjugate acids, such as **107**, by reaction with water. In the case of the stiba adduct, however, a mixture of 2,4-stibacyclohexadiene (**107c**) and its 2,5-isomer is obtained. The anions can be regenerated by base.



(**107a**) Z = P
 (**107b**) Z = As
 (**107c**) Z = Sb

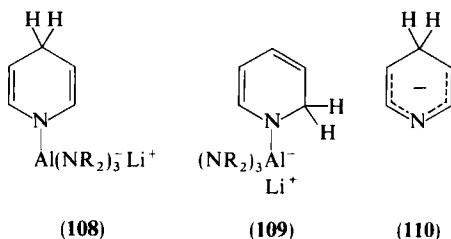
E. ADDITIONAL NUCLEOPHILES

1. The Hydride Ion

The σ-adducts are obtained with the hydride ion under conditions similar to those derived from organometallic reagents and may therefore involve strong association or covalent bonding with the metal ions in much the same way (see initial statement regarding structural formulas in Section II, D,2,a).

Adducts can be formed by hydride ion transfer onto pyridine and related heteroaromatics from a number of hydride donors.

Lithium aluminum hydride reacts readily with pyridine to yield lithium tetrakis-(*N*-dihydropyridyl)aluminate, $\text{LiAl}(\text{NR}_2)_4$ (structures **108** and **109**).¹⁵² The NR_2 groups represent 1,4-dihydro- and/or, 1,2-dihydropyridyl residues. The two diverse N-ligands may be part of the same molecule in association with the Al metal. The structure of the adduct has been investigated by IR and NMR spectroscopy and by deuterium-labeling experiments. The latter approach has been used to determine the 1,2 to 1,4 ratio, which is found to be close to 1:2 when the reaction is carried out at room temperature. The N—Al bond is assumed to be covalent, though of a markedly more ionic character as compared to the N—H bond in dihydropyridines.¹⁵²



Compounds **108**, **109**, and the like have served as intermediates for the preparation of β -alkyl-substituted N-heteroaromatics.^{136,153,154}

Similar adducts are obtained with 3,5-dicyanopyridine and some of its methyl derivatives in ether solution.¹³⁸ Under such conditions the major components of the product mixture consist of the salts $\text{LiAlH}_2(\text{NR}_2)_2$ and $\text{LiAlH}(\text{NR}_2)_3$, where the hydride ion of the starting LiAlH_4 is only partly replaced by dihydropyridyl residues. The IR data show that the short wavelength bands of the stretching vibrations of the C—C multiple bonds in the adducts are shifted, relative to substrate, from the $1560\text{--}1580\text{ cm}^{-1}$ to the $1610\text{--}1650\text{ cm}^{-1}$ region, i.e., near the analogous absorption maxima of the corresponding dihydropyridine derivatives located at $1633\text{--}1685\text{ cm}^{-1}$. A broad absorption is also found at $400\text{--}600\text{ cm}^{-1}$, which is attributed to the ligand—Al stretching vibration.

Adduct **110** has been obtained by decomposition of 1-ethoxycarbonyl-1,4-dihydropyridine with potassium *tert*-butoxide. It is the σ -adduct that would be expected to form by attack of the hydride ion on the 4-position of pyridine. ^1H - and ^{13}C -NMR studies suggest that **110** is planar and devoid of any homoaromatic character.¹⁵⁵ The ^{13}C chemical shifts [δ (in DMSO) 127.9

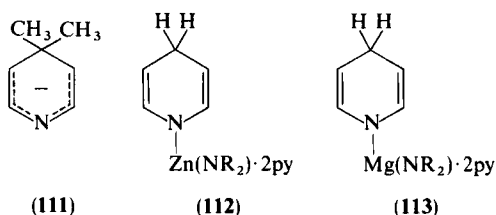
¹⁵² P. T. Lansbury and J. D. Peterson, *J. Am. Chem. Soc.* **85**, 2236 (1963).

¹⁵³ C. S. Giam and S. D. Abbott, *J. Am. Chem. Soc.* **93**, 1294 (1971).

¹⁵⁴ C. S. Giam and T. E. Goodwin, *J. Org. Chem.* **43**, 3780 (1978).

¹⁵⁵ G. A. Olah and R. J. Hunadi, *J. Org. Chem.* **46**, 715 (1981).

and 97.1 for C-2,6 and C-3,5, respectively] are quite similar to the corresponding values (in hexane-TMEDA) of 127.9 and 91.7 recorded for compound **111**.¹⁴⁰ Similar observations are found for the ^1H chemical shifts at the same positions, i.e., δ 6.65 and 4.88 (in DMSO) for H-2,6 and H-3,5 of adduct **111**, and 6.25 and 4.30 (in hexane) for H-2,6 and H-3,5 of **111**, respectively. In particular, a marked electron delocalization into the 3,5-positions is noted. Even though the data are not strictly comparable because of the change in solvent (DMSO versus hexane) and in the substituents (H, Me) at the 4-position, nevertheless they do seem to indicate that the electron distribution of both **110** and **111** is but slightly dependent on the metal ion, and that therefore the N-metal bond must be largely ionic. The planarity of anion **110** is also supported by MINDO/3 studies.¹⁵⁶ The possibility that **111** and related compounds exist as ion pairs has been stressed by Fraenkel *et al.*¹⁴⁰



Recently, de Koning *et al.*¹⁵⁷ have found that hydride transfer takes place exclusively to the 4-position of pyridine, using zinc hydride and magnesium hydride. The reaction is fairly slow and eventually is completed to yield the pyridine complex of bis(1,4-dihydro-1-pyridyl)zinc and its magnesium analog, $\text{Zn}(\text{NR}_2)_2 \cdot 2\text{py}$ and $\text{Mg}(\text{NR}_2)_2 \cdot 2\text{py}$, where NR_2 is the 1,4-dihydropyridyl residue. ^1H - and ^{13}C -NMR spectral data give consistent answers in agreement with the proposed structures **112** and **113**.

Like the related organolithium-pyridine adducts (see Section II,D,2,d), the dihydropyridyl metal adducts considered in this Section are found to be good hydride donors toward a number of carbonyl and other compounds.¹⁵² Hydride transfer from such adducts has also been shown to occur toward a variety of azaheterocyclic substrates, thus generating, in turn, the corresponding adducts. Such a transfer has been carried out with pyridine, *N,N*-dimethylnicotinamide, quinoline, isoquinoline, 2,2'-bipyridyl and its isomers, and 1,10-phenanthroline.¹⁵⁸

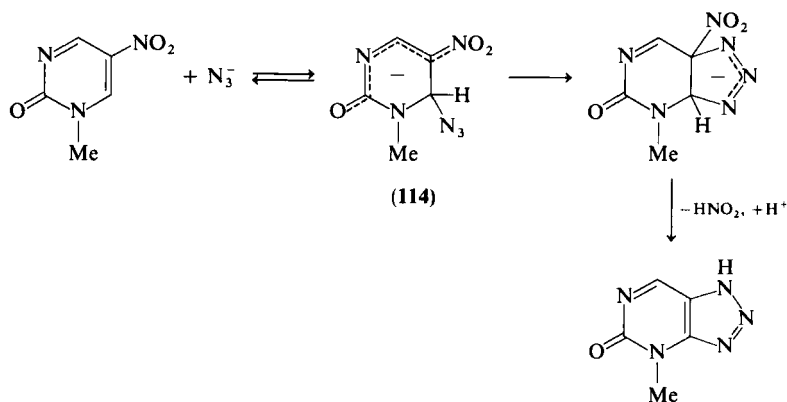
¹⁵⁶ N. Bodor and R. Pearlman, *J. Am. Chem. Soc.* **100**, 4946 (1978).

¹⁵⁷ A. J. de Koning, J. Boersma, and G. J. M. van der Kerk, *J. Organomet. Chem.* **186**, 159 (1980).

¹⁵⁸ A. J. de Koning, P. H. M. Budzelaar, J. Boersma, and G. J. M. van der Kerk, *J. Organomet. Chem.* **199**, 153 (1980).

2. The Azide Ion

An adduct with the azide ion has been reported for the reaction with 1-methyl-5-nitropyrimidine-2(1*H*)-one in DMSO.⁴² It is described as an intermediate for the formation of 4-methyl-1,4-dihydro-1,2,3,4,6-pentaazainden-5-one (3-methyl-2-oxo-8-azapurine) according to Scheme 8 and is assigned structure **114**. The ¹H-NMR spectrum displays a characteristic signal at δ 5.83 arising from a strong upfield shift of the H-6 signal of the starting substrate at δ 9.49. The spectral change is similar to that observed when RO⁻ ions are used as nucleophiles and is indeed analogous to that usually found under the $sp^2 \rightarrow sp^3$ hybridization change in the formation of Meisenheimer-type adducts.



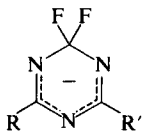
SCHEME 8

3. The Fluoride Ion

Polyfluoro-1,3,5-triazines have been shown to be suitable substrates for the formation of adducts with F⁻.¹⁵⁹ The sparingly soluble cesium fluoride dissolves readily in tetramethylenesulfone in the presence of 2,4,6-trifluoro-1,3,5-triazine. The ¹⁹F-NMR spectrum of the solution thus obtained shows two peaks of the same intensity, at 4 and 51 ppm upfield from CFCI₃, and is consistent with structure **115**. It is of interest that adduct **115** shows marked F⁻ donating properties. Addition of BF₃ · Et₂O leads to the disappearance of the signals of the adduct and to the regeneration of the peak of the substrate at 33 ppm upfield from CFCI₃. Alternatively, evaporation of the solvent also restores CsF and the substrate. Upon heating

¹⁵⁹ R. D. Chambers, P. D. Philpot, and P. L. Russell, *J.C.S. Perkin I*, 1605 (1977).

the tetramethylenesulfone solution of **115** at 60°C, the signals of the adduct disappear; by further heating at 100°C, a single broad band appears, indicating rapid exchange between the adduct and the reactants. On cooling to 0°C, the ^{19}F -NMR spectrum of **115** can be again detected.



(115) $\text{R} = \text{R}' = \text{F}$

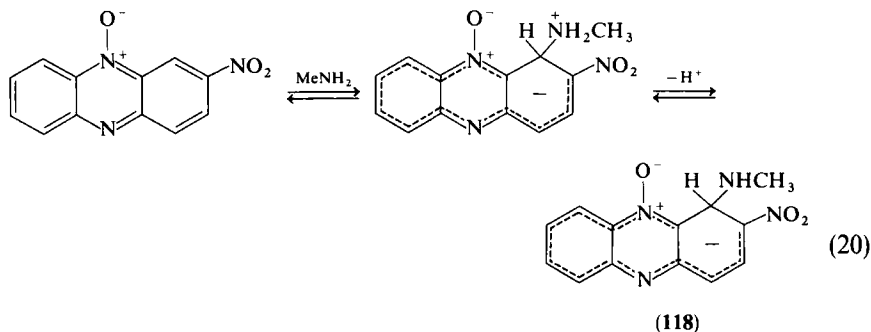
(116) $\text{R} = \text{F}$; $\text{R}' = (\text{CF}_3)_2\text{CF}$

(117) $\text{R} = \text{R}' = (\text{CF}_3)_2\text{CF}$

Analogous reactions with perfluoro(isopropyl-1,3,5-triazine) and perfluoro(diisopropyl-1,3,5-triazine) with CsF yielded adducts **116** and **117**, respectively, which were detected by ^{19}F -NMR. Use of potassium fluoride, either alone or associated with 18-crown-6, did not lead to the formation of the adducts. In contrast, from tris(perfluoroisopropyl)-1,3,5-triazine no adduct was detected. This is quite interesting because it would indicate the importance of the *gem*-difluoro substitution to stabilize the adduct,¹⁶⁰ in analogy with the effect of *gem*-dimethoxy substitution.⁷⁶

4. Amines

The formation of anionic σ -adducts resulting from the primary attachment of neutral nucleophiles followed by proton elimination has been described only occasionally. A definite example is the reaction of methylamine with 2-nitrophenazine 10-oxide in DMF, leading to adduct **118**.¹⁶¹ This structure is well supported by spectral evidence. It is characterized by two



¹⁶⁰ F. Terrier, G. Ah-Kow, M. J. Pouet, and M. P. Simonnin, *Tetrahedron Lett.*, 227 (1976).

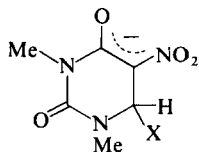
¹⁶¹ G. Minoli, A. Albini, G. F. Bettinetti, and S. Pietra, *J.C.S. Perkin II*, 1661 (1977).

absorption bands in the visible spectrum, at 445 and 555 nm, of equal intensity ($\epsilon = 1.35 \times 10^4 M^{-1} \text{ cm}^{-1}$) and by an upfield chemical shift of the H-1 resonance caused by its hybridization change, as expected. Because the primary attack by the amine is expected to produce a zwitterionic adduct, proton elimination should be a subsequent fast step toward **118**, according to Eq. (20).

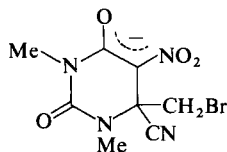
Attack of nucleophilic nitrogen is also involved in the formation of adduct **77** (see Section II,D,1).

5. Other Protic Nucleophiles

A number of protic nucleophiles including water, 2-mercaptoethanol, bisulfite ion, and hydroxylamine have been shown to form anionic σ -adducts by reaction with 1,3-dimethyl-5-nitro-uracil in aqueous solution.⁵⁷ These adducts have the general structure **119**, which is characterized by strong absorption maxima in the range 320–326 nm ($\epsilon \approx 1\text{--}2 \times 10^4 M^{-1} \text{ cm}^{-1}$), involving a small bathochromic shift with respect to the substrate ($\lambda_{\text{max}} = 308 \text{ nm}$). Also, $^1\text{H-NMR}$ data show a strong upfield shift of the ring proton of the order of 3.3 ppm.

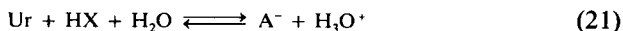


(119) $X = \text{OH}, \text{SO}_3^-, \text{SCH}_2\text{CH}_2\text{OH}, \text{NHOH}$



(120)

The equilibrium constant $K = [\text{A}^-][\text{H}_3\text{O}^+]/[\text{Ur}][\text{HX}]$ for the reaction in Eq. (21),



where Ur is the uracil derivative, A^- the adduct therefrom, and HX the nucleophilic reagent, has been evaluated for all four nucleophiles ($K = 3.21 \times 10^{-11}$, 1.38×10^{-6} , 4.27×10^{-6} , and 5.8×10^{-3} for HX = water, β -mercaptoethanol, hydroxylamine, and HSO_3^- , respectively). Although this is a limited set of nucleophiles, the log K values are widely spaced and correlate linearly with the γ parameter, which is a measure of the ability of a reagent to add covalently across the carbonyl group of aldehydes and ketones.¹⁶² This finding indicates that the free energy change is governed by electronic effects and does not suffer from diverse steric interactions of the

¹⁶² E. G. Sander and W. P. Jencks, *J. Am. Chem. Soc.* **90**, 6154 (1968).

nucleophilic reagent in the uracyl system and in the aldehyde (pyridine-4-carboxaldehyde) on which γ is based.

Adducts **119** are of relevance as reaction intermediates in the chemistry of several uracil and cytosine derivatives, which show a strong tendency to undergo covalent nucleophilic addition across the 5,6 double bond with such reagents as water, alcohols, hydroxylamine, and bisulfite ion.

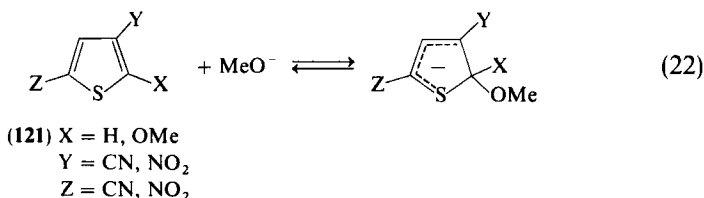
Indirect evidence for the formation of anionic adducts has been obtained for some dehalogenation reactions of 5-halouracils or 5-halo-5,6-dihydro-uracils with bisulfite ion in water.¹⁶³⁻¹⁶⁵ However, no adducts were detected in the course of these reactions. Similarly, the formation of adduct **120** was assumed in the reaction of 6-bromomethyl-1,3-dimethyl-5-nitro-uracil with KCN to yield 6-cyano-1,3-dimethyl-5-nitrocyclothyminine.¹⁶⁶ Clearly, in all these reactions involving the uracil system, the ring charge delocalization is quite limited, and the resulting stability of the adducts is markedly reduced.

III. Five-Membered Ring Adducts

A. FORMATION AND STRUCTURE DETERMINATION

1. General Features

Several electron-deficient derivatives of the 5-membered heteroaromatic rings react with nucleophilic reagents under mild conditions to yield Meisenheimer-type adducts. Most adducts have been obtained with the methoxide ion, either in methanol or DMSO solution. A typical reaction is illustrated by Eq. (22).



The structure determination of the adducts has generally been made by ¹H-NMR and UV-visible spectroscopy. The NMR spectrum of the adducts is characterized by a general upfield shift with respect to substrates (Tables

¹⁶³ G. S. Rork and I. H. Pitman, *J. Am. Chem. Soc.* **97**, 5559 (1975).

¹⁶⁴ G. S. Rork and I. H. Pitman, *J. Am. Chem. Soc.* **97**, 5566 (1975).

¹⁶⁵ F. S. Sedor, D. G. Jacobson, and E. G. Sander, *J. Am. Chem. Soc.* **97**, 5572 (1975).

¹⁶⁶ S. Senda, K. Hirota, T. Asao, and Y. Yamada, *Heterocycles* **4**, 1765 (1976).

XVIII-XXIII). The site of attachment of the nucleophile to 5-membered substrates is usually an α position except for special cases (see Sections III,A,2 and III,A,3). When the reaction occurs at a methoxy-substituted α position, the structure of the adduct is easily identified by the NMR equivalence of the geminal methoxy groups at that position and is accompanied by a relatively low upfield shift of the ring protons.

Upon attachment of the nucleophile to a hydrogen-bearing α position, a strong upfield shift ($\Delta\delta = 2\text{--}2.5$ ppm) is observed for the α hydrogen because of the $sp^2 \rightarrow sp^3$ change of carbon at that position. However, in the presence of dissimilar ring protons in the starting substrate, the site of reaction cannot unambiguously be deduced from the NMR spectrum of the adduct alone. It is usually identified with the aid of a specifically deuterated substrate. When the latter technique is adopted with α -deuterated substrates, the use of a deuterated solvent is required because base-catalyzed H-D exchange frequently occurs at α positions and competes with nucleophilic attachment.^{167,168}

The coupling constant between the ring proton at the α position undergoing nucleophilic attack and the one, if any, at either β position decreases significantly in going from substrate to adduct.^{17,167} In the case of selenophene derivatives,¹⁶⁹ the determination of the site of attachment has been carried out by $^{77}\text{Se}\text{--H}$ coupling measurements on examination of the $\text{Se}\text{--H}$ coupling constant accompanying the signal for the proton bound to the carbon undergoing hybridization change.

As to the electronic spectrum, a bathochromic shift is generally observed on adduct formation (see Table XXIV). The shift is large when the negative charge can be effectively delocalized as in the formation of dinitro and cyanonitro adducts. A small shift is observed in the reaction of 2-methoxy-3-nitrothiophene and is attributed¹⁷⁰ to a more limited reorganization in electronic structure, which is involved in going from substrate to adduct due to the presence of only one nitro group and of the methoxy group adjacent to it.

As for the role of the heteroatom, similarly substituted thiophene and selenophene adducts have very similar spectra in the visible region. This analogy may be of a diagnostic value in comparing two such adducts, one of which is unknown. Furan adducts have absorbance maxima in the visible region at slightly lower wavelengths than the corresponding thiophene adducts.

¹⁶⁷ G. Doddi, A. Poretti, and F. Stegel, *J. Heterocycl. Chem.* **11**, 97 (1974).

¹⁶⁸ M. P. Simonnin, F. Terrier, and C. Paulmier, *Tetrahedron Lett.*, 2803 (1973).

¹⁶⁹ C. Paulmier, M. P. Simonnin, A. P. Chatrousse, and F. Terrier, *Tetrahedron Lett.*, 1123 (1973).

¹⁷⁰ D. Spinelli, G. Consiglio, and R. Noto, *J. Chem. Res., Synop.*, 242 (1978).

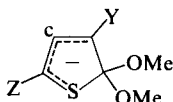
Other techniques (IR and elemental analysis) have been used less frequently and in association with spectroscopy techniques just discussed.

2. Nitro-, Dinitro-, and Cyanonitrothiophenes

The first 5-membered Meisenheimer-type adduct was obtained from 2-methoxy-3,5-dinitrothiophene (**121**: X = OMe, Y = Z = NO₂) by reaction with methoxide ion in methanol.^{16,55} The sodium (or potassium) salt can be isolated as a deep purple solid whose elemental analysis is consistent with the formation of a 1:1 adduct. The IR spectrum is characterized by the presence of strong bands in the 1000–1250 cm⁻¹ region, where geminal dialkoxy adducts²³ usually exhibit strong absorption. The electronic spectrum shows intense absorption at 312 and 532 nm, which accounts for the red color of the methanol solution.

The NMR spectrum of a DMSO-*d*₆ solution of the adduct shows two bands, with relative intensities 1:6, which are attributed to the ring and methoxyl protons, respectively. The resonance of the ring proton in DMSO-*d*₆ (δ 7.87) is shifted upfield as compared to that of the ring proton in the starting substrate (δ 8.47); also, the resonance of the methoxyl protons is shifted from 4.37 to 3.28. A single band for the methoxyl protons indicates the equivalence of the methoxy groups. This feature as well as all the preceding data support structure **122**, as obtained according to Eq. (22). In view of its high stability (see Section III,C), compound **122** would also be quite suitable for X-ray investigation. Unfortunately, no study of this kind has ever been reported for 5-membered ring σ -adducts.

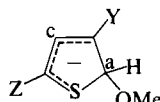
Several thiophene derivatives of the general series **121** (Eq. 22) have been investigated for adduct formation.^{169,171–173} The only missing member in the series is the one with Y = Z = CN. All the investigated substrates react with the methoxide ion in MeOH and/or DMSO to give the corresponding Meisenheimer adducts and undergo attack at the X group-bearing position α . The NMR data for such products are reported in Table XVIII.



(122) Y = Z = NO₂

(128) Y = CN; Z = NO₂

(129) Y = NO₂; Z = CN



(123) Y = NO₂; Z = CN

(126) Y = Z = NO₂

(127) Y = CN; Z = NO₂

¹⁷¹ G. Doddi, G. Illuminati, and F. Stegel, *J.C.S. Chem. Commun.*, 1143 (1972).

¹⁷² G. Doddi, G. Illuminati, and F. Stegel, *Tetrahedron Lett.*, 3221 (1973).

¹⁷³ G. Baldini, G. Doddi, G. Illuminati, and F. Stegel, *J. Org. Chem.* **41**, 2153 (1976).

TABLE XVIII
 $^1\text{H-NMR}$ DATA FOR σ -ADDUCT FORMATION FROM DINITRO- AND CYANONITROTHIOPHENES
 (REACTION WITH MeO^-)

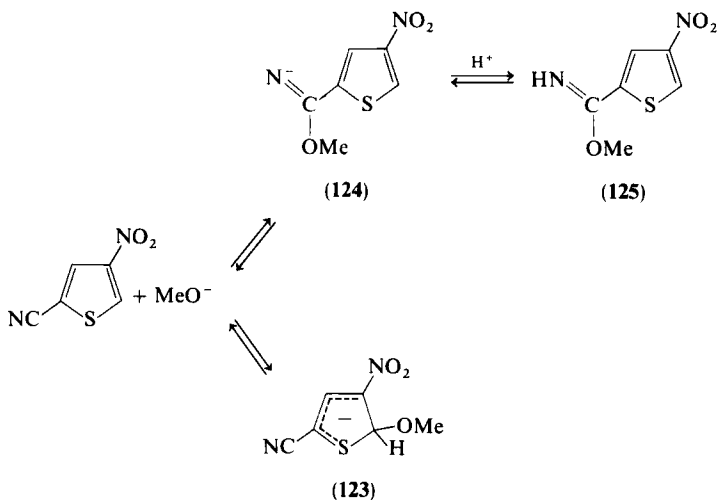
Precursor ^a and adduct	Solvent	Chemical shift (δ)			Coupling constant (Hz)	References
		H-a	H-c	OMe		
2,4-Dinitrothiophene	DMSO- d_6	9.05	8.58	— ^b	$J_{ac} = 2.1$	169
	CD_3OD	8.53	8.51	—	$J_{ac} = 2.1$	171
126	DMSO- d_6	6.36	7.82	3.20	$J_{ac} = 0.8$	169
	CD_3OD	6.50	8.04	n.d. ^c	$J_{ac} = 0.5$	171
2-Methoxy-3,5-dinitro- thiophene	DMSO- d_6		8.47	4.37	—	55
	DMSO- d_6		7.86	3.29	—	16, 55
4-Cyano-2-nitrothiophene	DMSO- d_6	8.90	8.60	—	$J_{ac} = 1.8$	169
	CH_3OH	8.52	8.27	—	$J_{ac} = 1.8$	171
127	DMSO- d_6	6.19	7.44	n.d.	$J_{ac} = 0.5$	169
	CH_3OH	6.20	7.46	n.d.	$J_{ac} = 0.1$	172
3-Cyano-2-methoxy-5- nitrothiophene	DMSO	—	8.52	4.29	—	173
	CH_3OH	—	8.05	4.25	—	173
128	DMSO	—	7.44	3.25	—	173
	CH_3OH	—	7.55	n.d.	—	173
2-Cyano-4-nitrothiophene	DMSO- d_6	9.12	8.62	—	$J_{ac} = 1.7$	169
	CH_3OH	8.87	8.30	—	$J_{ac} = 2$	172
123	DMSO- d_6	6.34	7.20	3.13	$J_{ac} = 0.5$	169
2-Methoxy-5-cyano-3- nitrothiophene	DMSO	—	8.37	4.26	—	173
	CD_3OD	—	8.20	4.25	—	173
129	DMSO	—	7.11	3.22	—	173
	CH_3OH	—	7.03	n.d.	—	173

^a Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^b — indicates data do not exist.

^c n.d., no data given.

2-Cyano-4-nitrothiophene (**121**: X = H, Y = NO_2 , Z = CN) shows an anomalous behavior in MeOH solution, as illustrated in Scheme 9. Whereas in DMSO- d_6 this compound shows the behavior common to the series¹⁶⁹ and is converted to adduct **123**, in methanol it undergoes attack at the 2-cyano group.¹⁷² The resulting anion **124** exhibits spectral features ($\lambda_{\text{max}} = 245$, 270(sh) nm; δ 8.67, d; δ 8.25, d; $J = 1.5$ Hz) similar to those of the starting substrate ($\lambda_{\text{max}} = 237$, 262(sh) nm; δ 8.87, d; δ 8.30, d; $J = 2$ Hz), and mild acidification and evaporation of the solvent yields methyl 4-nitro-2-thiophenecarboxyimide (**125**). It has been shown, by using the stopped-flow



SCHEME 9

technique and MeO^- concentrations higher than $5 \times 10^{-2} M$, that the reaction initially produces adduct **123** under kinetic control and eventually leads to the more stable carboxyimidate **125**.¹⁷⁴

As Scheme 9 shows, anion **124** is in equilibrium with several other species. When methanol is removed, the sodium salt of **124** is obtained. Upon dissolving the salt in methanol, the resulting solution shows NMR features identical to those originally observed for **124**, as obtained *in situ*. When the salt is dissolved in $DMSO-d_6$, the NMR spectrum of adduct **123** is obtained as a result of the solvent effect on the equilibria that are shifted all the way through to **123**. The behavior of **121** ($X = H$, $Y = NO_2$, $Z = CN$) reflects the lower ability of the cyano group relative to the nitro group, as located at an α position, to withdraw the negative charge of the attacking reagent from a vinylogous α' position. The reason why thermodynamic control favors the conjugate base of the carboxyimidate presumably is that a protic solvent stabilizes it by H bonding, due to the strongly localized negative charge on nitrogen. Anion-metal ion ion-pairing may also play a role. The formation of adduct **123** does not suffer from the interference of **124** in DMSO solution presumably not only because of the aprotic character and high polarity of the solvent but also in view of stabilizing solvation effects by dispersion interactions between polarizable species, i.e., DMSO and the highly charge-delocalized adduct.⁸³ When the starting substrate is 2-methoxy-3-nitro-5-cyanothiophene, i.e., the α position to be attacked is a CH_3O - rather

¹⁷⁴ F. Terrier, A. P. Chatrousse, and C. Paulmier, *J. Org. Chem.* **44**, 1634 (1979).

than an H-bearing carbon, only the Meisenheimer-type adduct is formed in both protic and aprotic solvents. This fact is to be correlated with the higher stability of the *gem*-dimethoxy-substituted adduct. Finally, no addition to the CN group has ever been reported for the interaction of the methoxide ion with cyanonitro-substituted benzenoid compounds.⁷⁷

Compounds **121** ($X = H$, $Y = Z = NO_2$, and $X = H$, $Y = NO_2$, $Z = CN$) have also been made to react with $Me_4N^+BH_4^-$.¹⁶⁹ The hydride ion is unequivocally shown to become attached to the H-bearing α position when a deuterio-substituted starting material is used. However, the adduct that presumably forms from **121** ($X = H$, $Y = CN$, $Z = NO_2$) as an intermediate escapes detection because of rapid decomposition by ring opening.

Although less activated than the preceding compounds, mononitrothiophenes still undergo adduct formation under diverse conditions.^{17,167,175} The structural data for a number of adducts of this kind (**130–133**) are reported in Table XIX.

As expected, there is a general tendency for the nucleophile to attack the α position. This preference is preserved even when a methoxy group occupies a β position (formation of **133** from 2-nitro-3-methoxythiophene). ¹H-NMR evidence indicates that in methanol solution an adduct at C-2 of 2-methoxy-5-nitrothiophene (**134**) is formed as an intermediate in a decomposition sequence probably involving ring opening.¹⁷⁶ However, in DMSO no evidence of such an adduct was recorded.¹⁷



(134)

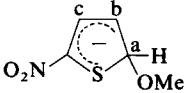
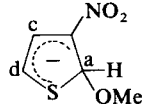
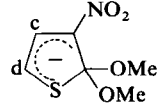
Two substrates of special interest are 2-(2-hydroxyethoxy)-3-nitrothiophene and its 3-(2-hydroxyethoxy)-2-nitro isomer. Both compounds form Meisenheimer-type spiro adducts, **135** and **136**, by ring closure at the 2- and 3-positions, respectively.¹⁷⁷ Intramolecular cyclization brings in an extra driving force for the formation of the adduct, which is also observed in the trinitrobenzene series.⁵¹ This would account for the structure of adduct **136**, which exceptionally bears the sp^3 -hybridized carbon on a β position. No other examples of such a structure from 5-membered heteroaromatic substrates is known even for transient species, except for benzoannelated derivatives (see Section III,A,3).

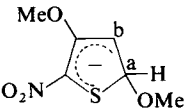
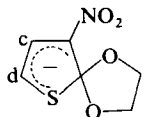
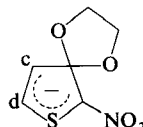
¹⁷⁵ C. Dell'Erba, M. Novi, G. Guanti, and D. Spinelli, *J. Heterocycl. Chem.* **12**, 327 (1975).

¹⁷⁶ G. Doddi, unpublished work.

¹⁷⁷ F. Sancassan, M. Novi, G. Guanti, and C. Dell'Erba, *J. Heterocycl. Chem.* **12**, 1083 (1975).

TABLE XIX
¹H-NMR DATA FOR σ-ADDUCT FORMATION FROM SOME NITROTHIOPHENES (REACTION WITH RO⁻)

Precursor ^a and adduct	Solvent	Chemical shift (δ)				OMe and other groups ^b	Coupling constant (Hz)	References
		H-a	H-b	H-c	H-d			
2-Nitrothiophene	DMSO- <i>d</i> ₆	7.98	7.20	8.09	— ^c	—	<i>J</i> _{ab} = 5.5; <i>J</i> _{bc} = 4.0; <i>J</i> _{ac} = 1.5	167, 175
	CD ₃ OD	7.77	7.08	7.93	—	—		167
 130	DMSO- <i>d</i> ₆	6.08	5.55	6.72	—	3.15	<i>J</i> _{ab} = 3; <i>J</i> _{bc} = 6; <i>J</i> _{ac} = 0	167, 175
	CD ₃ OD	6.17	5.92	6.77	—	—		167
3-Nitrothiophene	DMSO	8.76	—	7.65	7.74	—	<i>J</i> _{ac} = 1.2; <i>J</i> _{ad} = 3.4; <i>J</i> _{cd} = 5.3	175
 131	DMSO	6.12	—	5.82	6.30	3.12	<i>J</i> _{ac} = 0.5; <i>J</i> _{ad} = 3.4; <i>J</i> _{cd} = 5.3	175
2-Methoxy-3-nitrothiophene	DMSO	—	—	7.29	6.93	4.15	<i>J</i> _{cd} = 6.0	17
	CD ₃ OD	—	—	7.34	6.70	4.16	<i>J</i> _{cd} = 6.2	170
 132	DMSO	—	—	6.33	5.71	3.25	<i>J</i> _{cd} = 6.8	17
	CD ₃ OD	—	—	H-c + H-d: 6.11, 6.34		3.4	<i>J</i> _{cd} = 6.8	170

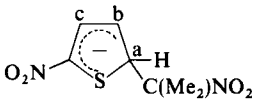
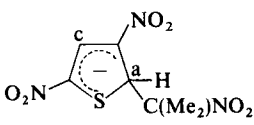
3-Methoxy-2-nitrothiophene	DMSO	8.01	7.23	—	—	4.07	$J_{ab} = 6.1$	17
 133	DMSO	5.60	4.78	—	—	3.63; 3.90	$J_{ab} = 3.5$	17
2-(2-Hydroxyethoxy)-3-nitrothiophene	DMSO- d_6	—	—	7.37	6.92	OCH ₂ CH ₂ O, 3.82; 4.36	$J_{cd} = 6.25$	177
 135	DMSO- d_6	—	—	6.18	5.73	OCH ₂ CH ₂ O, 4.0	$J_{cd} = 7.00$	177
3-(2-Hydroxyethoxy)-2-nitrothiophene	DMSO- d_6	—	—	7.27	7.94	OCH ₂ CH ₂ O, 3.76; 4.36	$J_{cd} = 6.15$; $J_{CH_2CH_2} = 4.85$	177
 136	DMSO- d_6	—	—	6.39	5.42	OCH ₂ CH ₂ O, 3.87; 4.24	$J_{cd} = 6.50$	177

^a Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^b Groups other than OMe are indicated near the δ value as appropriate.

^c — indicates data do not exist.

TABLE XX
¹H- AND ¹³C-NMR DATA FOR σ-ADDUCT FORMATION FROM SOME THIOPHENE DERIVATIVES
 AND THE 2-NITRO-2-PROPANIDE ION^a

Adduct and precursor ^b	Chemical shift (δ)				Coupling constant (Hz)
	H-a	H-b	H-c		
 137	4.92	5.30	6.56		$J_{ab} = 3.5;$ $J_{bc} = 6.3;$ $J_{ac} = 1.65$
2-Nitrothiophene	8.1	7.30	8.1		n.d. ^c
 138	5.52	— ^d	6.76		(¹ J _{CH}) _a = 199.4
2,4-Dinitrothiophene	9.04	—	8.59		$J_{ac} = 2.20;$ $(^1J_{CH})_c = 185.5$
	C-a	C-b	C-c	C-d	
138	56.8	123.5 ^e	131.8	127.0 ^e	
2,4-Dinitrothiophene	134.9	145.2	123.2	150.9	

^a Data in DMSO-*d*₆, from Reference 178.

^b Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^c n.d., no data given.

^d — indicates data do not exist.

^e These values may be interchanged (see Reference 178).

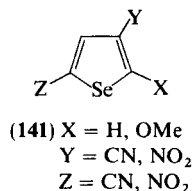
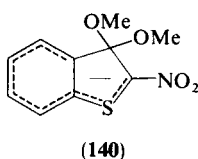
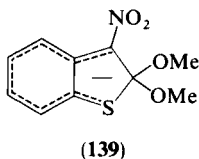
The reactions of the conjugate base of 2-nitropropane, used as the lithium or tetraalkylammonium salt, have been described for a number of 2-nitro-5-X-thiophenes (X = H, I, NO₂, CMe₂NO₂) and for 2,4-dinitrothiophene. They generally display a complex pattern leading to several products. Only for 2-nitrothiophene and 2,4-dinitrothiophene has evidence for the formation of σ-adducts **137** and **138**, respectively, been recorded.¹⁷⁸ Adduct **138** has in fact been isolated as the tetramethylammonium salt and characterized by elemental analysis and NMR spectroscopy, whereas **137** has been detected *in situ*. The NMR data are reported in Table XX. ¹H-NMR chemical shifts

¹⁷⁸ P. J. Newcombe and R. K. Norris, *Aust. J. Chem.* **31**, 2463 (1978).

display the same pattern as observed when the methoxide ion is used as the nucleophile. ^{13}C -NMR data are also recorded for adduct **138** and show a strong upfield shift at the reaction site carbon, upfield shifts at adjacent and vinylogous positions, and a slight downfield shift at the remaining nonvinylogous position. Because ^{13}C data are not available with other thiophene adducts, comparison can be made with the adduct from 1,3,5-trinitrobenzene and methoxide ion and shows a similar pattern in the corresponding positions of the two systems. The final products of the reaction of 2-nitrothiophene included 2-(5-nitro-2-thienyl)propan-2-ol, 2-isopropyl-5-nitrothiophene, and 2,2-bis(5-nitro-2-thienyl)propane, depending on experimental conditions, but not 2-(1-methyl-1-nitroethyl)-5-nitrothiophene. In contrast, the ring substitution was found for $\text{X} = \text{I}$, among other products, and for $\text{X} = \text{NO}_2$, even though no adduct has been detected in either case.

3. Benzothiophene and Benzothiazole Derivatives

Both adducts **139** and **140** can be obtained by the reaction of methoxide ion in methanol with 2-methoxy-3-nitro- and 3-methoxy-2-nitrobenzothiophene, respectively.¹⁷⁹ They are isolated as the sodium salts on evaporation of the solvent. Their structure was proved by ^1H -NMR ($\text{DMSO}-d_6$), IR, and UV-visible (MeOH) spectroscopy. Both adducts show similar spectral patterns. The *gem*-dimethoxy groupings are characterized by singlets at δ 3.43 and 3.10, which are shifted upfield relative to the parent compound, and by a strong IR bands at 1080 and 1070 cm^{-1} , respectively. The electronic spectrum displays three maxima for **139** at 310, 322, and 352 nm ($\epsilon = 1.20 \times 10^4$, 1.28×10^4 , and $1.14 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$, respectively) and two maxima for **140** at 278 and 334 nm ($\epsilon = 1.24 \times 10^4$ and $7.4 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$ respectively). A most interesting feature regarding these adducts is the formation of **140** as resulting from attachment of the nucleophile at the β position of the 5-membered ring, which is unusual for thiophene derivatives: in the absence of benzoannellation, the reagent prefers to attack α positions to form such adducts as **132** and **133** (Table XIX).



¹⁷⁹ F. De Santis and F. Stegel, *Gazz. Chim. Ital.* **103**, 649 (1973).

6-Nitrobenzothiazole reacts reversibly with MeO^- in DMSO or DMSO–MeOH mixtures to yield ring-opening products. ^1H -NMR data suggest that a σ -adduct resulting from attachment of the nucleophile to the C-2 position is likely to form in a primary step of the process¹⁸⁰ (see Section III,C,1).

4. Selenophene Derivatives

A number of Meisenheimer adducts from the reaction of selenophene derivatives **141**, which are analogs of series **121**, with methoxide ion have been investigated and characterized.^{169,181} Their formation is generally even easier than that of the related sulfur compounds.

Experimental precautions are required for NMR measurements in this group because the adducts rapidly undergo ring opening. The NMR spectra of the selenophene adducts in solution are similar to those of the corresponding thiophene adducts. The ^1H -NMR data for adducts **142–145**, as obtained from dinitro and cyanonitroselenophene derivatives, are reported in Table XXI. It is of interest that, unlike 2-cyano-4-nitrothiophene, its selenophene analog is converted to the anionic σ -adduct by nucleophilic attachment at the unsubstituted C-5 position without any competition from a reaction at the CN side chain.¹⁶⁹

Decomposition to ring-opening products prevents detection of any adducts when the hydride ion is used as the nucleophile.¹⁶⁹

5. Furan Derivatives

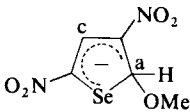
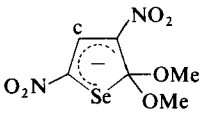
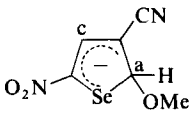
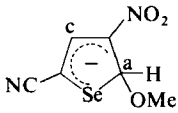
So far only a limited number of furans have been investigated.^{167,182} One reason for this is the difficult synthetic accessibility of the starting substrates. The compounds examined belong in series **146** and bear a nitro group at an α position. The structure of the adducts has been mainly studied by comparison with the spectral features of the adducts formed from the corresponding thiophene derivatives. By analogy with the ^1H -NMR spectra, the site of nucleophilic attack in the furan adducts **147–149** (Table XXII) has been assigned to the unsubstituted α position. The adducts show a marked tendency to decompose irreversibly. This fact has precluded their isolation. In particular, the adduct formed from 2,4-dinitrofuran has such a high

¹⁸⁰ G. Bartoli, F. Ciminale, and P. E. Todesco, *J.C.S. Perkin II*, 1472 (1975).

¹⁸¹ F. Terrier, A. P. Chatrousse, R. Schaal, C. Paulmier, and P. Pastour, *Tetrahedron Lett.*, 1961 (1972).

¹⁸² G. Doddi, F. Stegel, and M. T. Tanasi, *J. Org. Chem.* **43**, 4303 (1978).

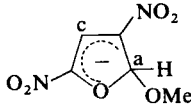
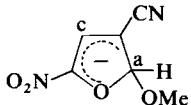
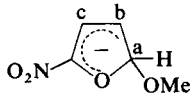
TABLE XXI
 $^1\text{H-NMR}$ FOR σ -ADDUCT FORMATION FROM SOME SELENOPHENE DERIVATIVES (REACTION WITH MeO^-)

Precursor ^a and adduct	Solvent	Chemical shift (δ)			Coupling constant (Hz)	References
		H-a	H-c	OMe		
2,4-Dinitroselenophene	DMSO- d_6	9.54	8.73	— ^b	$J_{ac} = 2.1$; $J_{\text{Se-Ha}} = 37.8$	169
 142	DMSO- d_6	6.61	8.11	3.20	$J_{ac} = 0.8$; $J_{\text{Se-Ha}} = 29.3$	169
2-Methoxy-3,5-dinitroselenophene	DMSO- d_6	—	8.64	4.40	—	181
 143	DMSO- d_6	—	8.16	3.31	—	181
4-Cyano-2-nitroselenophene	DMSO- d_6	9.48	8.70	—	$J_{ac} = 1.8$; $J_{\text{Se-Ha}} = 40.3$	169
 144	DMSO- d_6	6.45	7.55	3.19	$J_{ac} = 0.5$; $J_{\text{Se-Ha}} = 27.8$	169
2-Cyano-4-nitroselenophene	DMSO- d_6	9.63	8.82	—	$J_{ac} = 1.75$; $J_{\text{Se-Ha}} = 38.2$	169
 145	DMSO- d_6	6.69	7.55	—	$J_{ac} = 0.5$; $J_{\text{Se-Ha}} = 32.7$	169

^a Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^b — indicates data do not exist.

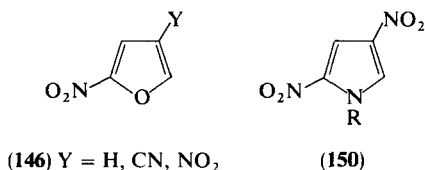
TABLE XXII
¹H-NMR FOR σ -ADDUCT FORMATION FROM SOME FURAN DERIVATIVES (REACTION WITH MeO⁻)

Precursor ^a and adduct	Solvent	Chemical shift (δ)			Coupling constant (Hz)	References
		H-a	H-b	H-c		
2,4-Dinitrofuran	CH ₃ OH(CH ₃ OD)	8.84	— ^b	7.98	$J_{ac} = 1.5$	182
 147	CH ₃ OH(CH ₃ OD)	6.35	—	7.32	$J_{ac} = 0.5$	182
4-Cyano-2-nitrofuran	CH ₃ OH(CH ₃ OD)	8.45	—	7.72	$J_{ac} = 1$	182
 148	CH ₃ OH(CH ₃ OD)	6.13	—	7.35	$J_{ac} = 0$	182
2-Nitrofuran	DMSO- <i>d</i> ₆	7.98	6.80	7.58	$J_{ab} = 2; J_{ac} = 1;$ $J_{bc} = 4$	167
	CD ₃ OD	7.64	6.65	7.32	$J_{ab} = 2; J_{ac} = 1;$ $J_{bc} = 4$	167
	DMSO- <i>d</i> ₆	6.01	5.72	6.72	$J_{ab} = 2; J_{ac} = 0;$ $J_{bc} = 6$	167
	CD ₃ OD	6.02	5.99	6.67	$J_{ab} = 2; J_{ac} = 0;$ $J_{bc} = 5$	167
 149						

^a Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^b — indicates data do not exist.

tendency to decompose as to require the NMR spectrum to be recorded at -50°C and the UV-visible spectrum by the stopped-flow technique.



Methyl 5-nitrofuroate has been reported to undergo ipso attack at the 2-position by the methoxide and benzylmercaptide ions to generate the corresponding σ -adducts.¹⁸³

6. Pyrrole Derivatives

Because pyrrole is the most highly π -electron excessive 5-membered heteroaromatic ring as compared to the S, Se, and O analogs, it is the least prone to form Meisenheimer-type adducts and to undergo nucleophilic substitution in the presence of the same activating groups. The acid nature of the hydrogen bound to the ring nitrogen and the tendency of the pyrrole ring to form a conjugate base in the presence of sufficiently strong bases makes adduct formation even more difficult to occur. Pyrrole derivatives carrying N-substituents, such as **150**, are devoid of the latter complication and are potentially more suitable substrates for adduct formation.

The first Meisenheimer-type adduct in this group has been described for the reaction of methoxide ion with 1-(4-nitrophenyl)-2,4-dinitropyrrole in DMSO.¹⁸⁴ Its suggested structure, as inferred by the ^1H -NMR spectrum, is shown by formula **151** (R = 4-nitrophenyl) (Table XXIII). Similar evidence has been obtained for R = phenyl and 3-nitrophenyl.¹⁸⁵ In the electronic spectrum, adducts **151a,b,c** (R = 4-nitrophenyl, 3-nitrophenyl, and phenyl, respectively) display a maximum in the region of 545 to 575 nm in DMSO-CH₃OH (2:1, v/v).¹⁸⁵ In contrast, for **150** (R = CH₃) the reaction with CH₃O⁻ in DMSO solution consists of a quick decomposition instead of adduct formation.¹⁸⁴ Evidence has recently been provided for the formation of adduct **152** (Table XXIII) from 2-methyl-1,4-dinitropyrrole in DMSO.¹⁸⁶

Table XXIV presents some UV-visible spectral data for some 5-membered ring σ -adducts.

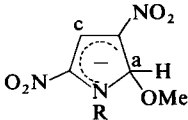
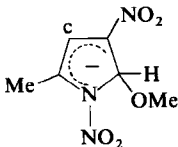
¹⁸³ T. Irie and E. Kurosawa, *J. Fac. Sci., Hokkaido Univ., Ser. III* **5**, 1 (1957).

¹⁸⁴ F. De Santis and F. Stegel, *Tetrahedron Lett.*, 1079 (1974).

¹⁸⁵ Thesis by A. Razzini (University of Rome and Centro C.N.R. Meccanismi di Reazione), unpublished work.

¹⁸⁶ Y. Kito, M. Namiki, and K. Tsuji, *Tetrahedron* **34**, 505 (1978).

TABLE XXIII
¹H-NMR DATA FOR σ -ADDUCT FORMATION FROM SOME PYRROLE DERIVATIVES (REACTION WITH MeO⁻, IN DMSO)

Adduct and precursor ^a	Chemical shift (δ)			Coupling constant (Hz)	References
	H-a	H-c	Other groups		
 151					
151a: R = 4-nitrophenyl	5.95	7.73	Ar: 8.13, 6.87	$J_{ac} \approx 0$	184
1-(4-nitrophenyl)-2,4-dinitropyrrole	8.66	8.07	Ar: 8.42, 7.93	$J_{ac} = 2$	184
151b: R = 3-nitrophenyl	5.92	H-c + Ar: 7-8		$J_{ac} \approx 0$	184
1-(3-nitrophenyl)-2,4-dinitropyrrole	8.07	8.67	Ar: 7.2-8.5	$J_{ac} = 2.3$	184
151c: R = phenyl	5.62	7.52	Ar: 6.6-7.7	$J_{ac} \approx 0$	184
1-phenyl-2,4-dinitropyrrole	8.52	7.90	Ar: 7.52	$J_{ac} = 2.3$	184
 152					
	<i>b</i>	6.93	OMe: 2.00	—	186
2-Methyl-1,4-dinitropyrrole	8.88	7.91	OMe: 2.65	$J_{ac} = 2.9$	186

^a Precursors are assigned the same letters as the corresponding ring positions of the related adducts.

^b Exchange with the solvent.

TABLE XXIV
UV-VISIBLE SPECTRAL DATA FOR SOME 5-MEMBERED RING σ -ADDUCTS
(IN METHANOL)

Precursor and adduct	$\lambda_{\max}$ (nm)	log ϵ	References
2-Methoxy-3,5-dinitrothiophene	243	3.96	16
122	343	4.02	
	312	3.87	
	530	4.36	
2,4-Dinitrothiophene	255	4.13	171
126	272		
	530	4.21	
3-Cyano-2-methoxy-5-nitrothiophene	241	3.94	173
	350	3.97	
128	258	3.89	
	402	4.28	
2-Cyano-5-methoxy-4-nitrothiophene	278	3.94	173
	313	3.72	
129	290	3.69	
	399	4.23	
4-Cyano-2-nitrothiophene	273	3.80	173
	298	3.75	
127	260	4.00	
	398	4.26	
2-Cyano-4-nitrothiophene	237		174
	262		
123	400	4.13	
2-Methoxy-3-nitrothiophene	328	3.71	170
132	340	4.13	
2-Methoxy-5-nitrothiophene	312		182
130	330	4.09	
143	530	4.32	56
2,4-Dinitroselenophene	270	4.10	174
142	530	4.20	
2-Cyano-4-nitroselenophene	245	3.86	174
	285	3.86	
145	400	4.16	
4-Cyano-2-nitroselenophene	230	4.12	174
	290	3.83	
144	400	4.18	
2,4-Dinitrofuran	218	4.03	182
	286	3.87	
147	270	3.64	
	500	4.14	
4-Cyano-2-nitrofuran	286	3.94	182
148	242	3.89	
	388	4.28	
2-Nitrofuran	304	—	182
149	318	4.09	

B. DECOMPOSITION REACTIONS OF THE ADDUCTS

There are several examples of fast decomposition reactions of the σ -adducts derived from 5-membered rings. These reactions can be viewed as resulting from effective kinetic competition of reaction paths other than return to the reactants. In all ascertained cases the products of decomposition result from ring opening, which presumably occurs subsequent to σ -adduct formation. Thus 2-nitrothiophene reacts with aliphatic secondary amines to yield bis-(4-dialkylamino-1-nitrobuta-1,3-dienyl) disulfides **156**. This compound is suggested to be the end product of a sequence originating from **153**, whose formation is not as yet established, according to Scheme 10.¹⁸⁷

In the case of the reaction of 2,4-dinitrofurane with MeO^- -MeOH, the resulting σ -adduct (see Section III,A,5) can only be detected under special conditions because of its fast decomposition to presumably ring-opened products.¹⁸² Ring opening has been ascertained for the reaction of 2-nitrofurane with MeO^- -MeOH to yield fragmentation products, monomethyl fumarate, and the corresponding aldehyde $\text{MeO}_2\text{CCH}=\text{CHCHO}$.¹⁸⁸ A σ -adduct (**149**) results¹⁶⁷ from a primary interaction between the reactants, as suggested by Irie *et al.*¹⁸⁸ (Table XXII).

C. RATES AND EQUILIBRIA

1. General Features

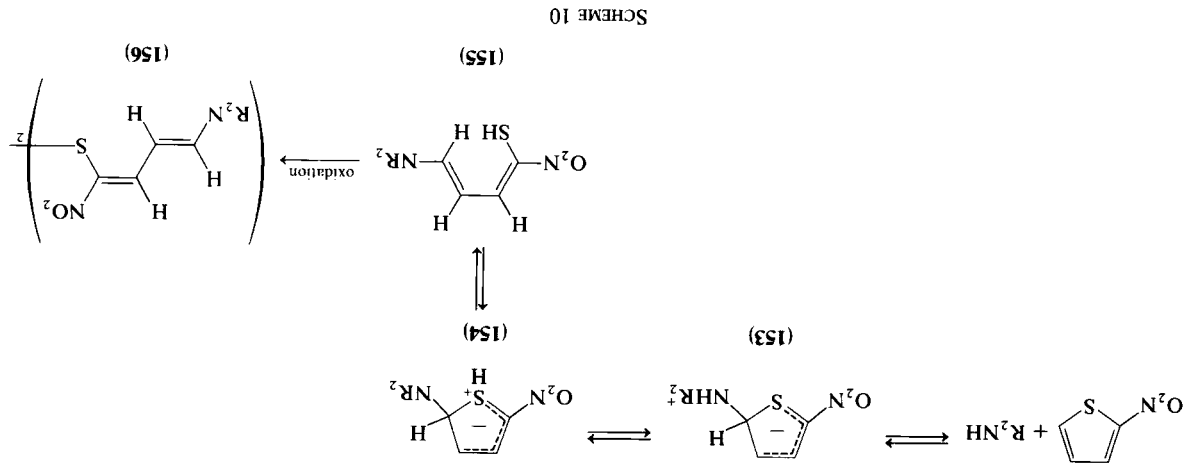
Quantitative studies for the formation of adducts from 5-membered heteroaromatic rings and methoxide ion have usually been carried out in methanolic solution and, in some cases (pyrrole derivatives), in Me_2SO -MeOH 2:1 (v/v). Data have been obtained by allowing the substrates to react with a measured excess of MeO^- and by following the increase in absorbance of the adduct. The observed pseudo first-order rate constant for the attainment of the equilibrium is found to obey the relation given in Eq. (23),

$$k_{\text{obs}} = k_f[\text{CH}_3\text{O}^-] + k_r \quad (23)$$

where k_f and k_r are the specific rates for the forward and reverse reactions, respectively, involving MeO^- as the nucleophilic reagent.

¹⁸⁷ G. Guanti, C. Dell'Erba, G. Leandri, and S. Thea, *J.C.S. Perkin I*, 2357 (1974).

¹⁸⁸ T. Irie, E. Kurosawa, and T. Hanada, *J. Fac. Sci., Hokkaido Univ., Ser. III* **5**, 6 (1957).



When very reactive substrates such as **121** and **141** ($X = \text{OMe}$, $Y = Z = \text{NO}_2$) are studied, very low reagent concentrations may be required and can be obtained by the use of buffer systems such as $\text{RCO}_2^- - \text{RCO}_2\text{H}$ and $\text{ArO}^- - \text{ArOH}$.^{55,56} Furthermore, in such cases the dilute solutions of the substrates in methanol and without any added MeO^- are found slowly to gain a coloration due to the adduct.^{55,56} A detailed kinetic analysis has been carried out by Terrier *et al.*⁵⁶ for adducts **122** and **143** in methanol solution. By use of an appropriate set of buffers, it has been possible to carry out the measurements for equilibrium and rate constant determinations in a wide spectrum of pH values in MeOH from 5.5 to 13.7.

The most general kinetic form for the observed pseudo first-order rate constant (k_{obs}) is given by Eq. (24), which involves two-term expressions for both the forward and reverse reactions,

$$k_{\text{obs}} = k_f[\text{CH}_3\text{O}^-] + k'_f + k_r + k'_r[\text{CH}_3\text{OH}_2^+] \quad (24)$$

where k'_f is the rate constant for the formation of the adduct by the reaction of the substrate with the unionized solvent and k'_r is the rate constant for the acid-catalyzed return from the adduct. The concentration of the hydrogen ion is obtained from the measured activity of the solvated proton according to the relationship $[\text{H}^+] = a_{\text{H}^+}/\gamma_{\pm}$, where $\gamma_{\pm}$ is the mean activity coefficient. The k'_f constant can be neglected at sufficiently high MeO^- concentrations; similarly, the term in k'_r disappears at $\text{pH} > 9$, when $[\text{CH}_3\text{OH}_2^+]$ becomes vanishingly small. Consequently at high pH values the expression for k_{obs} is given by Eq. (23). The activation parameters of some of the reactions have also been determined in the range of applicability of Eq. (23).^{56,174}

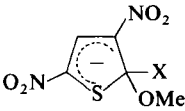
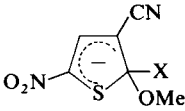
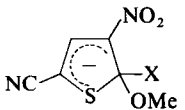
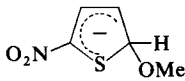
Ion-Pairing effects have been recorded occasionally in connection with the use of high alkali metal methoxide concentrations.¹⁷⁰

Equilibrium and rate constants are reported in Tables XXV and XXVI.

Data for a limited range of $\text{Me}_2\text{SO} - \text{MeOH}$ solvent mixtures (from 90:10 to 70:30, v/v) have been provided for the formation and decomposition of adduct **157**, which take place according to Scheme 11 in the course of a complex reaction of 6-nitrobenzothiazole with MeO^- .¹⁸⁹ Such data (Table XXVII) offer a typical example of the diverse response of a reacting system to the solvent, depending on the structure of the transition state or reaction product being formed. Thus while both rates of formation and equilibrium constants for the electron-delocalized anion **157** increase with increase in Me_2SO content in the solvent mixture, the corresponding data for **158** increase with increase in MeOH content. Apparently, solvation by Me_2SO is more important in the former case through dispersion interactions, whereas

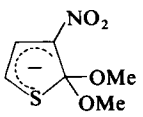
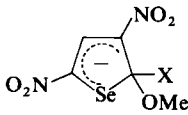
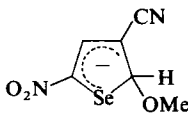
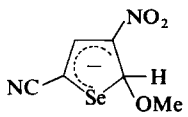
¹⁸⁹ G. Bartoli, M. Lelli, F. Ciminale, and O. Attanasi, *J.C.S. Perkin II*, 20 (1977).

TABLE XXV
RATE AND EQUILIBRIUM CONSTANTS FOR THE FORMATION OF σ -ADDUCTS BY THE REACTION OF SOME THIOPHENE AND
SELENOPHENE DERIVATIVES WITH MeO^- IN MeOH , AT 25°C

Adduct	X	$k_f (M^{-1} \text{sec}^{-1})$	$K (M^{-1})$	$k_r (\text{sec}^{-1})$	$k_{f,\text{OMe}}/k_{f,\text{H}}$	$K_{\text{OMe}}/K_{\text{H}}$	References
					2.4	$> 5 \times 10^2$	
122	OMe	40.7, 36 ^a	3.35×10^{5b}	7.8×10^{-5b}			56
126	H	15	800	1.87×10^{-2}			171
			850	1.75×10^{-2}			174
					6.2	1.7×10^2	
128	OMe	4.85	2.5×10^4	—			173
127	H	0.78	1.5×10^2	5.2×10^{-3}			172
		0.63	1.26×10^2	5×10^{-3}			174
					—	2.25×10^2	
129	OMe	2.14	1.53×10^3	—			172
123	H	2.38	6.8	0.35			174
					—	—	
130		1.8×10^{-3}	5.6	—			182

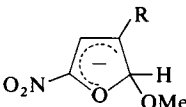
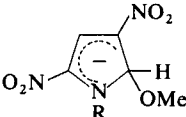
(continued)

TABLE XXV (continued)

Adduct	X	$k_f M^{-1} \text{ sec}^{-1}$	$K (M^{-1})$	$k_t \text{ sec}^{-1}$	$k_{f,\text{OMe}}/k_{f,\text{H}}$	$K_{\text{OMe}}/K_{\text{H}}$	References
 132^b		1.3×10^{-3}	6	22×10^{-4}	—	—	170
 143	OMe	$102^c, 69^b$	66.3×10^{5b}	1.04×10^{-5b}	—	—	56
142	H	27.7	5.8×10^4	4.8×10^{-4}			174
 144		1.37	1.43×10^4	9.55×10^{-5}	—	—	174
 145		2.62	490	5.4×10^{-3}	—	—	174

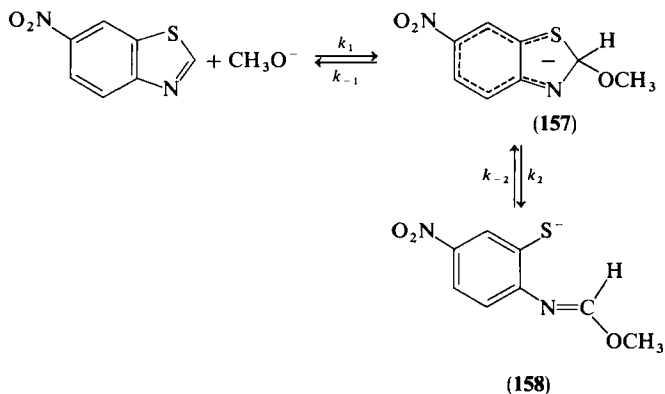
^a Reference 55.^b Data at 20°C.^c Reference 174.

TABLE XXVI
RATE AND EQUILIBRIUM CONSTANTS FOR THE FORMATION OF σ -ADDUCTS BY THE REACTION
OF SOME FURAN AND PYRROLE DERIVATIVES WITH MeO^- AT 25°C

Adduct	R	$k_f (M^{-1} \text{ sec}^{-1})$	$K (M^{-1})$	References
	149^a :H	1.37×10^{-2}	140	182
	148^a :CN	57	1.8×10^{-5}	182
	147^a :NO ₂	4.5×10^3	$\geq 5 \times 10^5$	182
	4-NO ₂ C ₆ H ₄ ^b	900	$> 2 \times 10^4$	185
	3-NO ₂ C ₆ H ₄ ^b	460	7.7×10^3	185
	C ₆ H ₅ ^b	94	1.3×10^2	185
151				

^a In MeOH.

^b In DMSO-MeOH 2:1 (v/v).



SCHEME 11

TABLE XXVII
SOLVENT EFFECTS ON THE RATES OF FORMATION AND DECOMPOSITION OF ADDUCT **157** FROM THE
REACTION OF 6-NITROBENZOTHAZOLE WITH MeO^- IN DMSO-MeOH MIXTURES,
AT 25°C (SCHEME 11)^a

DMSO-MeOH (v/v)	$k_1 (M^{-1} \text{ sec}^{-1})$	$k_{-1} (\text{sec}^{-1})$	$K_1 (M^{-1})$	$k_2 (\text{sec}^{-1})$	$k_{-2} (\text{sec}^{-1})$	K_2
90:10	136	1.13	120	1.8×10^{-2}	6.1×10^{-3}	3.0
80:20	48	4.1	11.7	4.9×10^{-2}	3.7×10^{-3}	13
70:30	30	11	2.8	12.7×10^{-2}	3.3×10^{-3}	38

^a Reference 189.

solvation by MeOH is stronger when the negative charge is concentrated on the sulfur atom, as in the latter case, because of H-bonding interactions.⁸³

2. Role of the Heteroatom

All of the available data consistently point to a general order of the influence of the heteroatom on the stability of the adducts as well as ease of formation. Both the equilibrium and the rate constants for the reactions of furan, thiophene, selenophene, and pyrrole derivatives with the methoxide ion provide the following common sequence:



This order is derived from comparisons within sets of three^{171,172,174,182} or two^{56,174,182} substrates under comparable conditions (Tables XXV and XXVI). Pyrrole derivatives form adducts so much more slowly than the other substrates that the related data (Table XXVI) could not be obtained in methanol but only in mixed, faster solvents (DMSO–MeOH).¹⁸⁵

The observed order clearly contradicts the results of recent calculations of hydride ion affinity as carried out by the MINDO/3 method, indicating thiophene to be more reactive than furan.¹⁹⁰

Among the factors responsible for the effect of the heteroatom are the aromaticity of the starting substrate and the electronegativity of the heteroatom Z. The less the aromatic character of the ring the less is the free energy change involved in going from initial state to adduct (or transition state). A greater electronegativity increases the polarization of the C—Z bond and is expected to exert a stabilizing effect on the adduct (or the transition state) by favoring the interaction with the nucleophile. This would explain why the tendency to form σ -adducts is so much greater for the derivatives of furan, which is the least aromatic and contains the most electronegative heteroatom, than for pyrrole derivatives and the other congeners. A third factor is the use of the *d* orbitals in the expansion of the octet of sulfur and selenium, which facilitates accommodation of the negative charge in the adduct and contributes toward rendering the thiophene and selenophene derivatives more reactive than pyrrole derivatives.

The comparison between thiophene and selenophene compounds has received close attention in detailed quantitative work by Terrier *et al.*^{56,174} As shown in Table XXV, when the reagent attacks a CH position, the equilibrium constants for the formation of the selenophene adducts **142**, **144**, and **145** are about two orders of magnitude greater than those of the

¹⁹⁰ A. F. Pronin, J. Kovac, R. Kada, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, 1598 (1979).

similarly substituted thiophene adducts **126**, **127**, and **123**. The stability differences are somewhat greater than that observed between the geminal dimethoxy adducts **122** and **143**. The greater stability of the selenophene adducts is derived mainly from lower reverse rates, whereas differences in the forward rates of thiophene and selenophene adducts are only slight.

The reactions of the thiophene derivatives in both forward and reverse directions are characterized by lower enthalpies and entropies of activation than the reactions of the selenophene analogs. In the forward reactions, enthalpy and entropy changes compensate nearly exactly and result in slightly greater rates of adduct formation for the selenophene derivatives despite the higher enthalpies of activation. The higher entropies of activation for the selenophene derivatives have been attributed to less solvated transition states as compared to the reactions of the thiophene analogs (Table XXVIII).

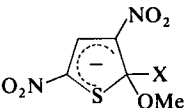
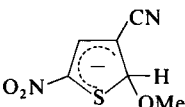
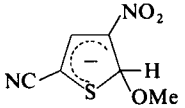
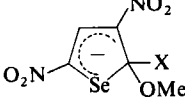
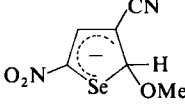
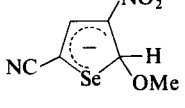
3. *Substituent Effects at Positions Other than the Reaction Center*

a. *Cyano and Nitro Groups.* Only a few substituents have been examined for equilibrium and kinetic effects with 5-membered adducts. They include H, NO₂, and CN. As illustrated by the data for adducts **126**, **127**, and **130** (Table XXV), the replacement of Y = NO₂ (**126**) by a less electron-withdrawing group (CN, H) leads to a decrease in the equilibrium constant, the effect being particularly strong for Y = H (**130**)¹⁸² where, in fact, only one electron-withdrawing substituent is present. These effects are analogous to those observed in 6-membered adducts⁶ and are, of course, related to a decreased capacity of the molecule to accommodate and delocalize a negative charge.

The stabilizing effect of an electron-withdrawing substituent also depends on the position of the substituent relative to the reaction center at position 2 of the substrate. Adjacent position 3 and its vinylog, position 5, are called ortho- and para-like, respectively. A 5-substituent is found to be more effective than a 3-substituent in accommodating a negative charge in the adduct. Thus the replacement of a nitro group by a cyano group leads to a stronger destabilizing effect at position 5 than at position 3 as shown by comparing the data for **122**, **128**, and **129** with the data for **126**, **127**, and **123** (Table XXV). These data also show that similar substituent effects are observed not only for CH adducts but also for geminal dimethoxy adducts. Also, selenophene adducts behave in a similar manner (compare **142**, **144**, and **145**).

A less uniform behavior is noted in the reaction rates. Thus, whereas in the formation of *gem*-dimethoxy adducts (compare **122**, **128**, and **129**), the

TABLE XXVIII
 ENTHALPY AND ENTROPY DATA FOR THE FORMATION OF σ -ADDUCTS BY THE REACTION OF
 SOME THIOPHENE AND SELENOPHENE DERIVATIVES WITH MeO^- IN MeOH , AT $25^\circ\text{C}^{a,b}$

	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta H^\ddagger$	$\Delta S^\ddagger$	ΔH°	ΔS°	ΔG°
							
122: X = OMe	41.4 ^c	74.5 ^c	—	—	—	—	—
126: X = H	51.9	-48.5	46.4	-122.2	5.4	74.1	-16.7
							
127	59.0	-51.5	71	-51.0	-12.1	-0.4	-12.1
							
123	66.5	-14.6	53.6	-74.1	13.0	59.4	-4.6
							
143: X = OMe	51.0 ^c	35.1 ^c	—	—	—	—	—
142: X = H	59.0	-19.7	79.5	-42	-20.5	22.2	-27.2
							
144	70.7	-3.3	95.8	0.6	-25.5	-4.2	-24.3
							
145	66.5	-16.0	81.2	-16.3	-15.1	0	-15.1

^a Enthalpy and entropy values in kJ mol^{-1} and $\text{J mol}^{-1} \text{K}^{-1}$, respectively.

^b Data from Reference 174, unless stated otherwise.

^c Data from Reference 56.

replacement of NO_2 by CN has a greater effect on k_f at the para- than at the ortho-like position, just as is generally observed with the equilibrium constants, in the formation of CH adducts (compare **126**, **127**, and **123**) an inversion is observed. A similar inverted trend in rates is found for the selenophene analogs (**142**, **144**, and **145**). The effects are rather modest; for example, in the thiophene series the replacement of NO_2 by CN causes a decrease in rate by a factor of 20 in the ortho-like position and 6.2 in the para-like position. Peculiar effects of this kind have been noted in the piperidinobromination of 3,5-disubstituted 2-bromothiophenes, with a hint of adduct formation being the rate-determining step.^{191,192} The inversions have been interpreted in terms of reduced steric requirements of the parent substrates and of bond-fixation effects in 5-membered aromatics.¹⁷⁴ However, a firm interpretation can hardly be obtained because relatively slight rate differences appear to result from nonuniform changes in enthalpy and entropy of activation in the two groups of data related to thiophene and selenophene compounds. In particular, replacement of NO_2 by CN gives rise to a greater increase in $\Delta H^\ddagger$ at the 5-position in the thiophene adduct **123** and at the 3-position in the selenophene adduct **144**. An interesting regularity, which is observed in both groups of adducts, is that the reverse slope k_r is lowest for adducts **127** and **144** and the related enthalpies and entropies of activation are largest. This is consistent with the steric interpretation because adducts **127** and **144** would be least assisted by steric relief in the $\text{C}-\text{OMe}$ bond-breaking process.

A satisfactory linear free-energy correlation is observed for the rates of adduct formation between 4-substituted 2-nitrothiophenes and 4-substituted 2-nitrofurans despite the fact that the varying substituent (H , CN , NO_2) is adjacent to the site of reaction.¹⁸² This indicates less serious steric interactions between vicinal positions in 5-membered rings than in benzenoid rings in view of the different geometry of the substrates. The slope of the $\log k_{\text{furan}}$ versus $\log k_{\text{thiophene}}$ plot is 1.4. The higher selectivity of the furans as the more reactive series may be surprising. However, a similar situation arises for furans and thiophenes in connection with the electrophilic trifluoroacetylation reaction and has been attributed to differences in aromatic character between the two ring systems.^{193,194}

b. *Fused-Ring Systems.* The equilibrium and rate data for adducts **139** and **140**, as obtained from 2-methoxy-3-nitro- and 3-methoxy-2-nitro-benzothiophene,¹⁷⁹ respectively, are reported in Table XXIX. The effect of

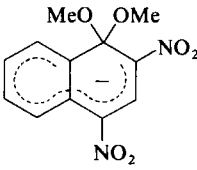
¹⁹¹ D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *J.C.S. Perkin II*, 620 (1975).

¹⁹² D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *J.C.S. Perkin II*, 989 (1975).

¹⁹³ S. Clementi and G. Marino, *J.C.S. Chem. Commun.*, 1642 (1970).

¹⁹⁴ G. Marino, *Adv. Heterocycl. Chem.* **13**, 235 (1971).

TABLE XXIX
COMPARISON OF RATE AND EQUILIBRIUM DATA FOR THE FORMATION OF SOME
 σ -ADDUCTS FROM BENZOTHIOPHENE, THIOPHENE, AND NAPHTHALENE DERIVATIVES
(REACTION WITH MeO^- IN MeOH , AT 25°C)

Adduct	$k_f (M^{-1} \text{sec}^{-1})$	$K (M^{-1})$	$k_r (\text{sec}^{-1})$	References
139	2.2×10^{-1}	370	5.8×10^{-4}	179
140	4.7×10^{-2}	600	7.5×10^{-5}	179
132	1.3×10^{-3}	6	2.2×10^{-4}	170
 159	0.88	220	4×10^{-3}	195

annulation of a benzenoid ring can be illustrated in the case of **139** by comparison with the data for **132**. Both equilibrium and rate constants for adduct formation show substantial increases by factors of about 50 and 100, respectively. These effects are of the same order as those long known for nucleophilic heteroaromatic substitution.¹

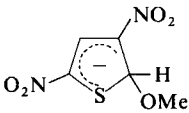
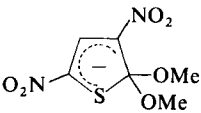
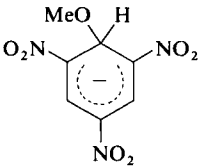
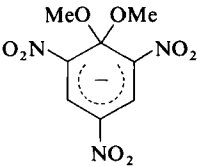
It is also of interest that the equilibrium constants for **139** and **140** are greater than that for adduct **159** derived from 1-methoxy-2,4-dinitronaphthalene,¹⁹⁵ showing that the stabilizing ability of a nitrothiacyclopentadienide moiety is no less than that of the dinitrocyclohexadienide moiety. However, because the benzothiophene and the naphthalene systems are not simply related structurally, it is not surprising that the rates of formation are not correlated with the equilibrium constants. However, this phenomenon has also been noted when comparing adducts from monocyclic thiophene and benzene systems (Table XXX)¹⁷¹ and, even, when comparing adducts **139** and **140**, the more stable **140** being formed more slowly.

There is some kinetic and thermodynamic evidence for the formation of a σ -adduct as a nonproductive transient species in the course of the methoxydechlorination of 6-chloro-3-methyl-7-nitroanthranil.¹⁹⁶ Rate and equilibrium constants have been determined.

¹⁹⁵ J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.* **33**, 977 (1968).

¹⁹⁶ L. Di Nunno and S. Florio, *Gazz. Chim. Ital.* **108**, 607 (1978).

TABLE XXX
COMPARISON OF 5-MEMBERED WITH 6-MEMBERED RING σ -ADDUCTS^a

		
	126	122
k_f ($M^{-1} \text{ sec}^{-1}$)	15	40.7
K (M^{-1})	800	6.62×10^{5b}
		
	23	8
k_f ($M^{-1} \text{ sec}^{-1}$)	5250	17.3
K (M^{-1})	22.6	1.7×10^4

^a References for the cited compounds are given in parentheses: **126** (173), **122** (56), **23** (68), and **8** (65).

^b At 20°C.

c. *N*-Substituents in the Pyrrole System. The effects of some *N*-substituents have been investigated for the reaction of MeO^- in the pyrrole series to yield adducts **151** ($R = \text{phenyl, 3-, and 4-nitrophenyl}$)¹⁸⁵ (Table XXVI). Although the rate constants for adduct formation are less spaced than the equilibrium constants, they change in the same order as a function of the NR group, the 4-nitrophenyl group favoring adduct formation better than the other groups. The factors involved are about 10 and 250 for the latter groups relative to phenyl.

4. Effects of Ipso Substituents

Usually Meisenheimer-type adducts form by nucleophilic attack on ring carbons bearing either a hydrogen atom or a methoxy group. There are sufficient equilibrium and rate data concerning thiophene and selenophene substrates to draw some general conclusions. In reference to general Eq. (22), for $X = \text{MeO}$ the equilibrium constant for the formation of the adduct is found to be substantially higher than that for $X = \text{H}$. The related

ratio, $K_{\text{MeO}}/K_{\text{H}}$, is 10^2 or greater for dinitro- and cyanonitro-substituted thiophenes.¹⁷¹⁻¹⁷³ A similar ratio is observed in the selenophene series.¹⁷⁴ Although the rate constants exhibit the same trend, the k_{MeO} values are greater than the k_{H} values only by small factors. Specific examples are reported in Table XXV.

5. *Meisenheimer-Type Adducts from 5- and 6-Membered Rings: A Comparison Concerning Stability and Rate of Formation for the Reaction with MeO⁻*

We wish to conclude Section III with a comparison of the equilibrium and rate features of the 5-membered and 6-membered ring adducts (see Section II,B,5,c).

We shall focus our attention on the formation of the typical adducts **126**, **122**, **23**, and **8**, as obtained from 2-X-3,5-dinitrothiophenes and 1-X-2,4,6-trinitrobenzenes (X = H, OMe). The essential data are assembled in Table XXX. At first glance, the most striking feature concerning these adducts is that, despite the different structures of the thiophene and benzene systems, (a) adducts **122** and **8** display the highest stabilities and form at only slightly different rates, and (b) the stabilities of the adducts decrease by similar factors on going from **122** to **126** and from **8** to **23**. In contrast, a major difference is the fact that the rate of formation of **122** is slightly higher than that of **126**, whereas that of **8** is much lower than that of **23**.

The similarities in behavior have been noted elsewhere¹⁷³ but should be considered with caution. Differences are likely to result from changes in free-energy levels of the initial state, transition state, and final product (σ -adduct). Obviously, the adduct stability will depend on the initial and final energy levels. It is possible that the energy content of the thiophene system is higher than that of 2,4,6-trinitroanisole. Furthermore, the C-2—C-1—C-6 angle in trinitroanisole is almost 120° , whereas the S—C-2—C-3 angle of the thiophene derivative should be near 111.5° . When the C-1 atom in the former forms a new bond by attachment with methoxide ion, the C-2—C-1—C-6 angle in the adduct is forced to a value close to that of a tetrahedral carbon atom (109.5°), and therefore a certain amount of strain affects the 6-membered ring. In the thiophene adduct, a tetrahedral value can also be expected for the S—C-2—C-3 angle, but this is much closer to that of the original substrate.⁵⁵ The ability to accommodate the negative charge of the reagent is also hard to compare in the two systems. The presence of only two nitro groups, rather than three, in the 5-membered ring is probably offset at least in part by the ability of the S atom to utilize the *d* orbitals. Finally, the different geometry of the 5-membered ring system relative to the 6-membered

ring system is such so as to reduce the steric factors probably involved in the latter.¹⁷³ Therefore, nearly all factors (*i-v*), as listed in Section II,B,5,c, contributing to the stability and/or ease of formation of the σ -adducts will be affected on going over to the 5-membered system.

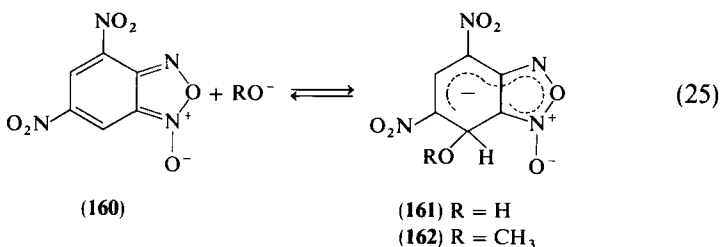
IV. Benzofurazans and Benzofuroxans

A. FORMATION AND STRUCTURE OF THE ADDUCTS

1. General Remarks

Benzofurazans and benzofuroxans have been included in this chapter because of their heteroaromatic character as 10π -electron ring systems. However, their interactions with nucleophilic reagents seem to be exclusively confined to attachment of the nucleophilic atom to the carbon atoms of the 6-membered ring away from the fused 5-membered heterocyclic moiety, which exerts a strong electron-withdrawing influence.

Although the tendency of benzofuroxan derivatives to interact with electron donors has been known since Drost's early report¹⁹⁷⁻¹⁹⁹ firm experimental evidence on the formation of Meisenheimer adducts was not reported until the 60s for the reaction of 4,6-dinitrobenzofuroxan with RO^- nucleophiles²⁰⁰⁻²⁰² (Eq. 25). Information on benzofurazans became available even later with an NMR study by Terrier, Simonnin, and their co-workers.²⁰³



The ^1H -NMR data for most σ -adducts and their precursors dealt with in this Section are reported in Table XXXI.

¹⁹⁷ P. Drost, *Justus Liebigs Ann. Chem.* **307**, 49 (1899).

¹⁹⁸ C. L. Jackson and R. B. Earle, *Am. Chem. J.* **29**, 89 (1903).

¹⁹⁹ R. J. Gaughran, J. P. Picard, and J. V. R. Kaufman, *J. Am. Chem. Soc.* **76**, 2233 (1954).

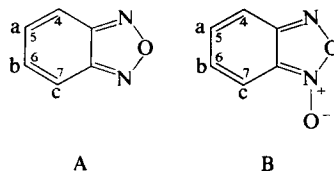
²⁰⁰ A. J. Boulton and D. P. Clifford, *J. Chem. Soc.*, 5414 (1965).

²⁰¹ N. E. Brown and R. T. Keyes, *J. Org. Chem.* **30**, 2452 (1965).

²⁰² W. P. Norris and J. Osmundsen, *J. Org. Chem.* **30**, 2407 (1965).

²⁰³ F. Terrier, F. Millot, A. P. Chatrousse, M. J. Pouet, and M. P. Simonnin, *Org. Magn. Reson.* **8**, 56 (1976).

TABLE XXXI
¹H-NMR DATA FOR σ-ADDUCTS FROM SOME BENZOFURAZAN (A) AND BENZOFUROXAN (B) DERIVATIVES (REACTION WITH RO⁻ IONS)



Precursor and adduct	Solvent	Chemical shifts (δ) and coupling constants (Hz)							References
		H-a	H-b	H-c	J_{ab}	J_{ac}	J_{bc}	MeO	
A. Benzofurazan Derivatives									
4-Nitro	DMSO- d_6	8.70	7.88	8.60	7	0.7	9		203
163	DMSO- d_6	7.16	5.13	5.33	10	−1	4		203
164	DMSO- d_6 -MeOD	5.50	6.53	7.02	5	—	10		203
4-Nitro-7-chloro	CD ₃ OD	8.58	7.82		8				207
168	CD ₃ OD	5.60	6.60		6				207
4-Nitro-7-methoxy	DMSO- d_6	8.73	7.07		8			4.22	207
167	DMSO- d_6 -MeOD	7.32	5.32		11			3.28	207

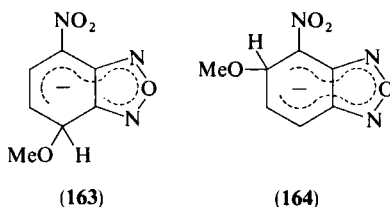
B. Benzofuroxan Derivatives

4-Nitro	DMSO- <i>d</i> ₆	8.62	7.55	8.12	7	1	9	203
173	DMSO- <i>d</i> ₆ -MeOD	7.14	5.34	5.24	10	-1	4	203
174	DMSO- <i>d</i> ₆ -MeOD	5.47	6.38	6.65	5	—	10	203
4-Nitro-7-methoxy	DMSO- <i>d</i> ₆	8.61	6.81		8		4.13	216
177	DMSO- <i>d</i> ₆ -CD ₃ OD	7.35	5.12		11		3.12	216
178	DMSO- <i>d</i> ₆ -CD ₃ OD	5.48	5.48		—		3.68	216
4,6-Dinitro	CD ₃ OD(?)	9.12		—		—		33
	CH ₂ Cl ₂	8.77		9.04				201
161 (RO ⁻ = OH ⁻)	DMSO	8.73 ^a		5.94 ^a		—		200
162 (RO ⁻ = OMe ⁻)	CD ₃ OD(?)	8.67		—		—		33
	MeOH	8.97 ^a		6.02 ^a		—	3.37	200
	CH ₂ Cl ₂	8.57		6.02		—		201
4,6-Dinitro-7-methoxy	CD ₃ OD	8.80					4.23 ^b	33
182	CD ₃ OD	9.03					3.10 ^b	33

^a Tentative assignments.^b In CD₃OD-CD₃CN (6:94 v/v).

2. Mononitrobenzofurazans

Adduct **163** arising from CH_3O^- ion attachment to the 7-position of 4-nitrobenzofurazan can be isolated as the potassium salt after adding one equivalent of CH_3OK to a methanolic solution of the substrate.²⁰³ The ^1H -NMR analysis of $\text{DMSO}-d_6$ - CH_3OD mixtures shows the signals of an ABX system that is unambiguously interpreted with the aid of double-resonance experiments. It is noteworthy that on increasing the concentration of methanol, H-6 undergoes a downfield shift apparently due to increased specific solvation of the anionic part of the σ -adduct, whereas the position of the H-7 signal remains almost unchanged. Structure **163** is also confirmed by ^{13}C -NMR spectroscopy.



A second adduct (**164**) can be detected in 7:3 v/v $\text{DMSO}-d_6$ - CH_3OD at -20°C . Under these conditions the spectrum displays a stable AMX pattern consistent with CH_3O^- ion attachment to the 5-position. On increasing the temperature the spectrum changes and shows new signals. Adduct **163** appears to be more stable than **164**.

Structural assignments of the species formed by the reaction of the methoxide ion with 4-nitrobenzofurazan benefited from the analogous behavior of 4-nitrobenzofuroxan.^{203,204}

Some evidence for adduct formation from 4-nitrobenzofurazan with OH^- , CH_3O^- , and PhS^- as nucleophilic reagents was reported by Ghosh and Whitehouse.²⁰⁵ Both 4- and 5-nitrofurazans in neutral to mildly alkaline aqueous solutions undergo UV-visible spectral changes, which were attributed to OH^- attachment to a ring carbon of the 6-membered ring.²⁰⁵

The 5- and 7-methoxy derivatives of 4-nitrobenzofurazan and 4-methoxy-5-nitrobenzofurazan all react smoothly with sodium methoxide to form the corresponding adducts **165**, **166**, and **167**,^{206,207} which reverted to

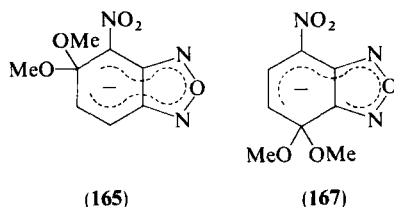
²⁰⁴ R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. G. Paterson, *J. Chem. Soc.*, 197 (1963).

²⁰⁵ P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.* **11**, 305 (1971).

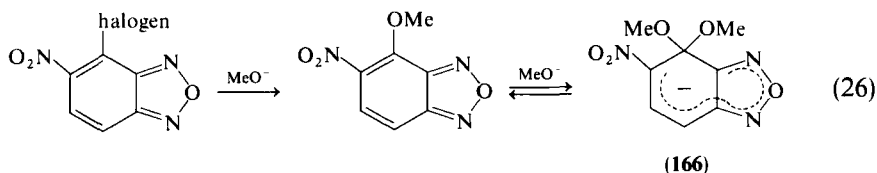
²⁰⁶ D. Dal Monte, E. Sandri, and P. Mazzaracchio, *Boll. Sci. Fac. Chim. Ind. Univ. Bologna* **26**, 165 (1965).

²⁰⁷ D. Dal Monte, E. Sandri, L. Di Nunno, S. Florio, and P. E. Todesco, *Chim. Ind. (Milan)* **53**, 940 (1971).

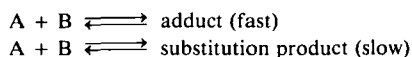
the starting reactants when dissolved in methanol and/or treated with acids. Conclusive structural proofs were subsequently obtained via $^1\text{H-NMR}$ by Dal Monte *et al.*²⁰⁸ and by Boulton and Kirby.²⁰⁹



Adducts **165**–**167** are also obtained from halogenonitrobenzofurazans by consumption of two equivalents of methoxide ion.^{206,208} When a 4-halogeno-5-nitrobenzofurazan was treated with one equivalent of methoxide ion, the transient formation of **166**, as shown by NMR spectroscopy, suggested that the addition of the second methoxide ion is much faster than the halogen replacement by the first one and that eventually the equilibrium shown in Eq. (26) is completely reverted to the more stable 4-methoxy-5-nitro derivative.²⁰⁸



Kinetic studies of 4-nitro-7-halogenobenzofurazans²⁰⁷ have shown that the reaction with the methoxide ion is of the following type:

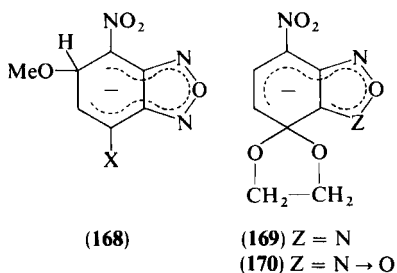


The transient adduct is shown to possess structure **168** ($\text{X} = \text{halogen}$) by NMR spectroscopy; the H-5 and H-6 assignments could be definitely established by comparison with the adduct obtained from 4-nitro-5-deutero-7-chlorobenzofurazan. Thus the detected adduct is not an intermediate but rather a nonproductive, reversibly formed side product. When only one equivalent of reagent is used, such an adduct is quickly formed extensively, but the original reactants present at the initial equilibrium will eventually be converted to 4-nitro-7-methoxybenzofurazan. This in turn reacts rapidly to yield the dimethoxy adduct **167**, which finally is reverted completely to the

²⁰⁸ D. Dal Monte, E. Sandri, L. Di Nunno, S. Florio, and P. E. Todesco, *J. Chem. Soc. B*, 2209 (1971).

²⁰⁹ J. J. K. Boulton and P. Kirby, *J.C.S. Chem. Commun.*, 1618 (1970).

substitution product when all the methoxide ion is consumed. With an excess of methoxide ion adduct **167** will appear to be the final product.



The methoxide ion has also been found to attack position 5 of 4-nitro-7-methylbenzofurazan to give adduct **168** (X = Me). By analogy with the kinetic behavior a similar reaction has been assumed for other members of the series (7-X = OMe, SMe, SPh, SO₂Ph).²¹⁰ Further evidence for the formation of 5-adducts in this series had been provided by a preliminary, nonproductive step of the base hydrolysis of a 4-nitro-7-aryloxybenzofurazan derived from lysozyme.²¹¹

By addition of one equivalent of base to solutions of 7-(2-hydroxyethoxy)-4-nitrobenzofurazan and 7-(2-hydroxyethoxy)-4-nitrobenzofuroxan in either water or a dipolar aprotic solvent, the spiro adducts **169** and **170** are completely formed²¹² and can be characterized by their UV-visible and ¹H-NMR spectra. They display substantial upfield chemical shifts relative to the ring signals for the starting substrate and a complex multiplet centered at δ 4.16 for the nonequivalent dioxolane methylene protons. Isolation of the adducts as the potassium salts from acetonitrile solution was accomplished by removal of the solvent.

3. Mononitro-2,1,3-benzothiadiazoles

The mononitro-2,1,3-benzothiadiazoles are the sulfur analogs of the similarly substituted benzofurazans. They display less tendency to form σ-adducts than benzofurazans as indicated by indirect evidence based on stopped-flow kinetic experiments.²¹³

The reaction of 4-nitro-2,1,3-benzothiadiazole with methoxide ion leads to 2,1,3-benzothiadiazole-4,7-dione monoxime as the final product.

²¹⁰ L. Di Nunno, S. Florio, and P. E. Todesco, *J.C.S. Perkin II*, 1469 (1975).

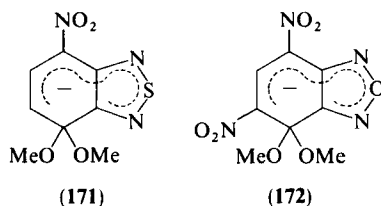
²¹¹ R. H. Sigg, P. L. Luisi, and A. A. Aboderin, *J. Biol. Chem.* **252**, 2507 (1977).

²¹² G. Ah-Kow, F. Terrier, and F. Lessard, *J. Org. Chem.* **43**, 3578 (1978).

²¹³ L. Di Nunno and S. Florio, *Tetrahedron* **33**, 855 (1977).

Transient species have been detected and assumed to consist of σ -adducts resulting from attack of the reagent at the 5- and 7-positions of the starting substrate as well as of the related nitroso compound that is formed as an intermediate.

The 7-halogeno-4-nitro derivatives undergo regular substitution, but their primary interaction with the reagent is attributed to 5-adduct formation, whereas the 7-methoxy-4-nitro derivative is probably attacked at C-7 to yield **171**. The stabilities of these adducts are found to be lower than those of their benzofurazan analogs by factors ranging from about 10^2 to 10^3 . This effect has been attributed to the higher aromatic stability and to the lower electron-withdrawing power of the fused heterocyclic ring of the benzothiadiazoles and resembles the trend shown by furan and thiophene in adduct formation (see Section III,C,2).



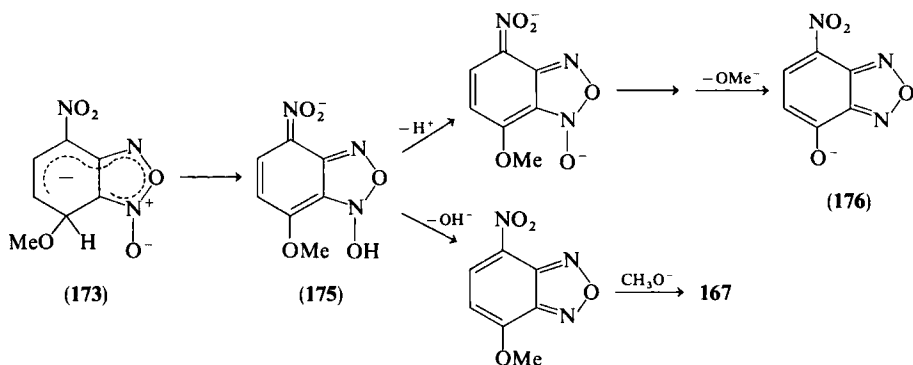
4. 4,6-Dinitro-7-methoxybenzofurazan

The crystal structure of the potassium salt of adduct **172** has been worked out by X-ray diffractometry.^{26,214} The electronic structure of the 6-membered ring of the adduct is markedly perturbed by the substituents and particularly by the furazan ring whose stronger electron-withdrawing power, relative to the nitro groups, is held to be responsible for major changes in the C—C bond distances. The NO₂ group at the C-4 position is better conjugated with the ring than the NO₂ group at C-6, which is adjacent to the geminally substituted *sp*³ carbon C-7 and is twisted by 11° with respect to the 6-membered ring plane due to steric hindrance.

5. 4-Nitrobenzofuroxans

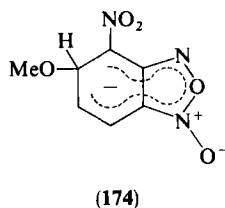
Terrier *et al.*²⁰³ have investigated the reaction of 4-nitrobenzofuroxan with MeOK in several MeOD-DMSO-*d*₆ mixtures. At 20°C in 3:7 (v/v) MeOD-DMSO-*d*₆, only one adduct (**173**) is formed, by attachment to position 7, which is characterized by an ABX pattern. With 7:3 (v/v)

²¹⁴ G. G. Messmer and G. J. Palenik, *J.C.S. Chem. Commun.*, 470 (1969).



SCHEME 12

MeOD-DMSO- d_6 at -20°C , the formation of adduct **173** is accompanied by that of the isomeric **174**, which displays an AMX pattern. The NMR spectral assignments are supported by a comparison with the NMR data of adducts **163** and **164** as formed from 4-nitrobenzofurazan. Adduct **174** is shown to form under kinetic control, and is converted later to the more stable adduct **173**.



Buncel *et al.*²¹⁵ found that at a higher temperature, or in the presence of an excess of nucleophile, subsequent transformation of **173** irreversibly leads to new products (Scheme 12). A proton transfer occurs first from the sp^3 carbon atom to the N -oxide group. The resulting intermediate **175** changes by two routes, leading to **176**, presumably by an intramolecular shift of the oxide substituent similar to a Smiles rearrangement, and to anion **167** by loss of OH^- and subsequent MeO^- attachment.

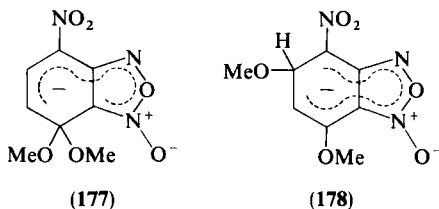
Buncel *et al.*²¹⁶ have found that 4-nitro-7-methoxybenzofuroxan reacts with methoxide ion, in 8:2 (v/v) DMSO- d_6 -MeOD and at room temperature, and undergoes attack at position 7, yielding adduct **177**. The latter can be isolated as the sodium salt from acetonitrile and characterized by IR absorp-

²¹⁵ E. Buncel, N. Chuaqui-Offermanns, B. K. Hunter, and A. R. Norris, *Can. J. Chem.* **55**, 2852 (1977).

²¹⁶ E. Buncel, N. Chuaqui-Offermanns, and A. R. Norris, *J.C.S. Perkin I*, 415 (1977).

tion at 1470 and 1250 cm^{-1} (asymmetric and symmetric stretching, respectively, of the NO_2) and by NMR.

At lower temperature (-15°C) and in 7:3 (v/v) $\text{DMSO}-d_6$ -MeOD, evidence is obtained for the primary formation of the isomeric adduct **178**, resulting from attack at position 5. Adduct **178** shows a signal at δ 5.48, which gradually decreases and finally disappears as the intensity of the spectrum of **177** increases.



In the $\text{DMSO}-d_6$ -MeOH solution the H-5 and H-6 signals fortuitously display the same chemical shift, whereas in CDCl_3 solution they are detected as two doublets, with a normal coupling constant ($J = 5$ Hz).

The observed reaction pattern for 4-nitro-7-methoxybenzofuroxan shows that the attack of the reagent on position 5 occurs under kinetic control, whereas the conversion of the *gem*-dimethoxy adduct **177** is favored by its greater thermodynamic stability.

6. 4,6-Dinitrobenzofuroxan

The very strong tendency of 4,6-dinitrobenzofuroxan (**160**) to react with nucleophiles has long been known. As early as 1899 Drost found that **160** reacts reversibly with aqueous alkalis to yield explosive salts.¹⁹⁷

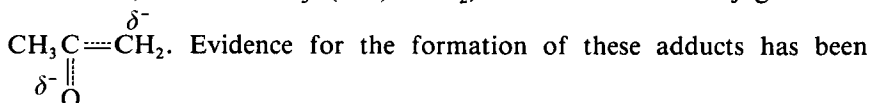
Adduct formation with OH^- occurs under very mild conditions (bicarbonate solution), and a solution of **160** in water displays the UV-visible spectrum of the adduct, indicating extensive conversion of the starting compound.²⁰²

The nature of the interaction of **160** with nucleophiles was not established until recently. 4,6-Dinitrobenzofuroxan was first believed to form a carbanion by ring proton abstraction.^{197,199} Jackson and Earle¹⁹⁸ suggested the formation of compounds analogous to those obtained from trinitrobenzene derivatives, but the first evidence regarding the exact nature of the interaction came independently from three groups through ^1H -NMR and IR studies. With the aid of D-H exchange experiments it was possible to rule out the proton abstraction hypothesis and to support σ -adduct formation for the reaction of **160** with the hydroxide ion.²⁰⁰⁻²⁰²

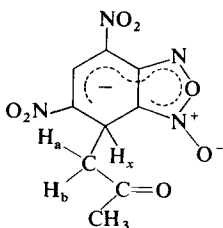
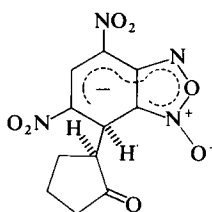
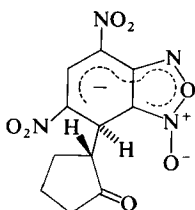
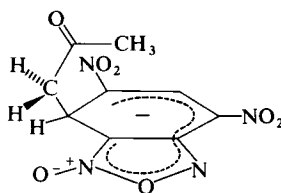
The NMR spectrum of the adduct displays a singlet at δ 8.73 and an AB system (δ 5.94 and 6.26, $J = 7.5$ Hz) that is ascribed to a tetrahedral CHOH

²¹⁷ M. J. Strauss, A. DeFusco, and F. Terrier, *Tetrahedron Lett.*, 1945 (1981).

(**182**, **183**, and **184**) in the absence of bases other than the solvent itself.²¹⁸ The reaction is carried out in Me_2SO , which is expected to favor the formation of the electron-delocalized anionic adduct. At any rate, under the given experimental conditions the reactive nucleophile is assumed to be the enol form of the ketone, such as $\text{CH}_3\text{C}(\text{OH})=\text{CH}_2$, rather than the conjugate base



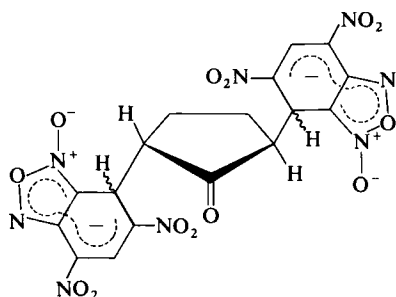
obtained by NMR methods. Isolation of the potassium salts of these anions is hampered by their explosive nature.

**(182)****(183)** (one enantiomer shown)**(184)** (one enantiomer shown)**(185)**

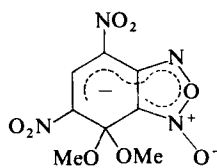
Some interesting features of the adducts are derived from the non-symmetric nature of the substrate. When acetone is used, the resulting adduct (**182**) is characterized by the presence of two geminal diastereotopic protons. From the equality of the coupling constants J_{ax} and J_{bx} in **182** it is presumed that bisected conformations such as **185** and the like are preferred. With cyclopentanone two enantiomeric pairs are formed because of the presence of two chiral centers (**183** and **184**). In the latter reaction the relative intensities of the signals of the adducts change with time, indicating the formation of a kinetically controlled adduct and, subsequently, of a more stable adduct. The structures of these adducts have been proposed to be **183** and **184**, respectively.²¹⁸ With an excess of 4,6-dinitrobenzofuroxan, cyclopentanone behaves as a bidentate nucleophile and becomes attached to two molecules of substrate, yielding a diadduct. The trans structure for this

²¹⁸ F. Terrier, M. P. Simonnin, M. J. Pouet, and M. J. Strauss, *J. Org. Chem.* **46**, 3537 (1981).

adduct (**186**) has been suggested to be more likely than the *cis* structure (not shown) due to steric compressions.

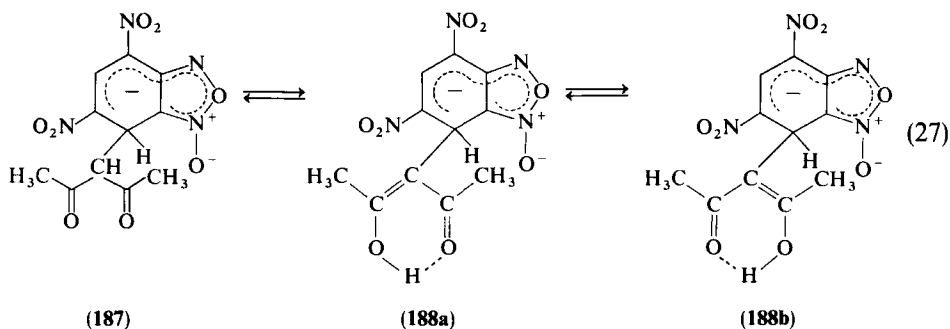


(186)



(189)

When the more acidic 1,3-diketones are used as the nucleophiles, the active species may be either the enol form or the enolate ion. In both cases a "diketonic" adduct is expected to be initially formed. This is indeed found to be the case in the reaction of 2,4-pentanedione, yielding **187** as a primary adduct, which subsequently equilibrates with the enol forms **188** (Eq. 27). When 1,3-cyclopentanedione is used, only the enol forms are obtained, however, presumably because enolization is faster than the diketonic adduct formation.²¹⁸



(187)

(188a)

(188b)

7. 4,6-Dinitro-7-methoxybenzofuroxan

Buncel *et al.*³³ have shown that 4,6-dinitro-7-methoxybenzofuroxan undergoes attachment of MeO^- in MeOH at position 7, yielding the *gem*-dimethoxy adduct **189**. No evidence has been obtained so far for the concurrent formation of other adducts, in contrast to the behavior of 4-nitro-7-methoxybenzofuroxan. Adduct **189** has been characterized by $^1\text{H-NMR}$ in methanol solution. Its formation occurs in a fast, reversible process followed by slow conversion to the conjugate base of 4,6-dinitro-7-

hydroxybenzofuroxan. The overall reaction resembles that reported for 2-methoxy-3,5-dinitropyridine, leading to the conjugate base of 2-hydroxy-3,5-dinitropyridine,³⁹ although no *gem*-dimethoxy adduct was involved in that case. The remarkable leaving-group ability of the heterocyclic residue (X) in the nucleophilic substitution of the starting substrate, viewed as CH₃X, appears to be general, inasmuch as it is also observed when Et₂NH is used as a nucleophile in CDCl₃ solution and can be related to the high acid strength of the 7-hydroxy derivative.

The ¹H-NMR of adduct **189** shows an unusual feature in that the H-5 position is shifted downfield (by 0.23 ppm) relative to the starting benzofuroxan, an effect that is in contrast to what is generally observed in the formation of anionic adducts. With the aid of related structures the effect can be interpreted in terms of a combination of the strong electron-withdrawing ability of the furoxan ring moiety, relative to a nitro group, and of a steric compression between the methoxy group and the adjacent *o*-nitro and *peri-N*-oxide groups that is relieved in the adduct. The deshielding of H-5 as a result of a discharge in steric compression would arise from magnetic anisotropy in the interaction with one of the oxygen atoms of the nitro group.

8. Nitropyridofuroxan

The high activating power of the furoxan ring in nucleophilic addition has also been observed by Bailey *et al.*²¹⁹ in 7-nitro-1,2,5-oxadiazolo[3,4-*c*]-pyridine 3-oxide, a nitropyrido[3,4-*c*]furoxan that easily undergoes covalent addition of water by nucleophilic attack at the position para to the nitro group. The structure of the covalent hydrate is supported by elemental analysis, osmometric molecular weight determination, and ¹H-NMR spectra in DMSO-*d*₆.²¹⁹

Table XXXI provides some ¹H-NMR data for σ -adducts from some benzofurazan and benzofuroxan derivatives.

B. REACTION RATES AND EQUILIBRIA

1. Reactions with Water at Varying pH

As for other heterocyclic systems (see Sections II and III) σ -adduct formation in the benzofurazan and benzofuroxan series can be monitored on the basis of UV-visible spectral changes.^{33,202,208,209,215,216,220-223}

²¹⁹ A. S. Bailey, M. W. Heaton, and J. I. Murphy, *J. Chem. Soc. C*, 1211 (1971).

²²⁰ A. P. Chatrouse and F. Terrier, *C. R. Acad. Sci., Ser. C* **282**, 195 (1976).

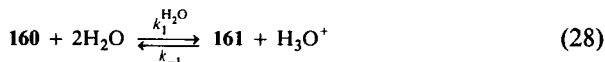
²²¹ F. Terrier, F. A. Millot, and W. P. Norris, *Bull. Soc. Chim. Fr.*, 551 (1975).

²²² F. Terrier, F. A. Millot, and W. P. Norris, *J. Am. Chem. Soc.* **98**, 5883 (1976).

²²³ G. Ah-Kow, *C. R. Acad. Sci., Ser. C* **287**, 231 (1978).

4,6-Dinitrobenzofuroxan (**160**) is such a powerfully activated substrate toward nucleophiles that it can react with unionized water in the appropriate pH range. A complete quantitative investigation of the reactions occurring in aqueous solution was carried out by Terrier *et al.*^{221,222} through the changes in absorbance at 465 nm between pH 1 and 13. The measurements of the reaction rates required the use of the stopped-flow technique.

The formation of adduct **161** was shown to occur according to Eqs. (28) and (29). The observed rate constant, k_{obs} , as obtained under first-order



conditions (dilute HCl, various buffers, and dilute KOH, at 0.2M ionic strength), is the rate of approach of the equilibrium between **160** and **161**. Rate measurements for this and similar reactions may refer either to the rate of formation of the adduct in relatively basic media or to the rate of return of the adduct to the starting substrate in relatively acid media. The k_{obs} values displayed a characteristic dependence on pH that could be understood in terms of Eq. (30):

$$k_{\text{obs}} = (k_{-1}a_{\text{H}^+}/\gamma_{\pm}) + k_{-2} + k_1^{\text{H}_2\text{O}} + (k_2K_{\text{w}}/a_{\text{H}^+}\gamma_{\pm}) \quad (30)$$

where the first two terms are related to the reverse reactions and the other two to the forward reactions. The dependence of these terms on pH showed that the formation of adduct **160** arises exclusively from attack of a water molecule below pH 7, whereas reaction (29) becomes significant above pH 7 and eventually provides the only mode of formation of **161**.

Some of the relevant data are collected in Table XXXII. From these data we note that the apparent nucleophilicity of water is lower than that of OH^- by a factor of 55.5 $k_2/k_1 = 5.3 \times 10^7$. The equilibrium constant for the ionization of the hydroxyl group of adduct **161** is K'_a .

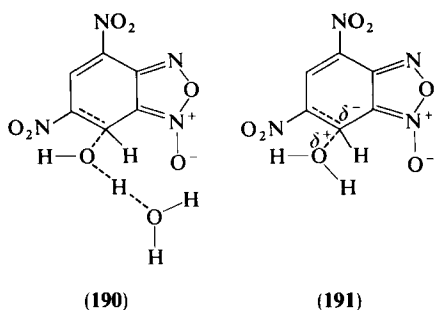
The powerful electron withdrawing effect of the furoxan ring can be illustrated by comparison with polynitro-substituted benzene and naphthalene compounds.²²² Although there are no rate data available for adduct formation from the latter compounds and water, a comparison is possible for the related equilibrium constants (K_1). Thus the "acid strength" of **160** as defined by Eq. (28) is nearly 10 orders of magnitude higher than that of 2,4,6-trinitrobenzene (TNB). A similar huge factor is involved in the equilibrium constants for the reactions with the hydroxide ion (K_2). Here the rate constants are available for comparison and show that adduct **161** is formed from **160** at a rate (k_2) greater than the corresponding reaction from TNB by a factor of 10^3 .

TABLE XXXII
KINETIC AND THERMODYNAMIC DATA FOR THE
FORMATION AND DECOMPOSITION OF ADDUCTS
161 AND **193** IN WATER AND IN 90% DMSO AT 25°C,
ACCORDING TO EQS. (26) AND (27)^a

	161	193
$k_1^{\text{H}_2\text{O}}$ (sec ⁻¹)	3.45×10^{-2}	1.0
k_{-1} (M ⁻¹ sec ⁻¹)	1.5×10^2	1.3×10^5
k_2 (M ⁻¹ sec ⁻¹)	3.35×10^4	8.8×10^6
k_{-2} (sec ⁻¹)	2.5×10^{-6}	1.1×10^{-2}
pK ₁	3.75	5.1
pK ₂	- 10.25	- 8.9
pK' _a	11.3	11.1

^a Reference 222.

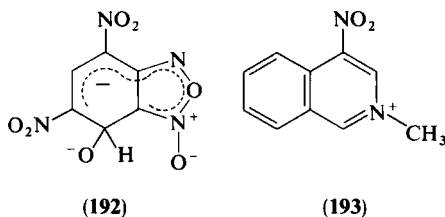
General base catalysis has been ascertained for reaction (28) and when combined with a solvent isotope effect of 1.67 for $k_1^{\text{H}_2\text{O}}/k_1^{\text{D}_2\text{O}}$ it can be taken as evidence in favor of a transition state such as **190** rather than **191**. A large negative entropy of activation ($\Delta S^\ddagger = -109.9 \text{ J mol}^{-1} \text{ K}^{-1}$) for this reaction also supports the hypothesis.



Reaction (29) is not intended necessarily to imply direct attack by the OH⁻ ion at the C-7 of the substrate. There is a possibility that the mechanism falls within the scope of a general base-catalyzed pattern whereby water is still the nucleophilic species and OH⁻ is the catalyst.

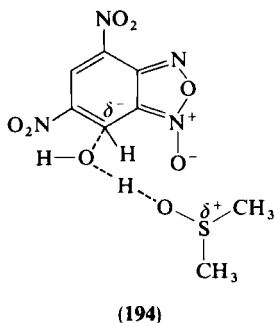
There are two additional features connected with the strong electron-withdrawing effect of the furoxan ring in **160**. In the first place, the OH group linked to the tetrahedral C-7 ionizes above pH 10.6 to give rise to the dianion **192**. The second feature is that the general behavior of **160** in aqueous solution is more closely analogous to quaternary nitrogen heterocycles such as **193** than to the aforementioned polynitroaromatic compounds. Both **160** and **193** are attacked by water, and the resulting adducts ionize to yield the

corresponding anions. Although the k_1 and k_2 values are markedly higher for **193** than for **160**, the OH ionization constants of **161** and the adduct from **193** have comparable magnitudes (Table XXXII).



The reactions of **160** in H_2O -DMSO mixed solvents ($0.5M$ ionic strength, $\text{Me}_4\text{N}^+\text{Cl}^-$) follow the same pattern as in water and have been treated by a similar kinetic analysis.²²⁴ On transfer from water to mixed solvent a considerable increase was found in the equilibrium constants and rates of formation of **161** in acidic (K_1 , k_1) and in basic conditions (K_2 , k_2), as expected from the known tendency of DMSO to solvate polarizable anions. Under the stated acidic conditions the H_2O molecule actually acts as the nucleophile.

The appropriate evaluation of the effect of the solvent change on the nucleophilic power of the water molecule is obtained by calculating the second-order rate constant, $k_1^{\text{H}_2\text{O}}/[\text{H}_2\text{O}] = k_1^{\text{H}_2\text{O}}$. The rate increase is found to be about a thousandfold. This factor may arise, at least in part, from a base-catalyzed attack of the water molecule whereby a molecule of DMSO, rather than a second molecule of water, acts as a catalyst. The transition state in such a case would be described by **194**.



The observed solvent effects are analogous²²⁴ to that previously described for the hydrolysis of 2,4-dinitrofluorobenzene.²²⁵ This would provide sup-

²²⁴ F. Terrier, H. A. Sorkhabi, F. Millot, J. C. Halle, and R. Schaal, *Can. J. Chem.* **58**, 1155 (1980).

²²⁵ J. Murto and A. M. Hiiri, *Suom. Kemistil. B* **37**, 177 (1964).

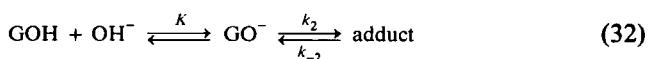
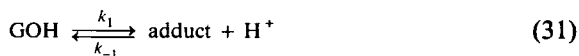
port for a mechanism via a rate-determining σ -adduct formation for the latter reaction.

2. Reactions with Other Nucleophiles in Aqueous Solution: Spiro Adducts

There is evidence for the formation of Meisenheimer adducts in aqueous solution with nucleophiles other than H_2O or OH^- . The formation of transient adducts has been assumed in the interaction of **160** with the basic components of buffer systems such as carbonate and bicarbonate ions²²² and phenoxide ions.²²⁴

The cyclization of 7-(2-hydroxyethoxy)-4-nitrobenzofurazan and 7-(2-hydroxyethoxy)-4-nitrobenzofuroxan to give the spiro Meisenheimer adducts **169** and **170**, respectively, was investigated by Terrier *et al.*²¹² in aqueous solution by a detailed equilibrium and rate analysis similar to the one described for the reaction of **160**.

The reaction proceeds according to two diverse routes, Eqs. (31) and (32), where GOH and GO^- in each case are the glycol ether and the related conjugate base, respectively. The stoichiometric equilibrium constant, $K_c = KK_2$, for Eq. (32) is of the order of 10^6 – 10^7 M^{-1} , i.e., much greater than $K_a = K_1$ for Eq. (31), which is of the order of 10^{-7} – 10^{-8} M . In each case adduct **169** is distinctly more stable than **170**.



The observed rate constants k_{obs} have been measured over a pH range of 1–12 by the stopped-flow method. The general expression for k_{obs} corresponding to the reaction system described by Eqs. (31) and (32) is closely related to Eq. (30).²²² The relative weights of the reverse and forward reaction terms are, however, appreciably different under varying conditions. Unlike the reaction of **160** in water, where the attack of H_2O prevails in the vicinity of pH 6, under no conditions is the reaction of the unionized glycol ether (plateau portion of the forward reaction plot) important.

$$k_{\text{obs}} = \frac{k_2 K K_w}{a_{\text{H}^+} \gamma_{\pm}}$$

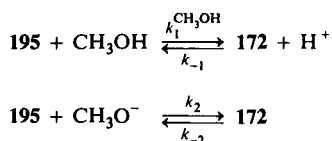
At $\text{pH} < 5$ general acid catalysis of the decomposition of the adducts is observed and suggests, in agreement with analogous features of spiro

adducts from benzene derivatives,^{226,227} that the reaction mechanism is concerted. The general base-catalyzed cyclization cannot be observed because the equilibrium (K_1) is predominantly shifted toward the glycol ether. At pH > 5 the formation and decomposition of **169** and **170** are shown to occur exclusively by Eq. (32).

We have already noted that the stability of **170** is lower than that of **169**. The factor involved in the change in KK_2 value is quite small (2.5); this difference can be attributed to a somewhat higher electron-withdrawing efficiency of the furazan ring relative to the furoxan ring under the given conditions. Presumably of different origin is the very large difference in reactivity for both formation and decomposition of the spiro adducts. The reactions involving **169** are faster than those related to **170** by factors ranging from 200 to 1600. This effect has been explained in terms of rate-depressing electrostatic interactions in the transition state between the spiro group and the *N*-oxide group of the furoxan ring.²¹²

3. Reactions with Methanol at Varying pH: The CH_3O^- - CH_3OH System

For the most reactive compounds in the series, i.e., 4,6-dinitrobenzofurazans and 4,6-dinitrobenzofuroxans, not only water²²² but also methanol²²⁰ is found to be an effective neutral nucleophile in the appropriate pH range. The thermodynamic and kinetic analysis for the reactions in methanol similar to that described above for the reactions in water has been applied to the formation of **172** from 4,6-dinitro-7-methoxybenzofurazan (**195**) in the pH range from 2.2 to 14. The formation of **172** has been followed spectrophotometrically and found to be complete in methanol. The reaction scheme is as follows



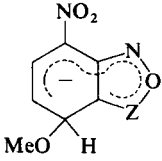
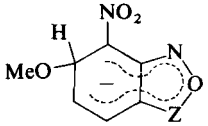
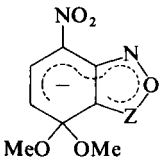
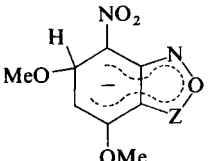
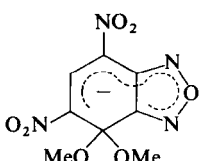
The forward and reverse rate constants have been evaluated and the $\text{p}K_a = \text{p}K_1$ determined independently. The reaction of neutral methanol ($k_1^{\text{CH}_3\text{OH}}$) is found to be the forward process at pH 6.5–8.5. Above pH 8.5 the attack by CH_3O^- starts competing for the formation of **172** and becomes the only important process beyond pH 9.5. The data for the formation of **172**

²²⁶ M. R. Crampton and M. J. Willison, *J.C.S. Perkin II*, 1681 (1974).

²²⁷ C. F. Bernasconi, C. L. Gehriger, and R. H. De Rossi, *J. Am. Chem. Soc.* **98**, 8451 (1976).

TABLE XXXIII

FORWARD AND REVERSE RATE CONSTANTS AND EQUILIBRIUM CONSTANTS FOR THE FORMATION OF σ -ADDUCTS BY THE REACTION OF CH_3O^- WITH 4,6-DINITRO-7-METHOXYBENZOFURAZAN AND SOME 4-NITROBENZOFURAZANS AND BENZOFUROXANS IN METHANOL AT 20°C

	Z	$k_f (M^{-1} \text{ sec}^{-1})$	$k_r (\text{sec}^{-1})$	$K (M^{-1})$	References
	N 163	3.8	1.3×10^{-3}	2920	228
	$\text{N}^+ - \text{O}^-$ 173	17.6	2.2×10^{-3}	8000	228
	N 164	845	5.2	163	228
	$\text{N}^+ - \text{O}^-$ 174	1420	3	475	228
	N 167	7.58	3.55×10^{-3}	2135	223, 228
		14.5 ^a	7.1×10^{-3a}	2050 ^a	207
	$\text{N}^+ - \text{O}^-$ 177	12.02	2.29×10^{-3}	5250	223, 228
	N 168:X = OMe	347	9.2	37.7	228
	$\text{N}^+ - \text{O}^-$ 178	348	5	69.6	228
		2.52×10^5	4.9×10^{-6}	5.1×10^{10}	220

^a Data at 25°C.

under the latter conditions are reported in Table XXXIII. Below pH 5.5 the acid-catalyzed decomposition of 172 ($k_{-1}[\text{H}^+]$) prevails over all the other reactions.

Adduct 172 and its furoxan analog 189 are rated as the most stable Meisenheimer adducts known so far and exceed the stability of adduct 143

²²⁸ F. Terrier, A. P. Chatrousse, and F. Millot, *J. Org. Chem.* **45**, 2666 (1980).

from 2-methoxy-3,5-dinitroselenophene by about four powers of ten (Table XXV).⁵⁶

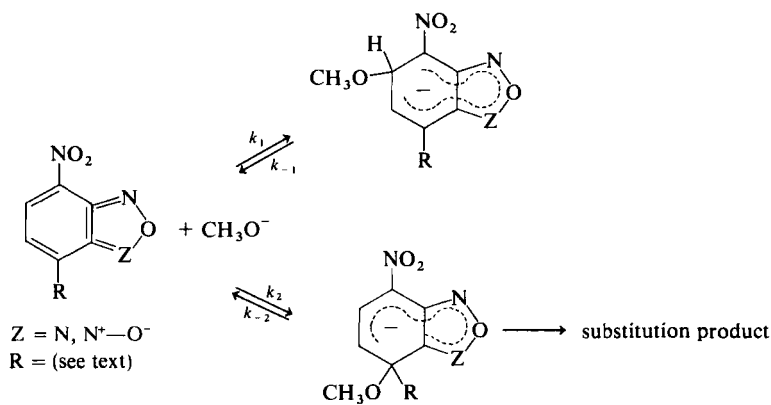
Turning to the mononitro derivatives (7-methoxy-4-nitro) Ah-Kow²²³ has determined the rate constants for the reactions with CH_3OH and CH_3O^- (for the latter reagent see Table XXXIII). As expected, the presence of only one nitro group leads to a decrease in the forward rate parameters by four to five powers of ten. Also noted is a marked increase in the reverse rate parameters. Unlike the dinitro derivatives, 7-methoxy-4-nitrobenzofurazan generates an adduct (**167**, $\text{pH}_{1/2} = 13.36$) that is slightly less stable than the one (**177**, $\text{pH}_{1/2} = 12.93$) derived from the furoxan analog. The same inverted trend is observed for the rate constants for the formation of the adducts.

At $\text{pH} < 4$ the decomposition of the adduct (**167** and **177**) is preceded by a very fast reaction, which corresponds to the appearance of a new species having a characteristic UV spectrum. The fast reaction is believed to consist of a protonation of the nitro group at oxygen.

The conditions favoring CH_3O^- - CH_3OH as the nucleophile-solvent system are most commonly employed for structural studies with substrates of varying reactivities, as described in the following sections.

4. Concurrent Methoxide Ion Attack at the 5- and 7-Positions of 4-Nitro Derivatives

In the course of an investigation on the methoxydehalogenation of 4-nitro-7-X-benzofurazans, Todesco *et al.* found that substitution at the 7-position is preceded by σ -adduct formation on primary attack at the 5-position.²¹⁶ They recognized that, in fact, substitution is the irreversible way out from an equilibrium system such as the one described in Scheme 13



SCHEME 13

and obtained a number of rate and equilibrium parameters for the 5-adduct formation ($Z = N$ and $R = H, CH_3, OCH_3, SR, \text{halogen}, SO_2Ph$) and for the 7-adduct formation ($Z = N$ and $R = OCH_3$).^{207,210} Some of these data are reported in Tables XXXIII and XXXIV.

The concurrent methoxide ion attack at the 5- and 7-positions of 4-nitrobenzofurazan, 4-nitrobenzofuroxan, and their 7-methoxy derivatives was studied in detail by Terrier *et al.*²²⁸ If the reagent concentration is high (5×10^{-4} – $0.1 M$) the 5-adduct is formed first because the related k_1 is much greater than k_2 (formation of the 7-adduct), and the observed first-order rate of equilibration between substrate and related 5-adduct (164, 174, 168 for $X = OMe$, or 178), which is very high, is given by

$$k_1^{obs} = k_{-1} + k_1[CH_3O^-]$$

Subsequently the system changes more slowly over to the 7-adduct. At low CH_3O^- concentrations, i.e., $[CH_3O^-] < 5 \times 10^{-4} M$, as obtained in buffer solutions, only the 7-adduct is observed because the isomerization of the 5-adduct to the more stable 7-adduct is allowed to take place. In this case the observed first-order rate is a measure of the equilibration between substrate and related 7-adduct (163, 173, 167, or 177) and is given by

$$k_2^{obs} = k_{-2} + k_2[CH_3O^-]$$

TABLE XXXIV

FORWARD AND REVERSE RATE CONSTANTS AND EQUILIBRIUM CONSTANTS FOR THE FORMATION OF SOME σ -ADDUCTS FROM SUBSTITUTED 4- AND 5-NITROBENZOFURAZANS AND CH_3O^- – CH_3OH AT 25°C

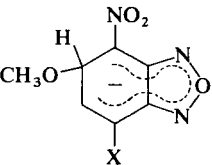
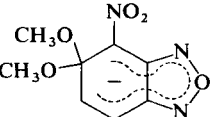
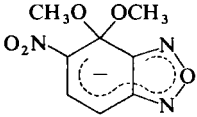
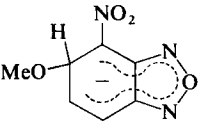
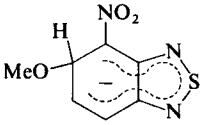
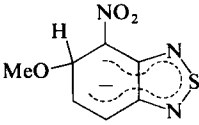
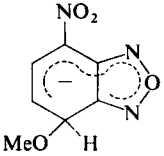
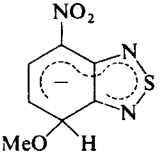
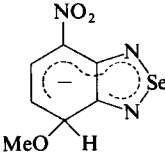
	X	$k_f (M^{-1} \text{ sec}^{-1})$	$k_r (\text{sec}^{-1})$	$K (M^{-1})$	References
	H	900	10	90	210
	Me	580	36	16.1	210
	OMe	350	16	22	210
	SMe	490	10	49	210
	SPh	520	9.6	54	210
	SO_2Ph	43,000	≈ 3	$\approx 14,300$	210
		147	1.16×10^{-1}	1,300	208
		20.1	5.56×10^{-3}	3,600 5,100	208 209

TABLE XXXV
RATE AND EQUILIBRIUM CONSTANTS FOR σ -ADDUCT FORMATION BY THE REACTION OF
4-NITROBENZOFURAZAN AND ITS S- AND Se-ANALOGS WITH MeO^- IN METHANOL^a

			
	164	196	197
k_f ($M^{-1} \text{ sec}^{-1}$)	1200	3.55	6.31
K (M^{-1})	141	8.87×10^{-3}	8.7×10^{-2}
			
	163	198	199
k_f ($M^{-1} \text{ sec}^{-1}$)	6	8.70×10^{-2}	8.70×10^{-2}
K (M^{-1})	2.94×10^3	0.14	2

^a Data obtained by extrapolation to zero DMSO concentration from determinations in DMSO-MeOH mixtures²²⁹ except for **163** and **164** which were studied in methanol.²²⁸

Some of the relevant data are reported in Table XXXIII. They show that whereas the forward rates for 5-adduct formation are greater than those for 7-adduct formation by about two orders of magnitude, the differences in reverse rates are even greater. As a result, the 7-adducts are about 20 times as stable as the 5-adducts. This difference in stability is not particularly large and is, in fact, more modest than the aforementioned rate changes.

A similar behavior is shown by 4-nitrobenzothiadiazole and 4-nitrobenzoselenadiazole in the reaction with MeO^- in Me_2SO -MeOH mixtures.²²⁹ Because the $\log k$ and $\log K$ values for 5- and 7-adduct formation correlate linearly with the mole fraction of Me_2SO , the data could be extrapolated to 100% methanol and be compared to those obtained for the benzofurazan analog in this solvent (Table XXXV).

The higher stability of the 7-adduct relative to the 5-adduct can reasonably be attributed to the fact that the nitro group can better accommodate the negative charge when it occupies a position para, rather than ortho, to the

²²⁹ C. Deicha and F. Terrier, *J. Chem. Res., Synop.*, 312 (1981).

point of attachment of the reagent.²²⁸ Furthermore, the 7-adduct may take advantage from a larger extent of electron delocalization in spite of the considerable degree of bond fixation indicated by the bond distances as determined in a similar σ -adduct.²¹⁴ These features are not reflected in the activation parameters, however. The free energy of formation of the 7-adduct is controlled by a very high and positive entropy change that presumably affects the enthalpy change by a compensation phenomenon. It is of interest that the 7-adduct formation is endothermic whereas the 5-adduct formation is exothermic. The large, positive entropy term is solely responsible for the greater stability of the 7-adduct and has been attributed to ion pairing with the counterion (K^+).²²⁸

5. *The Activating Power of the Furazan and Furoxan Moieties*

The furazan and furoxan moieties, viewed as annelated heterocyclic substituent groups of the benzene ring where the reaction takes place, have been found to exert a very strong activating and stabilizing effect toward Meisenheimer adduct formation. The unusually high activating effect of the furazan ring was noted by Boulton and Kirby²⁰⁹ in a quantitative investigation of the methoxydechlorination of chloronitrobenzofurazans. Meisenheimer adducts from the reaction of CH_3O^- with mononitrobenzofurazans and benzofuroxans in methanol have been found to have stabilities ranging from one to two orders of magnitude greater than that of the 1,3,5-trinitrobenzene adduct.²²⁸ The *gem*-dimethoxy adducts are less stable than that derived from 2,4,6-trinitroanisole, however (see Section IV,B,6).

Todesco *et al.*²⁰⁸ have noted that whereas the 4-halogeno-5-nitro- and the 5-halogeno-4-nitrobenzofurazans display an exceptionally high reactivity in methoxydehalogenation, the 5-halogeno-6-nitro isomers are far less reactive and have attributed this behavior to C-4—C-5 bond fixation and to the electron-withdrawing power of the ring oxygen.

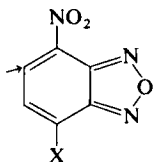
Small factors are usually involved in the relative influence of the furazan and furoxan groupings on the stabilities and rates of decomposition of the Meisenheimer adducts. In the reaction with the CH_3O^- - CH_3OH system the furoxan ring appears to be slightly more effective than the furazan ring in stabilizing adducts and transition states (Table XXXIII). Because the differences are small, it is not surprising to find opposite orders in other cases. Thus the adduct from 4,6-dinitrobenzofurazan is more stable than that from 4,6-dinitrobenzofuroxan.²¹² In spiro adducts a change in behavior is observed on going from water to methanol.^{212,228} In water the furazan spiro adduct is the more stable, whereas in methanol it is the less stable. The special

effects noted for the rates of adduct formation and decomposition of the spiro adducts in water²¹² have already been referred to in Section IV,B,2.

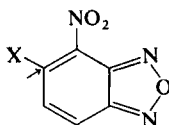
The influence of the furazan moiety on rate and equilibrium constants for σ -adduct formation from 4-nitrobenzofurazan has been compared with that of the related S and Se analogs.²²⁹ Whether the adducts are formed by attachment at the 5- or 7-position (see Section IV,B,4), the sulfur and selenium **196**, **197**, **198**, and **199** adducts are formed much more slowly and are much less stable than the related furazan adducts **164** and **163** (Table XXXV). These effects have been interpreted as due to a combination of the aromatic character of the starting substrates, which increases in the order S > Se >> O, and of the electron-withdrawing effect of the heteroatom.

6. Substituent Effects on the Rate of Adduct Formation

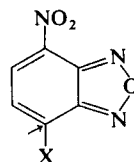
Todesco *et al.*²¹⁰ have attempted an assessment of the several factors through which substituents (X) influence the rate of adduct formation by the reaction of 4-nitrobenzofurazans with CH_3O^- - CH_3OH . Whenever possible they consider a number of substituents such as Me, OMe, SMe, SPh, SO_2Ph , and the halogens (F, Cl, Br). The data for the halogens are the rates of methoxydehalogenation on the assumption that the formation of the Meisenheimer adduct is rate determining in the substitution reaction. The influencing factors they consider include (a) a rate-depressing resonance stabilization, (b) repulsive interactions between X and the incoming group (CH_3O), and (c) the electron deficiency of the carbon atom being attacked. There seems to be little doubt that factor (a) plays a role in **200** because the CH_3O and RS groups are deactivating (Table XXXIV), but when the attack is ipso, as shown in **201** and **202**, the reactivity orders $\text{OMe} > \text{Cl} > \text{Br}$ and $\text{F} \gg \text{Cl} > \text{Br}$ clearly indicate that factor (a) is obscured by other factors such as (b). The fact that $k_{\text{H}}/k_{\text{OMe}}$ in **201** is greater than in **200** is also consistent with the idea that in **201** the ipso attack for X = OMe involves both (a) and (b). Also, factor (b) possibly obscures factor (c) in **201** because of the reactivity order $\text{H} \gg \text{Cl}, \text{Br}$. However we think that factor (c) does have a role since $k_{\text{F}}/k_{\text{Cl}}$ in **202** is appreciably greater than $k_{\text{H}}/k_{\text{Cl}}$ in **200**, which cannot be explained on the basis of factor (b) alone.



(200) X = H, Me, OMe, SMe, SPh, F, Cl, Br, SO_2Ph



(201) X = H, OMe, Cl, Br



(202) X = H, OMe, F, Cl, Br

The geometry of 4-nitrobenzofurazans and benzofuroxans is such as to shed light on the factors involved in the relative stabilities of monomethoxy and *gem*-dimethoxy adducts as found in the trinitrobenzene system. A major factor in the much higher stability of the *gem*-dimethoxy adduct in the latter system is known to be the steric relief accompanying the formation of the tetrahedral *gem* substituted carbon. Because there is no overcrowding in 4-nitro-7-methoxybenzofurazan, the stability of the *gem*-dimethoxy adduct derived therefrom should not be particularly greater than that of the monomethoxy adduct. Terrier *et al.*²²⁸ have shown that quite similar stabilities are indeed observed for the monomethoxy and *gem*-dimethoxy adducts with both furazan and furoxan derivatives as reported in Table XXXIII. In fact, the *gem*-dimethoxy adducts are slightly less stable presumably as a result of the resonance stabilization effect.

7. Other Nucleophile-Solvent Systems

4-Nitrobenzofuroxan has been recently investigated in the isopropoxide-isopropanol and cyanide-isopropanol systems.²³⁰ In both cases a reversible formation of a 7-adduct is followed by the stopped-flow method using similar spectral changes from substrate to adduct. The structure of the adduct is identified by analogy with the NMR and UV-visible properties of the product of the reaction as carried out with the MeO⁻-MeOH system. There is no evidence that the formation of the 7-adduct is preceded by that of the 5-adduct under the conditions of the experiments. Any formation of the 5-adduct would occur at $t_{1/2} < 1$ msec and at low concentrations to escape detection.

The rate data for the 7-adduct formation obey the form

$$k_{\text{obs}} = k_{-1} + k_1 [\text{nucleophile}]$$

and have been compared with those for the corresponding reactions of 1,3,5-trinitrobenzene. Reactivities and stabilities of the 4-nitrobenzofuroxan and 1,3,5-trinitrobenzene systems have comparable magnitudes. In both cases the reaction rate for Me₂CHO⁻ is higher than that for CN⁻. However, the stability of the adduct derived from CN⁻ is greater than that derived from Me₂CHO⁻ in the reaction with 4-nitrobenzofuroxan, whereas closely similar adduct stabilities are observed in the related reactions with 1,3,5-trinitrobenzene (Table XXXVI). The activation parameters revealed markedly more negative $\Delta S^\ddagger$ values in both reactions of the 4-nitrobenzofuroxan system. This effect has been attributed to higher solvation of the adducts

²³⁰ M. E. Moir and A. R. Norris, *Can. J. Chem.* **58**, 1691 (1980).

TABLE XXXVI
KINETIC AND THERMODYNAMIC DATA FOR THE FORMATION OF 7-ADDUCTS BY THE REACTION
OF 4-NITROBENZOFUROXAN (203) WITH Me_2CHO^- AND CN^- IN ISOPROPANOL AT 25°C.
COMPARISON WITH RELATED DATA FOR 1,3,5-TRINITROBENZENE (204)^a

Adduct	Me_2CHO^-		CN^-	
	203	204	203	204
$k_f (M^{-1} \text{ sec}^{-1})$	3.53×10^4	9.67×10^4	2.74×10^2	2.45×10^3
$K (M^{-1})$	2.43×10^3	5.6×10^4	$> 2.74 \times 10^4$	5.1×10^4
$\Delta H_f^\ddagger (\text{kJ}^{-1} \text{ mol}^{-1})$	20.9	24.3	36.8	49.0
$-\Delta S_f^\ddagger (\text{J mol}^{-1} \text{ K}^{-1})$	87.4	49.0	75.7	5.0

^a Reference 230.

derived from the nitrobenzofuroxan as compared to those derived from trinitrobenzene.

Adduct formation is followed by subsequent changes with both reactants, but the related spectral changes suggest that diverse decompositions of the adducts occur depending on the nucleophilic reagent. Although there is some analogy with the behavior of the trinitrobenzene adducts, these processes still await elucidation.

C. ROLE IN BIOCHEMICAL INVESTIGATION

1. Antileukemic Activity

4-Nitrobenzofurazan is a powerful inhibitor of nucleic acid and protein biosynthesis, with an especially high toxic effect on the metabolism of leukocytes *in vitro*, suggesting a potential antileukemic activity. Ghosh and Whitehouse²⁰⁵ have tested several benzofurazan and benzofuroxan derivatives as *in vitro* inhibitors of RNA synthesis, in order to explore the possibility of finding a structure-activity relationship. Of those examined, the benzofurazan compounds are generally more effective than the corresponding benzofuroxan derivatives. Particularly strong activity is found for such nitro group-bearing substrates as 4-nitrobenzofurazan, 4-nitrobenzofuroxan, and their 7-RS and 7-phenoxy derivatives. The activity of these substances is suppressed by preincubation with aliphatic thiols, glutathione being most effective, and, therefore, presumably involves interaction with nucleophilic groups of the cell, e.g., thiol or amino groups. During preincubation the nitro compounds yield characteristic colorations.

The relative order of biological activity of 4- and 5-nitro derivatives appears to be related to the relative stabilities of adducts formed from these substrates. Furthermore, freshly prepared solutions of adducts of 4-nitrobenzofurazan are also strongly active *in vitro*. These facts suggest that adducts might be formed within the cell and that the tendency to form adducts might be essential in promoting the biological activity of the starting substrates. However, this hypothesis is hampered by the finding²³¹ that certain electron-withdrawing substituents decrease the drug activity, in spite of their ability to increase the stability of the adducts. Perhaps the presence of other substituents may interfere with the capacity of the substrate to interact with the nucleophilic active site within the cell for either steric or solubility reasons. In this case the intrinsic ability of the substrate to undergo nucleophilic attack could be apparently decreased by the lower accessibility of the intracellular thiols.

The finding that adduct **173** as formed from 4-nitrobenzofuroxan, undergoes a decomposition reaction according to a complex pattern has also suggested that the biological activity might be related to some of the decomposition products.²¹⁵

Many basic studies on adduct formation from furazan and furoxan systems have been stimulated by the properties referred to above.

2. Adduct Formation with Nucleophilic Sites in Proteins

In the course of investigations using 4-chloro-7-nitrobenzofurazan as a reactivity probe for identifying the active sites of a number of enzymes such as papain, ficin, and bromelain, the intermediacy of Meisenheimer adducts derived from direct attack of thiolate groups located in the protein has been assumed on the basis of the spectral changes accompanying the process of replacement of the chloro group.^{232,233}

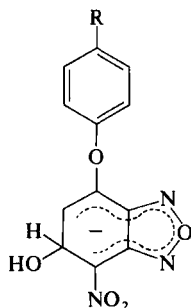
Interesting kinetic behavior is found for the adduct formation of 7-lysozyme-substituted 4-nitrobenzofurazan with OH^- , the attack involving the phenolic hydroxyl group of Tyr-23 of lysozyme.²¹¹ In the pH range 10.5–12.7 the formation of adduct **203** is markedly faster than that of adducts such as **204** obtained from nonproteic model compounds. The difference is attributed to a preliminary ionization of the distantly located OH of Tyr-20, followed by a rate-limiting conformational change and, finally, by a fast attack of OH^- . The OH^- nucleophile is believed to react much more

²³¹ P. B. Ghosh, B. Ternai, and M. W. Whitehouse, *J. Med. Chem.* **15**, 255 (1972).

²³² M. Shipton, T. Stuchbury, and K. Brocklehurst, *Biochem. J.* **159**, 235 (1976).

²³³ B. S. Baines, G. Allen, and K. Brocklehurst, *Biochem. J.* **163**, 189 (1977).

rapidly with the protein derivative than with the model compound because of the influence of a rate-enhancing hydrophobic microenvironment.²³⁴



(203) R = lysozyme residue

(204) R = AcNHCHCONH₂



ACKNOWLEDGMENTS

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²³⁴ We refer to the Sigg *et al.*²²¹ paper on the basis of their discussion on interesting results. However, we regret we were unable to read their Table II probably because of errors in typesetting.

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