HANDBOOK OF HETEROCYCLIC CHEMISTRY

Alan R. Katritzky, FRS

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George Tiers
March 1988

JOURNAL CODES FOR REFERENCES

For explanation of the reference system, see p. 15

ABC	Agric. Biol. Chem.
ACH	Acta Chim. Acad. Sci. Hung.
ACR	Acc. Chem. Res.
AC(R)	Ann. Chim. (Rome)
ACS	Acta Chem. Scand.
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AJC	Aust. J. Chem.
AK	Ark. Kemi
ANY	Ann. N.Y. Acad. Sci.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AX	Acta Crystallogr.
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chem. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochem. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CB	Chem. Ber.
CC	J. Chem. Soc., Chem. Commun.
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CI(L)	Chem. Ind. (London)
CJC	Can. J. Chem.
CL	Chem. Lett.
CPB	Chem. Pharm. Bull.
CR	C.R. Hebd. Seances Acad. Sci.
CR(C)	C.R. Hebd. Seances Acad. Sci., Ser. C.
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CZ	Chem.-Ztg.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B
DOK	Dokl. Akad. Nauk SSSR
E	Experientia
EGP	Ger. (East) Pat.
EUP	Eur. Pat.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GEP	Ger. Pat.
H	Heterocycles
HC	Chem. Heterocycl. Compd. [Weissberger–Taylor series]
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
IC	Inorg. Chem.
IJC	Indian J. Chem.
IJC(B)	Indian J. Chem., Sect. B
IJS	Int. J. Sulfur Chem.
IJS(B)	Int. J. Sulfur Chem., Part B
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JCP	J. Chem. Phys.
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JMC	J. Med. Chem.
JMR	J. Magn. Reson.
JOC	J. Org. Chem.
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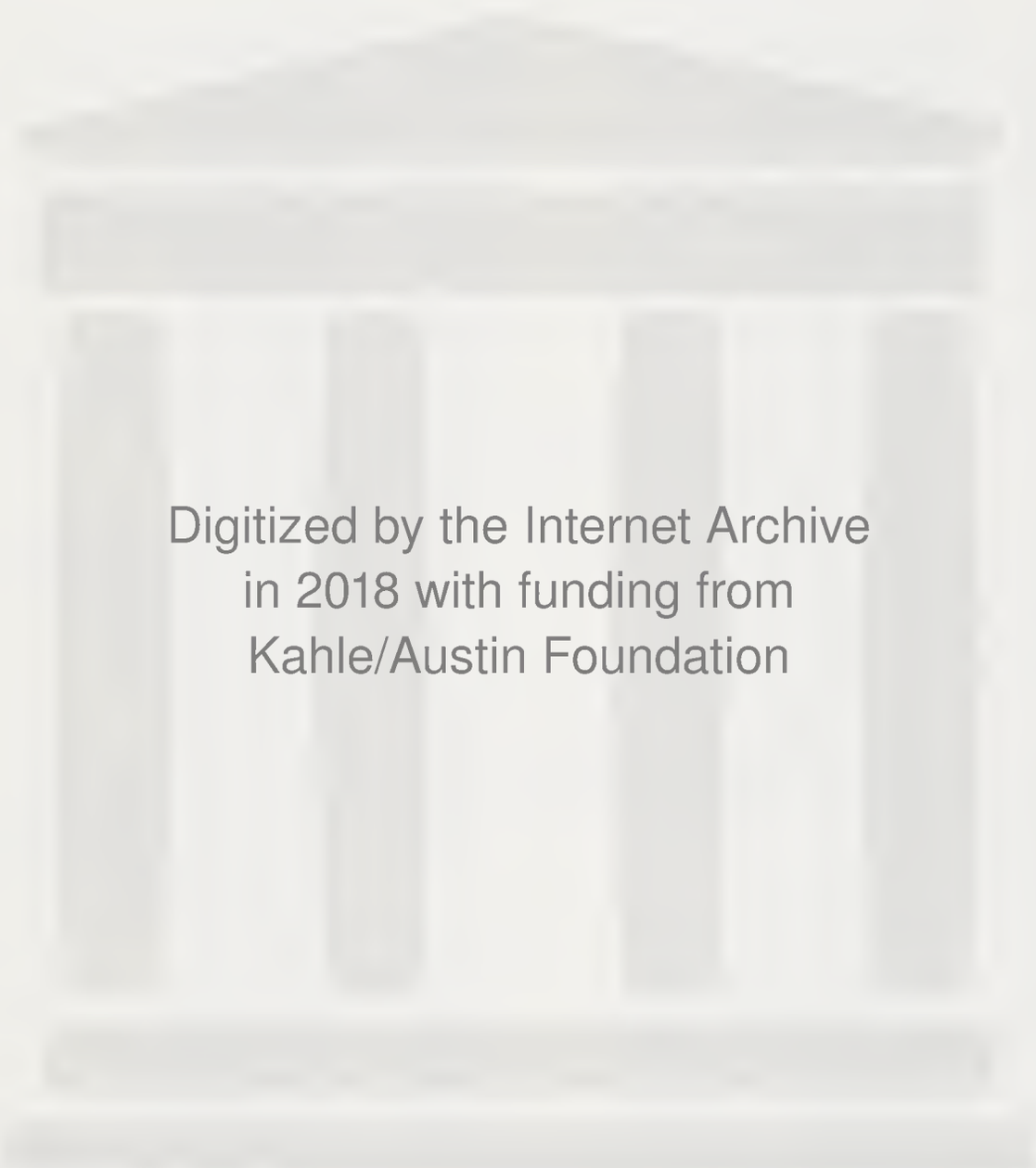

HANDBOOK OF HETEROCYCLIC CHEMISTRY

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University of Florida

in collaboration with

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Outline Contents

Foreword

This Handbook is designed with two purposes in mind.

(a) It is the sequel to the earlier textbooks by Katritzky and Lagowski: 'Heterocyclic Chemistry', published in 1960, and 'The Principles of Heterocyclic Chemistry', published in 1967. It is thus designed to provide a one-volume overall picture of the subject suitable for the graduate or advanced undergraduate student, as well as for research workers, be they specialists in the field or engaged in another discipline and requiring knowledge of heterocyclic chemistry.

(b) It represents Volume 9 of 'Comprehensive Heterocyclic Chemistry' (CHEC) and is based on the general chapters which appear scattered throughout the first eight volumes of the compendium. The reader is referred for more detailed factual matter to these volumes; specific references are denoted 'CHEC'.

The two purposes are symbiotic: the growth of the subject, particularly in the last two decades, renders impossible the inclusion of much detail in a one-volume work. However, the highly systematic nature of the subject and that of the treatment adopted in 'Comprehensive Heterocyclic Chemistry' are ideally suited for the treatment of the principles in one volume. The user can conveniently refer to the other eight volumes for further examples and more detailed explanations.

Because of the close relationship to 'Comprehensive Heterocyclic Chemistry' the Foreword, Contents and Introduction to the complete work, which appear in Volume 1 of the set, have been reprinted in the Handbook. The Foreword outlines the scope, significance and aim of the whole work, whereas the Introduction describes the plan of the work and the novel features it incorporates.

Finally, in Chapter 1.5 of the Handbook, I describe the divergencies between the treatment of heterocyclic chemistry in the Handbook and that found in the main work.

The author has many acknowledgements to make for help given toward the present book. As stated on the title page, it was a collaborative effort and I wish to thank the Volume Editors of 'Comprehensive Heterocyclic Chemistry' whose names are listed there for their considerable efforts. I also acknowledge my debt to the authors of all the monograph chapters from which material has been abstracted for this Handbook. Especially I thank Charles Rees for his constant encouragement and perceptive criticism. It was initially intended that this book would be written with Jeanne Lagowski; although pressure of work prevented this, her joint authorship of two vital chapters was crucial. The work would not have been finished without the expert assistance of Christa Schwarz and Cecilia Bell to whom I also owe my gratitude. The publishers, Pergamon Press, and their Senior Managing Editor, Dr Colin Drayton, have been most supportive of this exciting venture. Finally, I thank my wife for all that she has contributed.

ALAN R. KATRITZKY

Florida

Detailed Contents

**Z denotes a heteroatom (O, S or N).*

Part 1
Preliminaries

1.1

Foreword to 'Comprehensive Heterocyclic Chemistry'

Scope

Heterocyclic compounds are those which have a cyclic structure with two, or more, different kinds of atom in the ring. This work is devoted to organic heterocyclic compounds in which at least one of the ring atoms is carbon, the others being considered the heteroatoms; carbon is still by far the most common ring atom in heterocyclic compounds. As the number and variety of heteroatoms in the ring increase there is a steady transition to the expanding domain of inorganic heterocyclic systems. Since the ring can be of any size, from three-membered upwards, and since the heteroatoms can be drawn in almost any combination from a large number of the elements (though nitrogen, oxygen and sulfur are the most common), the number of possible heterocyclic systems is almost limitless. An enormous number of heterocyclic compounds are known and this number is increasing very rapidly. The literature of the subject is correspondingly vast and of the three major divisions of organic chemistry, aliphatic, carbocyclic and heterocyclic, the last is much the biggest. Nearly six million compounds are recorded in *Chemical Abstracts* and approximately half of these are heterocyclic.

Significance

Heterocyclic compounds are very widely distributed in Nature and are essential to life; they play a vital role in the metabolism of all living cells. Thus, for example, the following are heterocyclic compounds: the pyrimidine and purine bases of the genetic material DNA; the essential amino acids proline, histidine and tryptophan; the vitamins and coenzyme precursors thiamine, riboflavine, pyridoxine, folic acid and biotin; the B_{12} and E families of vitamins; the photosynthesizing pigment chlorophyll; the oxygen transporting pigment hemoglobin, and its breakdown products the bile pigments; the hormones kinetin, heteroauxin, serotonin, histamine and methoxatin; most of the sugars. There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products, for example antibiotics such as penicillin and cephalosporin, alkaloids such as vinblastine, ellipticine, morphine and reserpine, and cardiac glycosides such as those of digitalis. However, the large majority are synthetic heterocyclics which have found widespread use, for example as anticancer agents, analeptics, analgesics, hypnotics and vasopressor modifiers, and as pesticides, insecticides, weedkillers and rodenticides.

There are also a large number of synthetic heterocyclic compounds with other important practical applications, as dyestuffs, copolymers, solvents, photographic sensitizers and developers, as antioxidants and vulcanization accelerators in the rubber industry, and many are valuable intermediates in synthesis.

The successful application of heterocyclic compounds in these and many other ways, and their appeal as materials in applied chemistry and in more fundamental and theoretical studies, stems from their very complexity; this ensures a virtually limitless series of structurally novel compounds with a wide range of physical, chemical and biological properties, spanning a broad spectrum of reactivity and stability. Another consequence of their varied chemical reactivity, including the possible destruction of the heterocyclic ring, is their increasing use in the synthesis of specifically functionalized non-heterocyclic structures.

Aim of the Present Work

All of the above aspects of heterocyclic chemistry are mirrored in the contents of the present work. The scale, scope and complexity of the subject, already referred to, with its correspondingly complex system of nomenclature, can make it somewhat daunting initially. One of the main aims of the present work is to minimize this problem by presenting a comprehensive account of fundamental heterocyclic chemistry, with the emphasis on basic principles and, as far as possible, on unifying correlations in the properties, chemistry and synthesis of different heterocyclic systems and the analogous carbocyclic structures. The motivation for this effort was the outstanding biological, practical and theoretical importance of heterocyclic chemistry, and the absence of an appropriate major modern treatise.

At the introductory level there are several good textbooks on heterocyclic chemistry, though the subject is scantily treated in most general textbooks of organic chemistry. At the specialist, research level there are two established on-going series, 'Advances in Heterocyclic Chemistry' edited by Katritzky and 'The Chemistry of Heterocyclic Compounds' edited by Weissberger and Taylor, devoted to a very detailed consideration of all aspects of heterocyclic compounds, which together comprise some 100 volumes. The present work is designed to fill the gap between these two levels, *i.e.* to give an up-to-date overview of the subject as a whole (particularly in the General Chapters) appropriate to the needs of teachers and students and others with a general interest in the subject and its applications, and to provide enough detailed information (particularly in the Monograph Chapters) to answer specific questions, to demonstrate exactly what is known or not known on a given topic, and to direct attention to more detailed reviews and to the original literature. Mainly because of the extensive practical uses of heterocyclic compounds, a large and valuable review literature on all aspects of the subject has grown up over the last few decades. References to all of these reviews are now immediately available: reviews dealing with a specific ring system are reported in the appropriate monograph chapters; reviews dealing with any aspect of heterocyclic chemistry which spans more than one ring system are collected together in a logical, readily accessed manner in CHEC 1.03.

The approach and treatment throughout this work are as ordered and uniform as possible, based on a carefully prearranged plan. This plan, which contains several novel features, is described in detail in the Introduction (CHEC 1.01, Chapter 1.3 of the Handbook).

ALAN R. KATRITZKY
Florida

CHARLES W. REES
London

1.2

Contents of 'Comprehensive Heterocyclic Chemistry'

Volume 1

Volume 2

Volume 3

Volume 4

Volume 5

Volume 6

Volume 7

Volume 8

1.3

Introduction to 'Comprehensive Heterocyclic Chemistry'*

1.3.1 ARRANGEMENT OF THE WORK

Heterocyclic compounds are normally classified according to the size of the heterocyclic ring and the nature and number of the heteroatoms, and the present work is organized on this basis.

Part 1 (Volume 1) deals with (a) the nomenclature and the literature of heterocyclic compounds (CHEC 1.02 and 1.03), (b) various special topics (CHEC 1.04–1.16), and (c) rings containing less common heteroatoms (CHEC 1.17–1.22).

The literature chapter presents an organized collection of references to leading papers, review articles and books dealing with all aspects of heterocyclic chemistry which span more than one ring system. Reviews dealing with a specific ring system are reported in the appropriate monograph chapter, but those which cover several systems or heterocyclic compounds more generally are collected here.

The special topics discussed are (i) the biological aspects of heterocyclic compounds, *i.e.* their biosynthesis, toxicity, metabolism, role in biochemical pathways, and their uses as pharmaceuticals, agrochemicals and veterinary products; (ii) the use of heterocyclic compounds in polymers, dyestuffs and pigments, photographic chemicals, semiconductors and additives of various kinds; and (iii) the use of heterocyclic compounds as intermediates in the synthesis of non-heterocyclic compounds.

The less common heteroatoms are those other than nitrogen, oxygen and sulfur (and selenium and tellurium which are treated alongside sulfur), *i.e.* phosphorus, arsenic, antimony, bismuth, the halogens, silicon, germanium, tin, lead, boron and the transition metals.

Part 2 (Volumes 2 and 3) deals with mono- and poly-cyclic compounds with one or more six-membered heterocyclic ring, with nitrogen, oxygen and sulfur as the heteroatoms. Volume 2 contains the six-membered rings with one nitrogen atom (Part 2A) and Volume 3 the six-membered rings with two or more nitrogens and with oxygen and sulfur heteroatoms (Part 2B).

Part 3 (Volume 4) covers five-membered heterocyclic rings with one oxygen, sulfur or nitrogen as the heteroatom and **Part 4** (Volumes 5 and 6) covers the same sized rings with more than one heteroatom. Rings with two or more nitrogen atoms only (Part 4A) are in Volume 5 and those with nitrogen, oxygen and sulfur (Part 4B) are in Volume 6.

Part 5 (Volume 7) covers heterocyclic compounds with rings smaller than five and larger than six. The separate monograph chapters deal with three-membered rings with nitrogen, oxygen and sulfur, with two heteroatoms, and their fused derivatives, four-membered rings with nitrogen, oxygen and sulfur, with two or more heteroatoms, and their fused derivatives, cephalosporins, penicillins, seven-membered rings with nitrogen, oxygen, sulfur, and with two or more heteroatoms, eight-membered rings, larger rings, crown ethers and cryptands, and heterocyclophanes.

Part 6 (Volume 8) contains the Author and Subject Indexes, together with a Ring Index and a Physical Data Index which are described below in Section 1.3.7.

*Chapter 1.01 of 'Comprehensive Heterocyclic Chemistry', by A. R. Katritzky, University of Florida, and C. W. Rees, Imperial College of Science and Technology.

1.3.2 RELATIONSHIP OF HETEROCYCLIC TO CARBOCYCLIC AND ALIPHATIC CHEMISTRY

1.3.2.1 Carbocyclic Chemistry

Carbocyclic compounds are very usefully divided into (a) saturated (alicyclic) compounds, (b) aromatic compounds and (c) the intermediate partially unsaturated (alicyclic) compounds. Heterocyclic compounds can be subdivided in exactly the same way, and equally usefully.

In the main, the physical and chemical properties of saturated and partially unsaturated alicyclic compounds closely resemble those of the analogous acyclic compounds formally derived by cleavage of the carbon ring at a point remote from any functionality. Relatively small, but often significant, differences in properties arise from conformational effects, and from strain effects in small rings, and these differences can be striking in properties which are particularly sensitive to molecular shape.

In marked contrast to these are the fully 'unsaturated' aromatic compounds, epitomized by benzene, in which the carbocyclic rings formally consist of a conjugated set of alternating single and double bonds. Such systems have a specially stabilized cyclic π-electron system in which all of the bonding molecular orbitals are exactly filled and the antibonding orbitals are all empty. The aromatic properties initially associated with six-electron systems, as in benzene, the cyclopentadienyl anion and the cycloheptatrienyl cation, were later extended to any planar, monocyclic, fully conjugated polyene with a closed shell of $(4n + 2)$ π-electrons. Although not easily rigorously defined and quantified, the concept of aromaticity has been of enormous value in the understanding of carbocyclic chemistry. Since it is associated with molecular orbital energies, aromaticity is not particularly sensitive to the nature, and number, of the ring atoms and the concept is thus of equal generality in heterocyclic chemistry. The main features of carbocyclic aromatic systems are (a) their stability, and hence their ready formation, and regeneration after chemical attack, (b) their tendency to undergo substitution reactions which preserve the aromatic system rather than addition reactions which destroy it, (c) the uniformity of the bond lengths in the ring, which are not alternating single and double, and (d) their special spectroscopic characteristics, particularly NMR. All of these features reappear, to a greater or lesser extent, in heteroaromatic chemistry.

1.3.2.2 Saturated Heterocyclic Compounds

As noted above, the formation of an alicyclic ring from an acyclic compound makes relatively little difference to the properties of the compound. The same principle applies to the formation of a saturated heterocyclic compound from the corresponding acyclic compound, provided that the environment of the heteroatom is not changed significantly. Thus saturated cyclic ethers, sulfides and amines are very similar in physical and chemical properties to the analogous dialkyl ethers, sulfides and di- and tri-alkylamines. Differences arise in small ring compounds where chemical reactivity is enhanced greatly by strain in three-membered rings and to a lesser but still significant extent in four-membered rings. Furthermore, properties which depend critically on steric requirements, particularly of lone pairs of electrons on the heteroatom, can be significantly altered. Thus a very good approximation of the properties of tetrahydropyran and piperidine can be obtained from those of ethyl propyl ether and ethylpropylamine, respectively. Piperidine is a typical secondary aliphatic amine of the same base strength as ethylpropylamine; however, it is substantially more reactive as a nucleophile, because of the reduction in steric encumbrance of the nitrogen lone pair caused by ring formation.

1.3.2.3 Partially Unsaturated Heterocyclic Compounds

The same general principles also extend to the partially unsaturated rings, though with the extra complications expected from the presence of the double bond(s), especially in small rings. If the double bond is conjugated with the heteroatom, then the expected consequences of electron delocalization are observed; thus such oxygen and nitrogen compounds are enol ethers and enamines, respectively, and will show the appropriate modified reactivity. Again, as anticipated, dihydro heteroaromatic compounds usually oxidize very readily to the aromatic compound.

Many reduced heteroaromatic compounds are important and are dealt with in the General

Chapters and appropriate Monograph Chapters, but usually more briefly than for the corresponding heteroaromatic systems because of this overall similarity with the corresponding acyclic compounds.

1.3.2.4 Heteroaromatic Compounds

Although the range of heteroaromatic structures has, like the carbocyclics, expanded considerably in recent times, the central core of the subject is still based on the 6π-electron system. These structures are related to, and formally derived from, benzene by successive replacement of one or two annular CH groups by trivalent or divalent heteroatom groups, respectively; the overall pattern of filled bonding molecular orbitals is retained. Thus replacement of one CH group by O^+, S^+ or N gives the six-membered pyrylium, thiinium or pyridine systems and replacement of two CH groups by O, S or NH gives the five-membered furan, thiophene or pyrrole. Multiple replacements are also possible and systems with up to four heteroatoms in five- and six-membered rings are common. The 6π-electron structure is preserved since the trivalent and divalent heteroatoms contribute one and two electrons, respectively, to the aromatic orbitals.

1.3.3 CHARACTERISTICS OF HETEROATOMS IN RINGS

The replacement of one CH group in benzene by —N= to give pyridine introduces an electron-withdrawing heteroatom into the ring. The electron-withdrawing effect is accentuated when a CH in pyridine is replaced by a positively charged atom (NR^+, O^+ or S^+). Thus the six-membered heteroaromatic rings are electron deficient (π-deficient). The introduction of further heteroatoms into a six-membered ring reinforces these effects and thus the chemistry of, for example, pyrazine is related to that of pyridine in much the same way as that of pyridine is related to benzene. In view of this, the chemistry of all the six-membered heterocycles is considered together in Part 2.

The replacement of two CH groups in benzene by a neutral NR, O or S introduces into the new ring an electron-donating heteroatom. This electron-donor character is accentuated in the pyrrole anion where N^- is introduced. Thus the five-membered rings with one heteroatom are electron rich (π-excessive), and the chemistry of pyrrole, furan and thiophene is dominated by this effect and is again considered together as a whole in Part 3.

However, five-membered rings containing two or more heteroatoms necessarily possess both a pyridine-like heteroatom *and* a pyrrole-like heteroatom. Thus their chemistry shows similarities to those of both the six-membered rings *and* the five-membered rings with one heteroatom; this is dealt with in Part 4.

1.3.4 THE GENERAL CHAPTERS

The three General Chapters on structure, reactivity and synthesis which preface the monograph chapters in each of Parts 2 to 5 are an important and integral feature of this work. Their purpose is to introduce each family of ring systems and to emphasize the logical correlations within them, and so to help in the understanding of known reactions and in the prediction of new ones. These 12 General Chapters thus provide an overview of the whole subject of heterocyclic chemistry and they should be of particular interest to students and teachers. As far as possible, the general arrangement of these chapters conforms to the following pattern and sequence.

1.3.4.1 General Chapters on Structure

These cover the following topics: (*a*) theoretical methods, with emphasis on the utility of such methods; (*b*) molecular dimensions, as determined by X-ray, electron diffraction and microwave spectra; (*c*) molecular spectra, covering NMR, IR, UV, mass and photoelectron spectra; (*d*) thermodynamic aspects, such as stability, ring strain, aromaticity, shape and conformation of saturated and partially saturated rings; (*e*) tautomerism, including prototropic and ring–chain; (*f*) betaine and other unusual structures.

1.3.4.2 General Chapters on Reactivity

These are divided into sections dealing with the aromatic compounds first, with their fully or partially saturated derivatives, and with reactions of substituents. Thus the order is (i) reactivity at the ring atoms of aromatic compounds [(*a*) general survey; (*b*) thermal and photochemical reactions involving no other species; (*c*) reactivity towards electrophiles (including oxidants); (*d*) reactivity towards nucleophiles (including reducing agents); (*e*) reactivity towards radicals, carbenes and nitrenes, and at surfaces; (*f*) reactions with cyclic transition states]; (ii) reactivity of saturated and partially saturated compounds; (iii) reactivity of substituents [(*a*) general survey of the effect of rings on reactions of substituents; (*b*) survey of the effect of rings on reactions of individual substituents in the order: fused benzene rings; *C*-linked (alkyl, aryl, acyl, carboxy, cyano); *N*-linked (nitro, amino); *O*-linked (hydroxy, alkoxy); *S*-linked; halogens; metals; other non-hetero fused heterocyclic rings].

1.3.4.3 General Chapters on Synthesis

These consider ring syntheses from non-heterocyclic compounds first, followed by transformation of other heterocyclics. Syntheses in which no new heterocyclic ring is formed are dealt with primarily in the appropriate reactivity section, but with cross-referencing when necessary. Ring syntheses from acyclic precursors are dealt with as logically as possible according to the number and nature of the new ring bonds formed in the process.

1.3.5 THE MONOGRAPH CHAPTERS

The monograph chapters represent the heart of the work and the biggest portion. Monograph chapters dealing with single ring systems are divided into the same three sections (on structure, reactivity and synthesis) as the General Chapters and organized similarly, together with a fourth section where appropriate on applications and important compounds. Where two or more ring systems are covered in one chapter, they are where appropriate treated together, in the same sections. The following conventions concerning the treatment of fused rings should be noted.

Fused benzene rings are treated as substituents. Thus quinoline, for example, is considered as a substituted pyridine, albeit a very special and important one, and treated alongside other substituted pyridines in the discussion of its structure, reactivity and synthesis. Reactions of quinoline at positions 1–4 are considered as reactions at ring atoms, whilst reactions at positions 5–8 are regarded as reactions of the 'substituent'.

For fused heterocyclic rings, structures containing two (or more) *non*-fused heterocyclic rings are treated in the monograph chapter appearing last in the sequence; thus thiamine is considered under thiazole (in Part 4) rather than as a pyrimidine (in Part 2). However, fused heterocyclic ring systems are treated in separate monograph chapters. These appear in the sequence according to (a) that single ring system which appears latest in the classification, and (b) the next ring system. Thus pyridoimidazoles precede purines, but both follow imidazoles.

The applications sections of monograph chapters provide access to important compounds used in medicine or industry, to industrially important sources of compounds, and to key natural products.

1.3.6 THE REFERENCE SYSTEM

A relatively new reference citation system has been employed which rapidly becomes familiar with use and then has distinct advantages over the more common superscript number method. In this system no reference numbers appear in the text, in tables, in footnotes or at the end of chapters. Instead, each time a reference is cited there appears in angle brackets a letter code assigned to the journal, preceded by the year (tens and units only except for non-twentieth century references) and followed by the page number. For example, "It was shown ⟨80TL2727⟩ that . . . ." where 80 refers to 1980, TL to *Tetrahedron Letters* and 2727 to the page number. For journals which are published in separate parts, or which have more than one volume per year, the appropriate part or volume is indicated, *e.g.* ⟨73JCS(P2)1594⟩ refers to *J. Chem. Soc., Perkin Trans. 2,* 1973, p. 1594. A full list of journal codes is reproduced in each Volume. Patents have three-letter

codes as appropriate, *e.g.* ⟨60USP2922790⟩ refers to *U.S. Pat.* 2 922 790 (1960). Books which are frequently referred to are also given a code, preceded by the letter B, *e.g.* ⟨B-73NMR96⟩ refers to T. J. Batterham, 'NMR Spectra of Simple Heterocyclics', Wiley, New York, 1973, p. 96. Journals and books which are referred to rarely are coded MI for miscellaneous, books again being indicated by the B- prefix.

This reference system is considered to be more useful than the conventional superscript number method since it enables the reader to see immediately in which year and in which journal (at least for the more common journals whose letter codes soon become familiar) the work cited was published. The reader is thus able to go directly to the original literature reference without having to consult a bibliography. It also provides the author and editor with the considerable advantage of being able to add or delete references up to the final submission of the manuscript without altering the numbering system.

All the references for all the chapters in a given volume are collected together in a merged list at the end of that volume (where they are most easily located). There are no separate chapter bibliographies. In the final list, references are given both in code and in full conventional form, with authors' names. They appear in an ordered sequence, numerically by year, then alphabetically by journal code, and then by page number. Cross references to the text citation are also given in the reference list.

1.3.7 THE INDEXES

1.3.7.1 Author and Subject Indexes

The Author Index of over 20 000 names has been compiled from the 30 000 or so references in the text and tables. The style is such, *e.g.*

Meyers, A. I., **1,** 237, 319 ⟨78TL5179⟩; **3,** 423 ⟨81JOC3881⟩

that the reader can proceed to the text page where the work is cited, directly to the original literature, or to the literature reference at the end of each volume. More details are given at the beginning of the index in Volume 8.

The Subject Index of over 20 000 entries has been compiled from keywords, names and formulae in the text and tables. It covers general classes of compound, specific compounds, general types of reaction, specific and named reactions, spectral and other properties, and other topics in heterocyclic chemistry. More details are again given at the beginning of the index in Volume 8.

1.3.7.2 Ring Index

The Ring Index, similar in style and organization to the Patterson and *Chemical Abstracts* Ring Indexes, gives the formula, full name and ring numbering of all the parent ring systems. Under these are included all the heterocyclic compounds mentioned in the text, tables, formulae, equations and schemes (except for trivial cases, *e.g.* when pyridine is used as a solvent). Compounds are classified according to their fully unsaturated parent compound. Thus substituted, partially saturated and fully saturated derivatives of (say) pyrrole are all indexed under pyrrole. Benzo and similar derivatives are indexed under the most unsaturated parent system, *e.g.* quinoline, thienofuran, benzoxepin. This provides a useful cross referencing of the main text material where benzo derivatives are classified as substituted derivatives of the parent monocyclic system (see above).

Index entries are divided into two categories, primary and secondary. *Primary* index entries are used when a significant part of the text is devoted to a particular ring system; this may be a whole chapter, or a section or subsection. *Secondary* index entries are used when a heterocyclic system is mentioned in a chapter devoted to another (primary) system. This may be, for example, as a starting material or as a product, or in a discussion comparing properties.

1.3.7.3 Physical Data Index

The Physical Data Index summarizes the quantitative data given for specific compounds in the text, tables and figures in Volumes 1–7. It does not give any actual data but includes references

both to the appropriate text page and to the original literature. The structural and spectroscopic methods covered include UV, IR, Raman, microwave, MS, PES, NMR, ORD, CD, X-ray, neutron and electron diffraction, together with such quantities as dipole moment, pK_a, rate constant and activation energy, and equilibrium constant.

1.4
Explanation of the Reference System

References are designated by a number–letter coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted; the advantages of this system are outlined in Chapter 1.3. The system is based on that previously used in the following two monographs: (a) A. R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic N-Oxides', Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, 'The Tautomerism of Heterocycles', in 'Advances in Heterocyclic Chemistry', Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journal codes is given in alphabetical order together with the journals to which they refer on the end papers of each volume, including the present Handbook.
2. The references are given in full at the end of the relevant volume of CHEC.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, *etc.*
5. For non-twentieth century references the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are *not* included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three letter codes.
9. Frequently cited books are assigned codes, but the whole code is now prefixed by the letter 'B-'.
10. Less common journals and books are given the code 'MI' for miscellaneous. The CHEC chapter number containing the reference is embodied in the reference code, *e.g.* 〈73MI42602〉 occurs in Chapter 4.26 of CHEC. Refer to the complete contents of CHEC on pp. 5–7 to find the volume containing the full citation details.
11. Where journals have changed names, the same code is used throughout, *e.g.* CB refers both to *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

1.5
Special Features of the Handbook

1.5.1 TOPICS COVERED AND ARRANGEMENT

The individual chapters of this Handbook are based on the general chapters of CHEC. However, considerable modifications have been made to these general chapters.

The general chapters for CHEC were written by five different groups of authors. Although each started out from the same master plan, individual initiatives very properly led to somewhat different interpretations. However, for this Handbook, it was considered important where possible to present the material in a strictly standard order, and therefore rearrangements have been made to the order in which the material is presented.

For the 'Structure' and 'Reactivity' chapters, the Handbook usually follows the order of material used in the corresponding general chapters for the five-membered ring with several heteroatoms. Certain portions of the text have been deleted and additional material has been incorporated, particularly for the six-membered rings, to give the Handbook a more appropriate balance.

Reference lists have been deleted. Under the reference system employed, a reference can usually be identified by its citation (see p. 15); complete details are given in the reference list in the appropriate volume of CHEC.

The synthesis section, while retaining many concepts from the original, has been largely rewritten with the aim of achieving an integrated approach.

1.5.2 SCOPE OF THE HANDBOOK

The following are not covered in this Handbook for reasons of space, and the interested reader is referred to the designated chapters of CHEC:

(i) Heterocycles with heteroatoms other than O, N and S: CHEC 1.17–1.22.
(ii) Biosynthesis and toxicity of heterocycles: CHEC 1.04 and 1.05.
(iii) Applications of heterocycles: CHEC 1.06–1.16.
(iv) The review literature of heterocyclic compounds: CHEC 1.03.

Part 2
Structure of Heterocycles

2.1
Overview

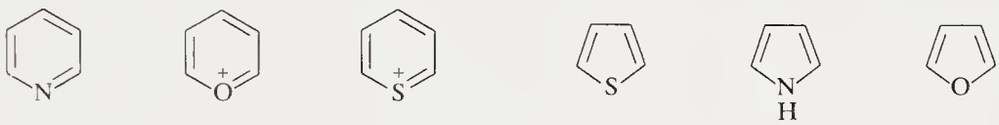
2.1.1 RELATIONSHIP OF HETEROCYCLIC AND CARBOCYCLIC AROMATIC COMPOUNDS

Heterocyclic compounds (like carbocyclic compounds) can be divided into heteroaromatic and heteroalicyclic types. The chemistry of the heteroalicyclic compounds is in general similar to that of their aliphatic analogues, but that of heteroaromatic compounds involves additional principles.

Aromatic compounds possess rings in which each of the ring atoms is in the same plane and has a *p*-orbital perpendicular to the ring plane, and in which $(4n + 2)$ π-electrons are associated with each ring.

Six-membered aromatic heterocycles are derived from benzene by replacing CH groups with N, O^+ or S^+, which are isoelectronic with the CH group. One CH group can be replaced to give pyridine (**1**), the pyrylium ion (**2**) and the thiinium (thiopyrylium) ion (**3**). Replacement of two or more CH groups with retention of aromaticity is possible.

The five-membered aromatic heterocycles thiophene (**4**), pyrrole (**5**) and furan (**6**) are formally derived from benzene by replacement of two CH groups, with one S, NH or O, each of which can contribute *two* electrons to the aromatic sextet. Other five-membered aromatic heterocycles are derived from compounds (**4**), (**5**) and (**6**) by further replacement of CH groups with N, O^+ or S^+.



(1) (2) (3) (4) (5) (6)

2.1.2 ARRANGEMENT OF STRUCTURE CHAPTERS

Each of the chapters on structure commences with a survey of the possible heterocyclic structures with the size of the ring in question. Structures are generally subdivided into those in which the ring atoms are all in conjugation with each other (*aromatic* or *antiaromatic*) and those in which at least one sp^3-hybridized ring atom interrupts the conjugation. The first class is further subdivided into those possessing exocyclic conjugation, and those without.

Theoretical methods are surveyed, followed by data on molecular dimensions obtained from X-ray diffraction or microwave spectroscopy. The various types of NMR spectroscopic characteristics are then surveyed, including ^1H, ^{13}C and nitrogen NMR spectroscopy. This is followed by a discussion of UV and visible and then IR, mass and photoelectron spectroscopy. Each of the spectroscopic sections deals with both the various parent rings and the effect of substituents.

The next main section deals with thermodynamic aspects. It starts by consideration of the intramolecular forces between heterocyclic molecules which influence melting and boiling points, solubility and chromatographic characteristics. This is followed by a section on stability and stabilization, including thermochemistry and conformation of the saturated ring systems, and then a discussion of aromaticity.

The last major section deals with tautomerism, including angular tautomerism where applicable and then substituent tautomerism.

2.1.3 NOMENCLATURE*

Some of the rules of systematic nomenclature used in *Chemical Abstracts* and approved by the International Union of Pure and Applied Chemistry are collected here. Important trivial names are listed at the beginning of individual chapters.

The types of heteroatom present in a ring are indicated by prefixes: 'oxa', 'thia' and 'aza' denote oxygen, sulfur and nitrogen, respectively (the final 'a' is elided before a vowel). Two or more identical heteroatoms are indicated by 'dioxa', 'triaza', *etc.*, and different heteroatoms by combining the above prefixes in order of preference, *i.e.* O, S and N.

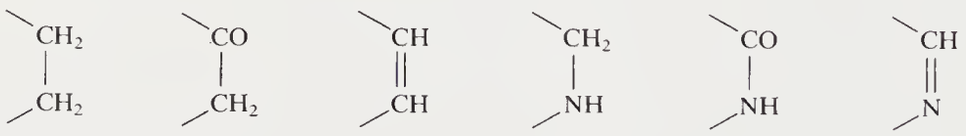
Ring size and the number of double bonds are indicated by the suffixes shown in Table 1. Maximum unsaturation is defined as the largest possible number of non-cumulative double bonds (O, S and N having valencies of 2, 2 and 3, respectively). Partially saturated rings are indicated by the prefixes 'dihydro', 'tetrahydro', *etc.*

Table 1 Stem Suffixes for Hantzsch–Widman Names

	Rings with nitrogen			*Rings without nitrogen*		
Ring size	*Maximum unsaturation*	*One double bond*	*Saturated*	*Maximum unsaturation*	*One double bond*	*Saturated*
3	-irine	—	-iridine	-irene	—	-irane
4	-ete	-etine	-etidine	-ete	-etene	-etane
5	-ole	-oline	-olidine	-ole	-olene	-olane
6	-ine	—	—	-in	—	-ane
7	-epine	—	—	-epin	—	-epane
8	-ocine	—	—	-ocin	—	-ocane
9	-onine	—	—	-onin	—	-onane
10	-ecine	—	—	-ecin	—	-ecane

Numbering starts at an oxygen, sulfur or nitrogen atom (in decreasing order of preference) and continues in such a way that the heteroatoms are assigned the lowest possible numbers. Other things being equal, numbering starts at a substituted rather than at a multiply bonded nitrogen atom. In compounds with maximum unsaturation, if the double bonds can be arranged in more than one way, their positions are defined by indicating the nitrogen or carbon atoms which are not multiply bonded, and consequently carry an 'extra' hydrogen atom, by '1*H*-', '2*H*-', *etc.* In partially saturated compounds, the positions of the hydrogen atoms can be indicated by '1,2-dihydro', *etc.* (together with the 1*H*-type notation if necessary); alternatively, the positions of the double bonds can be specified; for example 'Δ^3-' indicates that a double bond is between atoms 3 and 4. A positively charged ring is denoted by the suffix '-ium'.

The presence of a ring carbonyl group is indicated by the suffix '-one' and its position by a numeral, *e.g.* '1-one', '2-one', *etc.*; the numeral indicating the position of the carbonyl group is placed immediately before the name of the parent compound unless numerals are used to designate the position of heteroatoms, when it is placed immediately before the suffix. Compounds containing groups (**8**) or (**11**) are frequently named either as derivatives of (**7**) and (**10**) or of (**9**) and (**12**).



(**7**) (**8**) (**9**) (**10**) (**11**) (**12**)

Ring C=S and C=NH groups are denoted by the suffixes '-thione' and '-imine'; *cf.* '-one' for the C=O group.

*For a detailed discussion, see CHEC 1.02.

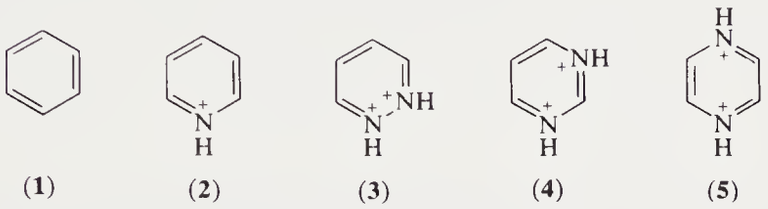
2.2

Structure of Six-membered Rings*

2.2.1 SURVEY OF POSSIBLE STRUCTURES: NOMENCLATURE

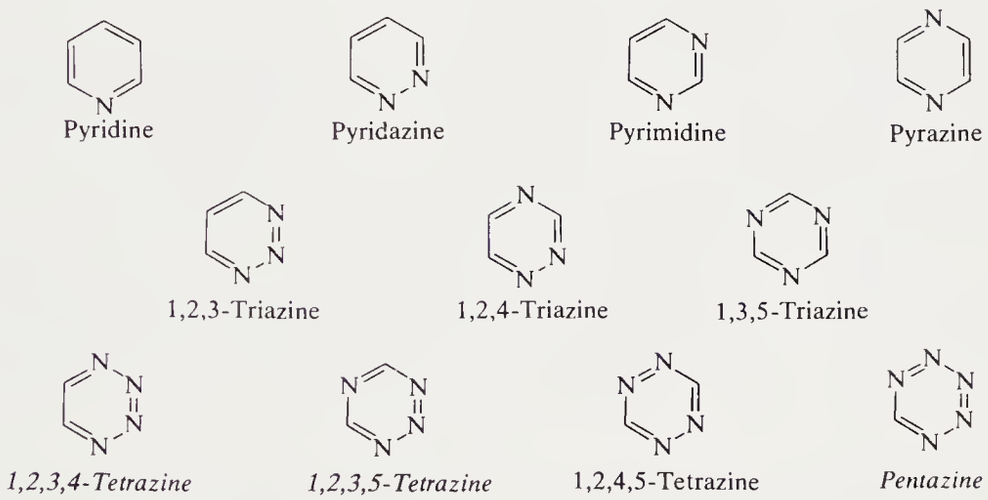
2.2.1.1 Aromatic Nitrogen Systems without Exocyclic Conjugation

Since N^+ and C are isoelectronic, the simplest and most direct hetero-analogue of benzene (**1**) is the pyridinium ion (**2**). Further 'azonia substitution' of this kind gives the disubstituted species (**3**)–(**5**).



(**1**) (**2**) (**3**) (**4**) (**5**)

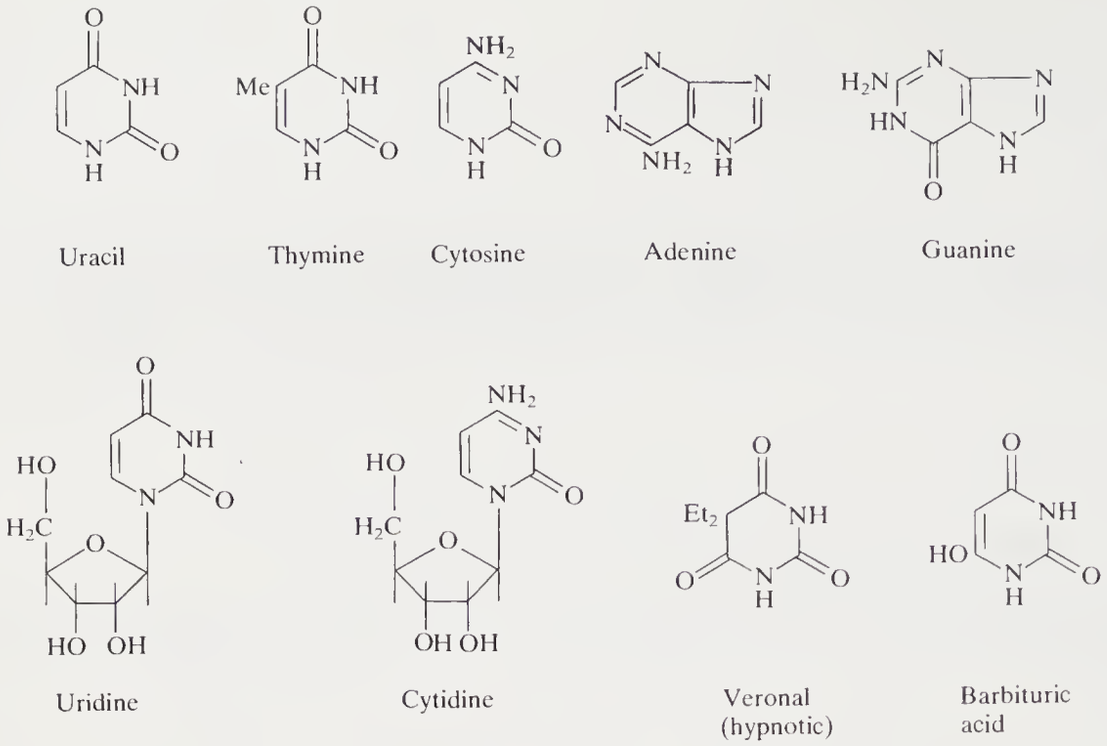
Deprotonation from the azonium group leaves a lone pair of electrons on the nitrogen atom, and a neutral aza substituent. The known monocyclic azines (see Scheme 1a) include all the possible triazines, but only one tetrazine—the 1,2,4,5-isomer. Some 1,2,3,5-tetrazines have been reported, but only when heavily substituted or fused, and some reduced 1,2,3,4-tetrazines have been prepared, but no aromatic derivatives (see CHEC 2.21). No pentazines are known.



Scheme 1a Monocyclic heteroaromatic nitrogen systems with six-membered rings (italicized names: compounds as yet unknown)

Pyrimidine natural products are particularly important (Scheme 1b). The nucleic acids contain pyrimidine and purine bases; ribonucleic acids (RNA) contain D-ribose and uracil, deoxyribonucleic acids (DNA) contain 2-deoxy-D-ribose and thymine and both types contain phosphate residues, cytosine, adenine and guanine. Nucleosides are pyrimidine or purine glycosides (*e.g.* uridine, cytidine).

*Adapted from Chapter 2.01 of 'Comprehensive Heterocyclic Chemistry', by A. McKillop and A. J. Boulton, University of East Anglia.

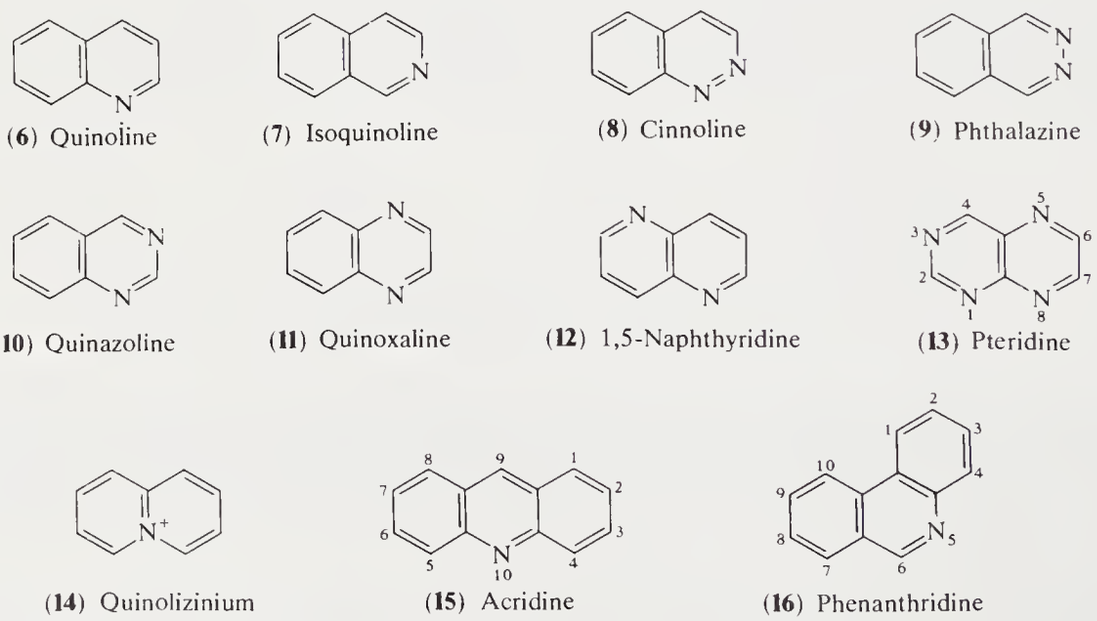


Scheme 1b Important derivatives

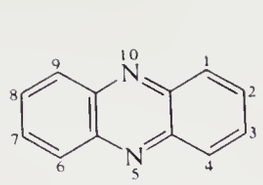
Synthetic derivatives (*e.g.* veronal) of barbituric acid are hypnotics.

When two fused six-membered rings (naphthalene analogues) are considered, possibilities become very numerous. There are two monoazanaphthalenes, quinoline (**6**) and isoquinoline (**7**), four benzodiazines [cinnoline (**8**), phthalazine (**9**), quinazoline (**10**) and quinoxaline (**11**)], with the two nitrogen atoms in the same ring, and six naphthyridines [*e.g.* (**12**), named and numbered in a systematic way] with the nitrogens in different rings. Of the higher polyazanaphthalenes which have been prepared (examples with up to six nitrogen atoms are known), the important pteridine system (**13**) should be noted. Both the benzotriazines are known, but 1,2,3,4-benzotetrazine is not. Other fused diazines include purine and alloxazine.

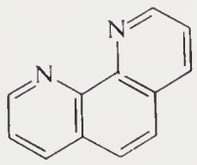
Azonia substitution at a naphthalene bridgehead position gives the quinolizinium ion (**14**). The two most well-known monoaza systems with three aromatic fused rings are acridine (**15**), derived structurally from anthracene, and phenanthridine (**16**), an azaphenanthrene. The better-known diaza systems include phenazine (**17**) and 1,10-phenanthroline (**18**), while systems with three linearly fused pyridine rings are called anthyridines, *e.g.* the 1,9,10-isomer (**19**).



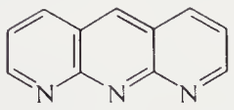
Scheme 2 Polycyclic aromatic nitrogen systems



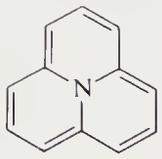
(**17**) Phenazine



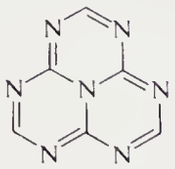
(**18**) 1,10-Phenanthroline



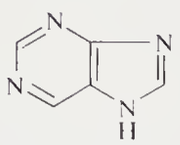
(**19**) 1,9,10-Anthyridine



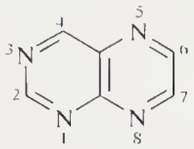
(**20**)



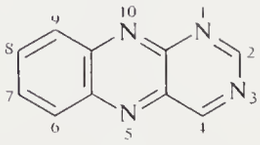
(**21**)



Purine



Pteridine



Alloxazine

Scheme 2 Polycyclic aromatic nitrogen systems (*continued*)

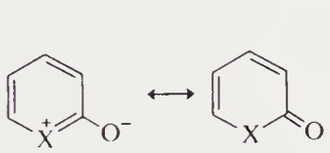
Although most ring systems are numbered according to a fairly straightforward set of rules (see CHEC 1.02), there are several exceptions. Acridine, for instance, now has its 'meso' positions numbered 9 and 10 (see structure **15**). (At least two other systems have been widely used in the past.) Phenazine, however, is numbered systematically, as in structure (**17**). Phenanthridine (**16**) is now numbered in the systematic fashion as indicated.

Heterocycles structurally based on the phenalene ring system frequently possess distinctive colors. With nitrogen as the central atom we have the unstable 9a-azaphenalene (**20**), recently prepared ⟨76JCS(P1)341⟩. The cyclazine nomenclature is commonly applied to this and related compounds: thus, (**20**) is (3.3.3)cyclazine. Further aza substitution is possible, *e.g.* as in the heptaazaphenalene (**21**).

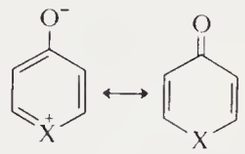
2.2.1.2 Aromatic Systems with Exocyclic Conjugation

Important compounds of three classes result when a positively charged ring carries a negatively charged substituent.

(i) In certain relative orientations the charges may formally cancel. The 2- and 4-pyridone structures (**22**, **23**; X = NH) possess complete π-conjugation and 'aromatic' stabilization.



(**22**)



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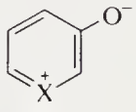
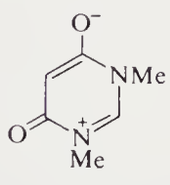


(**24**)

(ii) The isomeric structure (**24**; X = NH, O, S) contains the elements of azomethine or carbonyl ylides, which are 1,3-dipoles. More complex combinations lead to '1,4-dipoles', for instance the pyrimidine derivative (**25**) and the 'cross-conjugated ylide' (**26**).

(iii) Charge-separated species formed by attachment of an anionic group to an azonia nitrogen are also 1,3-dipoles: pyridine 1-oxide (**27**) and the ylide (**28**).



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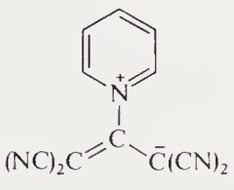

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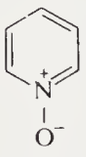

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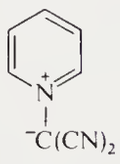
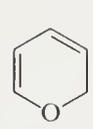


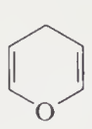
(**28**)

2.2.1.3 Ring Systems Containing One Oxygen or Sulfur

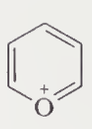
Replacement of CH in benzene by an oxonia group (O^+) gives the pyrylium cation, but no neutral oxygen analogue of pyridine is possible. Both 2*H*- and 4*H*-pyran contain sp^3-hybridized carbon atoms. Many trivial names exist for oxygen heterocycles and the more important of these are shown in Scheme 3.



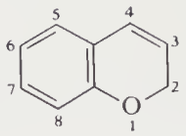
2*H*-Pyran



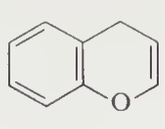
4*H*-Pyran



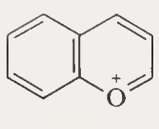
Pyrylium



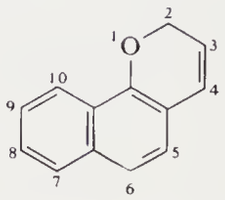
2*H*-Chromene
(2*H*-1-benzopyran)



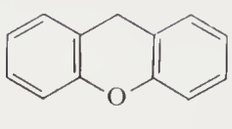
4*H*-Chromene
(4*H*-1-benzopyran)



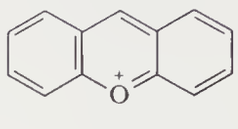
1-Benzopyrylium



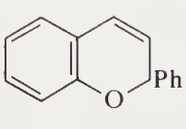
Benzo[*h*]chromene
(2*H*-naphtho[1,2-*b*]pyran)



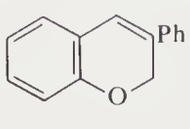
Xanthene
(9*H*-xanthene)



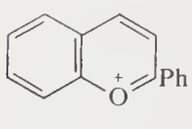
Xanthylium



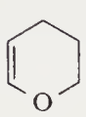
Flavene
(2-phenyl-2*H*-1-benzopyran)



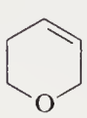
Isoflavene
(3-phenyl-2*H*-1-benzopyran)



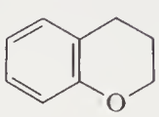
Flavylium
(2-phenyl-1-benzopyrylium)



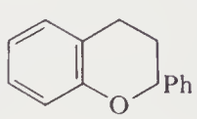
3,4-Dihydro-2*H*-pyran



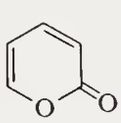
3,6-Dihydro-2*H*-pyran



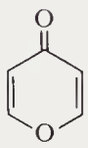
Chroman
(3,4-dihydro-2*H*-1-benzopyran)



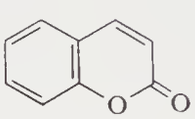
Flavan
(2-phenyl-3,4-dihydro-2*H*-
1-benzopyran)



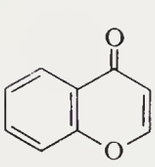
Pyran-2-one
(2*H*-pyran-2-one)



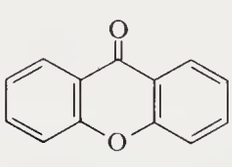
Pyran-4-one
(4*H*-pyran-4-one)



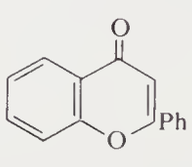
Coumarin
(2*H*-1-benzopyran-2-one)



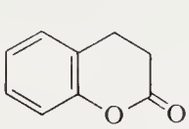
Chromone
(4*H*-1-benzopyran-4-one)



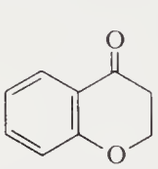
Xanthone
(9*H*-xanthen-9-one)



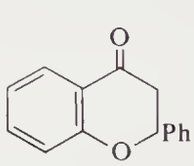
Flavone
(2-phenyl-4*H*-1-benzopyran-4-one)



Dihydrocoumarin
(3,4-dihydro-2*H*-1-benzopyran-2-one)



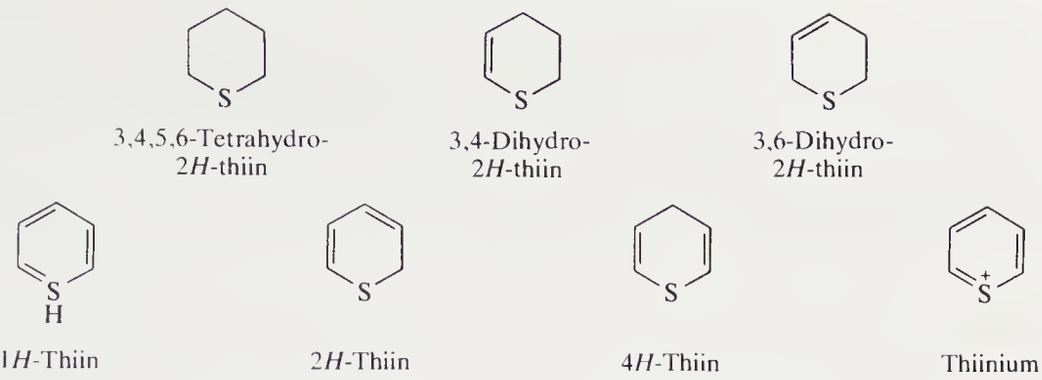
Chroman-4-one
(2,3-dihydro-4*H*-1-benzopyran-4-one)



Flavanone
(2-phenyl-2,3-dihydro-
4*H*-1-benzopyran-4-one)

Scheme 3 Oxygen heterocycles

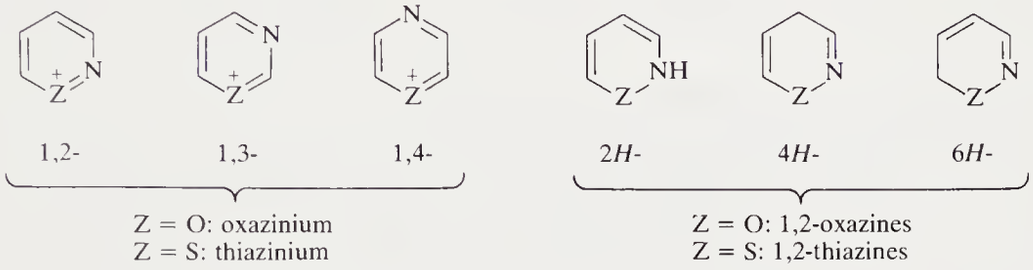
A few of the corresponding sulfur systems are given in Scheme 4; because of the availability of sulfur *d*-orbitals, the neutral species 1*H*-thiin is now a possibility and some substituted derivatives exist. These are the 'thiabenzenes', and with just the single heteroatom in the ring (C_5S rings) they are very unstable, non-planar structures which are largely ylidic in character (CHEC 2.25). Aza substitution results in stabilization.



Scheme 4 Monocyclic thiins: structure and nomenclature

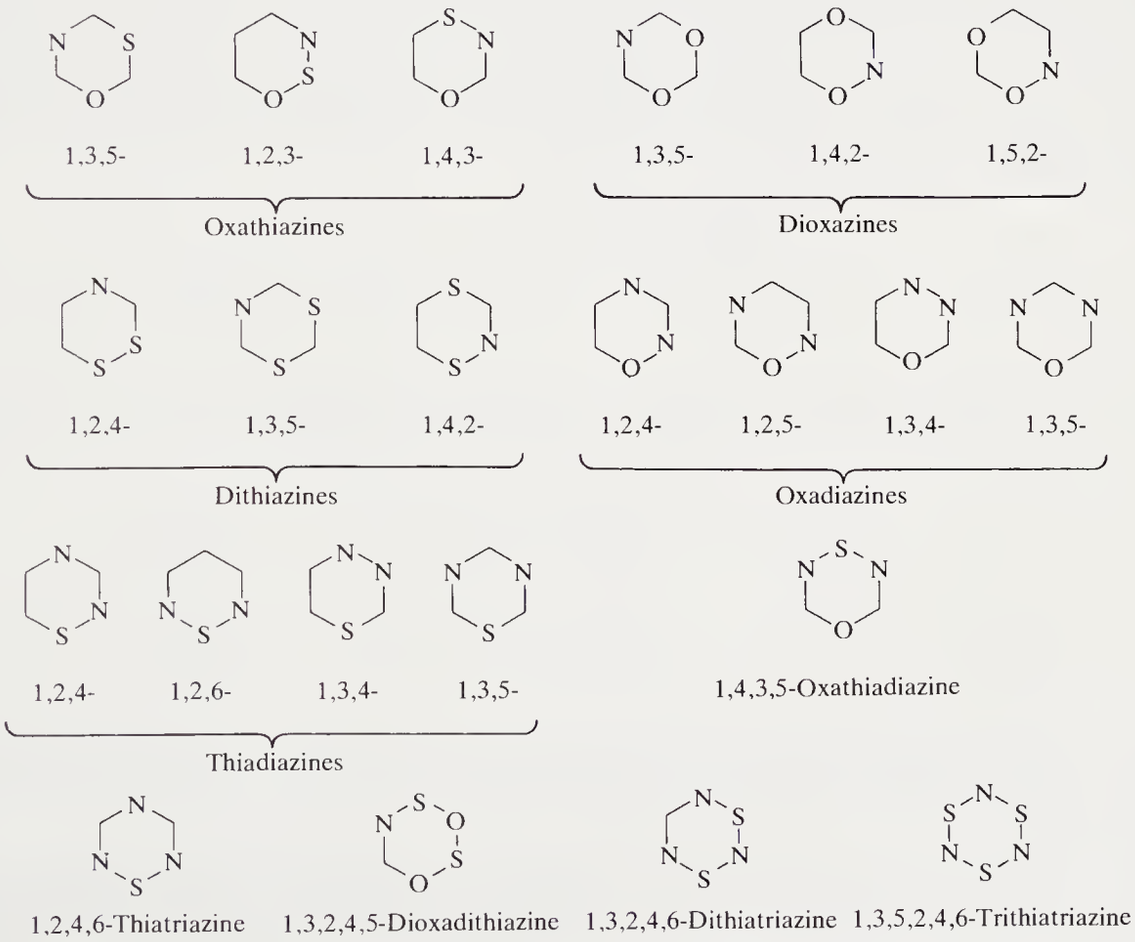
2.2.1.4 Rings Containing Nitrogen with Oxygen and/or Sulfur

Compounds with two heteroatoms are illustrated in Scheme 5. The oxazines and thiazines contain a saturated carbon atom; the corresponding aromatic cations are oxazinium and thiazinium.



Scheme 5 Oxazines and thiazines

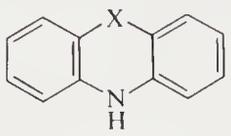
The range of possible ring systems with three, four or five heteroatoms is considerable: some of the more common systems are delineated in Scheme 6.



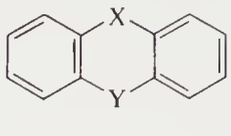
Scheme 6 Six-membered monocyclic systems containing nitrogen with oxygen and/or sulfur (the name printed corresponds to the ring with maximum unsaturation)

2.2.1.5 Fully Conjugated but Non-aromatic Compounds

Cyclic π-conjugation is also present in six-membered rings containing two double bonds and two atoms (NH, O, S) each carrying a lone pair of electrons. The eight π-electrons imply 'antiaromaticity'. Many such systems are known. Particularly when the heteroatoms are oxygen or sulfur, the rings are often folded (heteroatoms 1,4-) or puckered (1,2-). The best-known examples are the dibenzo-fused systems phenothiazine (**29**; X = S), phenoxazine (**29**; X = O), thianthrene (**30**; X = Y = S), phenoxathiin, or phenoxthionine (**30**; X = S, Y = O) and dibenzo-*p*-dioxin (**30**; X = Y = O). An aromatic sextet of electrons can be formulated for the sulfur-containing rings by invoking *d*-orbital participation for one of the S atoms (acceptor) and assuming that the other S atom behaves as a *p*-donor. Although most physical methods indicate at least non-aromaticity for these compounds, chemical reactivity does show some evidence of undergoing substitution rather than addition reactions, particularly for 1,4-dithiin derivatives (see Section 3.2.2.1.2).



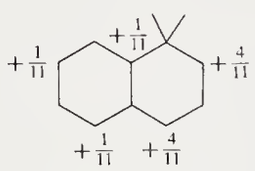
(**29**)



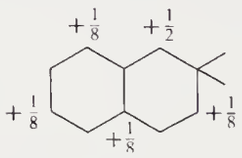
(**30**)

2.2.2 THEORETICAL METHODS: CALCULATIONS*

Molecular orbital methods have been applied with considerable success for correlation of physicochemical properties of azines such as electronic spectra and ionization potentials ⟨65AHC(5)69⟩. The reactivities of the azines are amenable to a semiquantitative treatment not applicable to the five-membered heteroaromatic systems. Thus, they may be considered aza derivatives of even alternant hydrocarbons for which 'Dewar reactivity numbers', *N*, are easily derived. The latter are approximations to the relative energies of forming the Wheland intermediates at alternative positions. In naphthalene, for example, N_α (**31**) is less than N_β (**32**) implying a lower energy, and therefore more facile formation of the intermediate at the former position. In the aza analogues deactivation by the heteroatom leads to preferential substitution in the benzenoid ring. On this basis electrophilic substitution of isoquinoline would be expected to take place at the 5- and/or 8-positions. However, attack at the latter should be somewhat less favorable since this places a positive charge (1/11 *e*) on the nitrogen, an electronegative atom. Indeed, nitration of quinoline does lead to substitution at both positions with that at the former predominating.

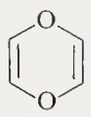


(**31**) $N_\alpha = 1.81$

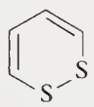


(**32**) $N_\beta = 2.12$

(**33a**) (**33b**)



(**34**)



(**35**)

Theoretical calculations suggest that canonical forms with double bonds between two nitrogen atoms (*e.g.* **33a**) contribute less to the resonance hybrid than to those without such N=N double bonds (*e.g.* **33b**).

The valence electron distribution in the pyrylium cation indicates that the positive charge is carried by the carbon atoms rather than by oxygen. Calculations also indicate a higher positive charge at C-2 and C-6 than at C-4.

*Much of the introductory discussion given in Section 2.4.2 for the azoles applies equally to other heterocycles.

HMO indices for coumarin overestimate the reactivity of the 4-position, whereas SCF-MO free valences correctly predict that C-3 is the most reactive site toward homolytic substitution.

The non-aromaticity of 1,4-dioxin (**34**) has been supported by calculations using the Hückel $\sigma\pi$-approximation which gives a negative Dewar resonance energy of -5.4 kJ mol^{-1} (*cf.* benzene 86 kJ mol^{-1}).

A technique which combines perturbation theory and the graph-theoretical definition of resonance energy also predicts a negative resonance energy for both 1,4-dithiin and 1,2-dithiin (**35**).

2.2.3 STRUCTURAL METHODS

2.2.3.1 X-Ray Diffraction

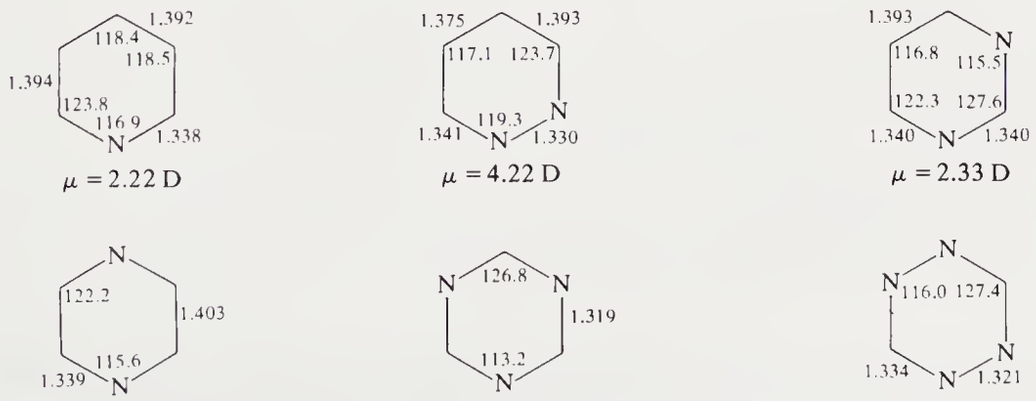
A compilation of X-ray data for heterocyclic compounds ⟨70PMH(5)1⟩ contains many examples of six-membered rings (see Table 1).

Table 1 X-Ray Structures of Compounds with Six-membered Rings and One or More Heteroatoms[a]

Ring	*Ring position* 1	2	3	4	5	6	*Examples of compounds studied*
C_5N	N	—	—	—	—	—	Pyridines, pyridones, pyridine *N*-oxides, piperidines
C_4N_2	N	—	N	—	—	—	Pyrimidines, thymine, barbituric acid
	N	—	—	N	—	—	Pyrazines, piperazines
C_3N_3	N	—	N	—	N	—	*s*-Triazines, cyanuric acid
C_2N_4	N	N	—	N	N	—	1,2,4,5-Tetrazines, dihydro derivatives[b]
C_5O	O	—	—	—	—	—	α-D-Glucose, α-L-sorbose, kanamycine monosulfate monohydrate
C_4O_2	O	—	—	O	—	—	1,4-Dioxanes
C_3O_3	O	—	O	—	O	—	Trioxane
C_5S	S	—	—	—	—	—	Thiins, 6-benzoyl-3-hydroxy-1-methyl-5-phenylthiabenzene 1-oxide
C_4S_2	S	S	—	—	—	—	1,2-Dithiane-3,6-dicarboxylic acid
	S	—	S	—	—	—	2-Phenyl-1,3-dithiane
	S	—	—	S	—	—	1,4-Dithianes, 1,4-dithiins
C_3S_3	S	—	S	—	S	—	1,3,5-Trithiane
C_4NO	O	—	—	N	—	—	Morpholine
C_4NS	S	—	—	N	—	—	Cycloalliin hydrochloride monohydrate, 4-methyl-thiomorpholine 1,1-dioxide
C_4OS	O	—	—	S	—	—	*trans*-2,3-Dichloro-1,4-oxathiane
C_3O_2S	S	O	—	—	—	O	Trimethylene sulfite

[a]For further details see ⟨70PMH(5)1⟩.
[b]See CHEC 2.21.3.2.

In Scheme 7 the bond lengths and internal bond angles are given for some of the simple azines, based on X-ray diffraction, gas-phase electron diffraction or microwave spectroscopy.

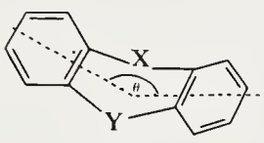


Scheme 7 Molecular dimensions and dipole moments of some simple azines

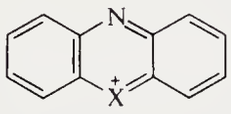
The C—N bond length is usually some 4% shorter than the C—C. To accommodate this with minimal disturbance of the other bond angles a small displacement of the N atoms toward the center of the ring, with consequent opening of the CNC bond angle from 120°, would be required. This is more or less what is observed in pyridinium salts (where NH^+ replaces one CH in benzene). However, the internal angle at the aza nitrogen in the free bases (where N: replaces CH) is generally found to be slightly less than 120°; the nitrogen nuclei are slightly further from the center of gravity than the carbons. These are comparatively minor deviations from a completely regular hexagon. Available data on pyrylium or thiinium salts are generally of heavily substituted ions. In the oxygen rings the trend outlined above with the pyridines is apparently *not* continued: in the studied examples the COC angle (about 124°) is slightly larger than that for a regular hexagon, and the interior angles in the ring at the carbons next to the oxygen are smaller (*ca.* 118°). Thiinium salts are characterized by long C—S bonds (*ca.* 1.72 Å) and a small CSC angle of *ca.* 104°.

With two O, S or NR groups and two C=C double bonds in a ring, the systems are not aromatic, and usually not planar. Thianthrene (**36**; X = Y = S) and its various sulfoxides and sulfones have a fairly sharp dihedral angle between the planes of the benzene rings ($\theta = 128°$ in thianthrene ⟨63AX310⟩). Phenoxathiin (**36**; X = S, Y = O) and phenothiazine (**36**; X = S, Y = NH) are also non-planar ($\theta = 136°$ and *ca.* 158°, respectively) ⟨66AX429, 68CC833⟩, but dibenzodioxin (**36**; X = Y = O) is apparently planar ($\theta = 180°$) ⟨78AX(B)2956⟩. Phenoxazine (**36**; X = O, Y = NH) probably has coplanar benzene rings, according to an early study ⟨40MI20100⟩, with a pyramidal nitrogen atom. When the central ring is rendered aromatic by oxidation (in the phenoxazinium and phenothiazinium ions (**37**; X = O and S), respectively), planarity is found as expected. The same effect is seen with the alloxazines (**38**), which are planar, and the dihydroalloxazines (**39**), which are not.

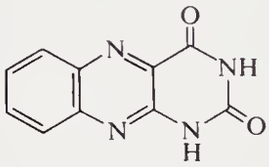
Many X-ray studies have also been carried out on saturated and partially saturated rings, *e.g.* piperidines and piperidones.



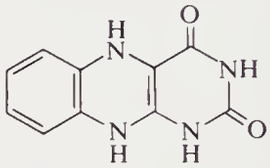
(**36**)



(**37**)



(**38**)



(**39**)

2.2.3.2 Microwave Spectroscopy ⟨74PMH(6)53⟩

Microwave spectra allow the determination of precise bond lengths and angles and some of the data in Scheme 7 were obtained in this way. In Table 2 details of molecular geometry are deduced from microwave spectra.

Table 2 Geometry of Six-membered Rings from Microwave Spectra[a]

Shape	*Molecules*
Planar	4-Pyrone,[b] 2-pyrone, 4-pyranthione, 4-thiopyrone
Twist-chair	2,3-Dihydropyran
Chair	Piperidine,[c] morpholine, 1-methylmorpholine, 1,3,5-trioxane

[a]Abstracted from ⟨74PMH(6)53⟩.
[b]Conjugation shown by bond lengths: short C—O and C—C, long C=C and C=O.
[c]Both *ax*-NH and *eq*-NH forms found; the latter predominates.

Microwave spectra allow the determination of conformations. For example, 2-formylpyridine is shown to be planar with the carbonyl group *trans* to the nitrogen atom.

Microwave spectra also provide precise values for dipole moments and values for pyridine and many substituted pyridines are available (Table 3 of CHEC 2.04).

2.2.3.3 ^{1}H NMR Spectra

2.2.3.3.1 Chemical shifts

The protons on the benzene ring experience a deshielding effect due to the aromatic ring current, which brings the chemical shift of the benzene protons to δ 7.24 p.p.m. The same ring current persists in the polyazabenzenes as in benzene itself. Attempts to use estimates of ring current for calculating aromaticity from comparisons of proton chemical shifts suffer from the difficulty of finding suitable models.

In the aza derivatives of the aromatic hydrocarbons the nitrogen atoms exert a strong deshielding influence on the α-hydrogen atoms, and a similar but smaller effect on the γ-hydrogens. The protons at the β positions in pyridine are in fact slightly shifted upfield of the benzene resonance. Further aza substitution produces similar effects, but strict additivity is not observed. For instance, two adjacent nitrogen atoms, as in pyridazine, exert a much larger deshielding effect on the α-protons than the sum of the α- and β-effects of a single nitrogen atom. Conversion of pyridine into the pyridinium cation causes a downfield shift of all the hydrogens, especially the β and γ.

Tables 3 and 4 summarize the chemical shifts of the protons in various aza heterocycles. ^{1}H NMR data for the corresponding heteroaromatic cations are given in Table 5.

Table 3 ^{1}H NMR Chemical Shifts of the Simple Monocyclic Azines (*cf.* benzene, δ 7.24) ⟨B-73NMR⟩

	$\delta(^1H)$ (p.p.m. TMS) (Position of N atoms indicated)							
Position	*Pyridine*	*Pyridazine*	*Pyrimidine*	*Pyrazine*	*1,2,3-Triazine*	*1,2,4-Triazine*	*1,3,5-Triazine*	*Tetrazine*
1	N	N	N	N	N	N	N	N
2	8.52	N	*9.26*[a]	8.6	N	N	9.18	N
3	7.16	9.17	N	8.6	N	9.63	N	(10.48)[b]
4	7.55	7.52	*8.78*	N	9.06	N	9.18	N
5	7.16	7.52	*7.36*	8.6	7.45	8.53	N	N
6	8.52	9.17	*8.78*	8.6	9.06	9.24	9.18	(10.48)

[a]Measured in $CDCl_3$.
[b]Calculated values; shifts for some monosubstituted tetrazine derivatives lie in the range 10.26–10.45 p.p.m. in CD_3OD, 10.11–10.25 p.p.m. in $CDCl_3$ ⟨81JOC5102⟩.

Table 4 ^{1}H NMR Chemical Shifts of Protons on the Heterocyclic Rings of Simple Benzazines (*cf.* naphthalene, column 1)

	$\delta(^1H)$ (p.p.m. TMS) (Position of N atoms indicated)							
Position								
1	7.72	N	9.15	N	N	N	9.44	N
2	7.33	8.81	N	N	9.23	9.74	N	N
3	7.33	7.27	8.45	9.15	N	8.74	N	N
4	7.72	8.00	7.50	7.75	9.29	N	9.44	9.85

Table 5 ^{1}H NMR Spectral Data for Six-membered Heteroaromatic Cations[a]

		$\delta(^1H)$ (p.p.m.)			J (Hz)			
Compound	*Anion/Solvent*	*2*	*3*	*4*	*2:3*	*2:4*	*2:6*	*3:4*
Pyridinium	D_2SO_4/D_2O	8.78	8.09	8.62	5.8	1.7	0.7	7.5
1-Methylpyridinium	I^-/D_2O	8.77	8.04	8.53	—	—	—	—
Pyrylium	ClO_4^-/MeCN	9.59	8.40	9.20	3.5	2.4	1.5	8.0
2,6-Dimethylpyrylium	$SbCl_6^-/SO_2$	3.04[b]	7.98	8.86	—	—	—	—
2,4,6-Trimethylpyrylium	ClO_4^-/SO_2	2.90[b]	7.77	2.74[b]	—	—	—	—
Thiinium	ClO_4^-/MeCN	10.13	8.97	9.00	7.7	1.7	1.6	6.1

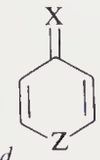
[a]From ⟨B-73NMR⟩ which see for original references.
[b]Methyl shifts.

The spectra of protonated polyaza heterocycles are frequently complicated by the occurrence of covalent hydration. This is more common with polycyclic systems, *e.g.* pteridine.

The extensive delocalization and aromatic character of pyridones, pyrones, *etc.* are shown by their chemical shift and coupling constant values (Table 6). By contrast, pyrans and thiins show chemical shifts characteristic of alkenic systems (Table 7). For these and for rings containing only a single endocyclic bond (Table 8), ^{1}H NMR spectroscopy offers a most useful tool for structure determination.

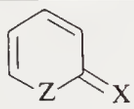
Table 6 ^{1}H NMR Spectral Data for Six-membered Heteroaromatic Rings with Exocyclic Carbonyl or Thione Groups[a]

A γ-Compounds



Compound		Neutral species (D_2O, CCl_4 or $CDCl_3$)				Cation (TFA or D_2SO_4)			
		$\delta(^1H)$ (p.p.m.)		J (Hz)		$\delta(^1H)$ (p.p.m.)		J (Hz)	
Z	*X*	*2*	*3*	*2:3*	*2:5*	*2*	*3*	*2:3*	*2:5*
NH	O	7.98	6.63	7.532	0.260	8.5	7.4	7.6	—
NMe	O	7.81	6.49	8.4	—	8.4	7.4	7.6	—
NH	S	8.37	7.87	7.0	—	—	—	—	—
O	O	7.92	6.39	5.9	0.4	8.49	7.06	—	—
O	S	7.51	7.15	5.7	0.5	8.87	8.14	~5.7	~0.5
S	O	7.89	7.09	10.4	0.5	9.40	8.19	~10.1	~0.5
S	S	7.90	7.58	10.1	0.5	—	—	—	—

B α-Compounds

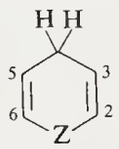


Compound			$\delta(^1H)$ (p.p.m.)			
Z	*X*	*Solvent*	3	4	5	6
NH	O	$CHCl_3$	6.60	7.3	6.20	7.23
		10–20% D_2SO_4	7.3	8.2	7.3	8.2
O	O	$CDCl_3$	6.38	7.56	6.43	7.77
			J (Hz)			
			3:4	*4:5*	*4:6*	*5:6*
NH	O	DMSO	10	7	2	7
O	O	$CDCl_3$	9.4	6.3	2.4	5.0

[a]Data abstracted from ⟨B-73NMR⟩ and ⟨71PMH(4)121⟩ which see for original references.

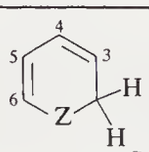
Table 7 ^{1}H NMR Data for Six-membered Heterocyclic Rings with Two Endocyclic Double Bonds[a]

A 4*H*-Systems



Z	*Solvent*	$\delta(^1H)$ (p.p.m.)			J (Hz)			
		2	*3*	*4*	*2:3*	*2:4*	*2:6*	*3:4*
NH	C_6D_6	5.73	4.42	3.15	—	—	—	—
NPh	CCl_4	6.27	4.53	2.92	9.0	1.6	—	3.9
O	—	6.12	4.63	2.66	7.0	1.7	1.5	3.4
S	—	5.97	5.54	2.84	10.0	1.1	2.9	3.9

B 2*H*-Systems

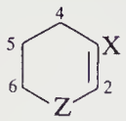


Z	*Solvent*	α(^1H) (p.p.m.)				
		2	*3*	*4*	*5*	*6*
NPh	CCl_4	4.26	5.21	5.88	4.94	6.41
S[b]	CCl_4	3.16	4.99	—	6.08	6.08

[a]Data abstracted from ⟨B-73NMR⟩ and ⟨71PMH(4)121⟩ which see for original references.
[b]Data refer to the 4-methyl derivative.

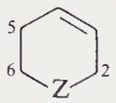
Table 8 ^{1}H NMR Data for Six-membered Heterocyclic Rings with One Endocyclic Double Bond[a]

A Δ^2-Systems



Compound Z	X	Solvent	$\delta(^1H)$ (p.p.m.) 2	3	4	5	6
NH	COMe	$CDCl_3$	7.12	7.48	2.28	1.77	3.23
O	H	CCl_4	6.22	4.54	1.93	1.93	—

B Δ^3-Systems



Z	Solvent	$\delta(^1H)$ (p.p.m.) 2	3	4	5	6
NH	$CDCl_3$	3.33	5.75	5.75	2.07	2.95
NMe	CCl_4	2.76	5.58	5.58	—	—
O	—	4.03	5.76	5.76	2.10	—

[a]Data abstracted from ⟨B-73NMR⟩ and ⟨71PMH(4)121⟩ which see for original references.

Solvent-induced and lanthanide-induced shifts are of great value in structure assignments in heterocyclic compounds, because cyclic nitrogen atoms, carbonyl groups, *etc.* undergo specific hydrogen bonding or coordination resulting in differential shifts of groups in different positions.

2.2.3.3.2 Coupling constants

The normal pattern of coupling constants for aromatic six-membered rings is found in the heterocyclic aza systems, except that the *ortho* coupling to a proton α to a heterocyclic nitrogen is reduced from 7–8 Hz to 4.5–6 Hz. The $J_{2,3}$ of pyrylium salts is still lower (*ca.* 3.5 Hz), but in pyridinium salts and pyridine *N*-oxide it is of intermediate value (*ca.* 6.5 Hz) (see Table 5).

The 'direct' coupling constants (D_{ij}) of pyridine, obtained from a spectrum of the molecule in a nematic liquid crystal solvent ⟨B-73NMR, p. 10⟩, provide information about the geometry.

2.2.3.4 ^{13}C NMR Spectra

2.2.3.4.1 Aromatic systems: chemical shifts

Chemical shift data for a number of monocyclic, unsubstituted six-membered heteroaromatic compounds are given in Table 9.

Table 9 ^{13}C NMR Chemical Shifts of the Simple Monocyclic Azines (*cf.* benzene, δ 128.5 p.p.m.)

Position	$\delta(^{13}C)$ (p.p.m. TMS) (Position of N atoms indicated) Pyridine	Pyridazine	Pyrimidine	Pyrazine	1,2,3-Triazine	1,2,4-Triazine	1,3,5-Triazine	Tetrazine
1	N	N	N	N	N	N	N	N
2	149.5	N	158.4	145.9	N	N	166.1	N
3	125.6	153.0	N	145.9	N	158.1	N	161.9
4	138.7	130.3	156.9	N	149.7	N	166.1	N
5	125.6	130.3	121.9	145.9	117.9	149.6	N	N
6	149.5	153.0	156.9	145.9	149.7	150.8	166.1	161.9

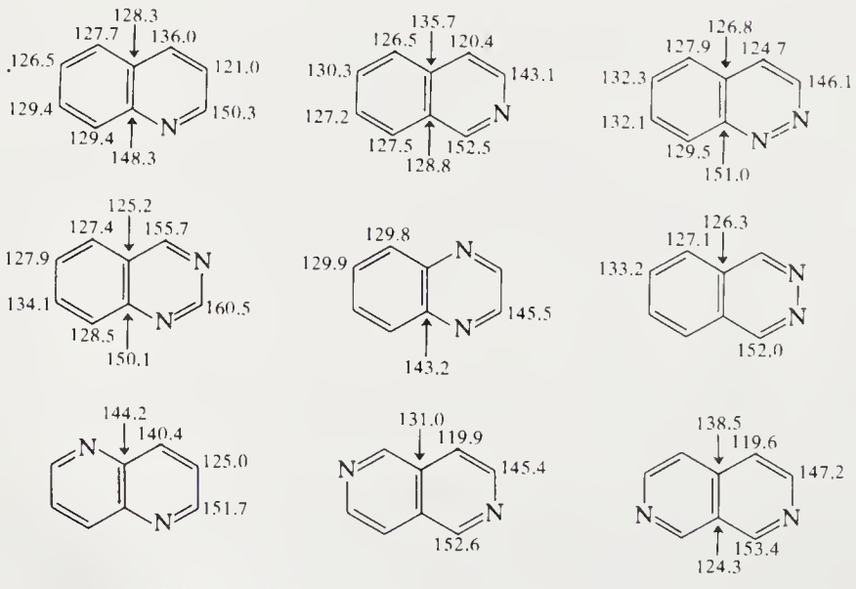
Ring carbon atoms α to a heteroatom are most heavily deshielded, those γ to a heteroatom are also deshielded relative to benzene, while those in a β-position are more benzene-like. Introduction of a second nitrogen atom α or γ to a ring carbon atom results in further deshielding by approximately 10 and 3 p.p.m. respectively, whereas the effect on a β carbon atom is a shielding of

approximately 3 p.p.m. Substituent effects follow the same general trend as in substituted benzenes, *i.e.* the chemical shifts of ring carbon atoms which either carry the substituent or are *para* to it differ in a predictable way relative to the unsubstituted heterocycle, whereas those of ring carbon atoms *meta* to the substituent are little affected by it. These effects are most conveniently exemplified in the pyridine series; typical data for a variety of monosubstituted pyridines are listed in Table 10. Fusion of an aromatic or heteroaromatic ring to an azine changes the electronic distribution and hence the chemical shifts of remaining ring carbon atoms in the azine portion of the molecule, although the difference from those in the parent azine is usually less than 10 p.p.m. Shift data for a number of common condensed azine systems are given in Scheme 8.

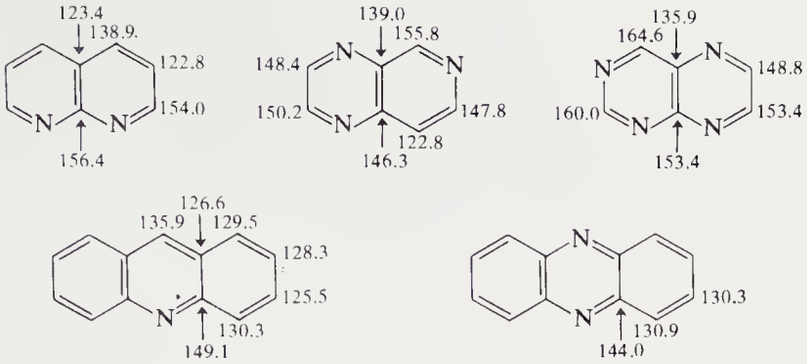
Table 10 ^{13}C NMR Chemical Shifts of Monosubstituted Pyridines[a]

Substituent position	*Substituent*	$\delta(^{13}C)$ (p.p.m.) *C-2*	*C-3*	*C-4*	*C-5*	*C-6*
	H	150.6	124.5	136.4	124.5	150.6
2	Br	*142.9*	129.0	139.5	123.7	151.0
	CHO	*153.1*	121.6	137.5	128.3	150.3
	CN	*133.8*	129.2	137.9	127.8	151.5
	COMe	*153.9*	121.4	136.9	127.5	149.3
	Me	*158.7*	123.5	136.1	120.8	149.5
	NH_2[b]	*160.9*	109.5	138.5	113.6	148.7
	OH[b,c]	*162.3*	119.8	140.8	104.8	135.2
	OMe[b]	*163.1*	110.5	138.7	116.7	146.6
3	Br	151.7	*121.6*	139.1	125.4	148.7
	CHO	152.0	*132.1*	136.2	124.8	155.0
	CN	153.2	*110.5*	140.6	124.8	153.8
	COMe	150.1	*123.9*	132.5	121.5	153.8
	Me	150.9	*133.1*	136.4	123.4	147.3
	NH_2[b]	137.7	*145.7*	122.0	125.1	138.8
	OH[b]	137.8	*153.5*	121.4	123.8	140.0
	OMe[b]	137.3	*155.2*	120.0	123.8	141.4
4	Br	152.6	127.6	*133.2*	127.6	152.6
	CHO	151.3	123.6	*141.7*	123.6	151.3
	CN	151.7	126.4	*120.5*	126.4	151.7
	COMe	151.2	121.6	*143.0*	121.6	151.2
	Me	150.1	125.0	*147.0*	125.0	150.1
	NH_2[b]	148.5	110.4	*155.8*	110.4	148.5
	OH[b,c]	139.8	115.9	*175.7*	115.9	139.8
	OMe[b]	150.7	109.8	*164.9*	109.8	150.7

[a]Neat liquids, unless otherwise specified; values for *ipso* position (carrying substituent) italicized; data from ⟨72CPB429, 73OMR(5)551⟩.
[b]In DMSO-d_6.
[c]Compound in NH form.



Scheme 8 ^{13}C chemical shifts for bicyclic systems

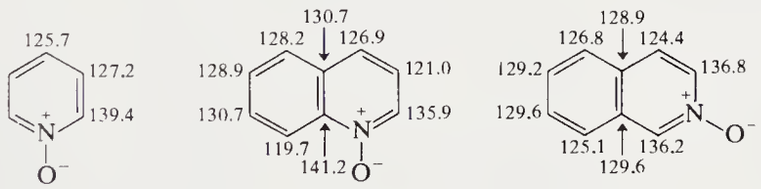


Scheme 8 ^{13}C chemical shifts for bicyclic systems (*continued*)

Protonation of azines results in shielding of the α carbon atoms and deshielding of the β and γ carbon atoms (Table 11), particularly the latter, and these effects have been accounted for in terms of additivity parameters. The upfield protonation parameter for the α carbon atom has been assigned to changes in the C—N bond order, while the β and γ parameters have been assigned to charge polarization effects. The parameters are highly reproducible for monoprotonation but deviate significantly from additivity for diprotonated heterocycles. A related effect is observed on quaternization, but in this case the operation of a β-substituent effect results in the overall change at the α carbon atom normally being small (Table 11). A further important general trend in the azines arises on *N*-oxidation, which results in shielding of the α and γ carbon atoms, especially the latter, and clearly indicates the high electron density at these positions in the ring (Scheme 9). The corresponding conjugate acids of the *N*-oxides have chemical shifts very similar to those of the protonated parent heterocycles.

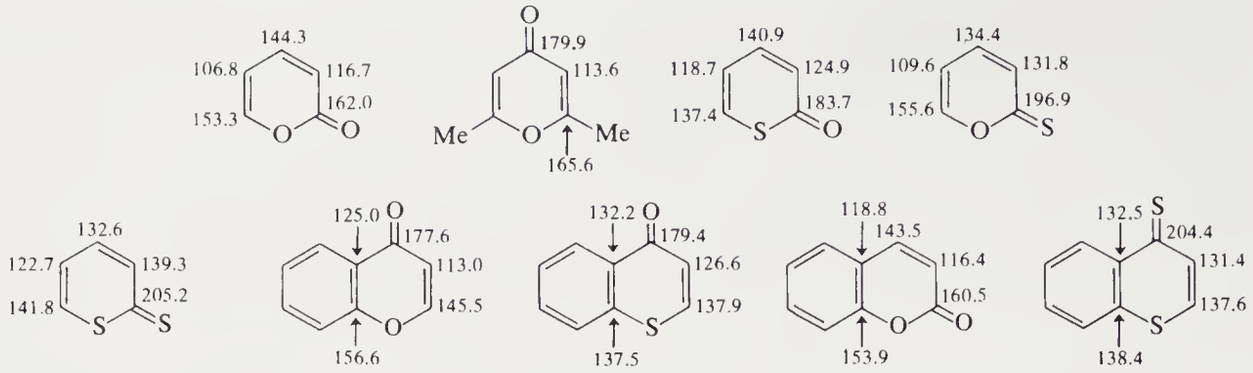
Table 11 ^{13}C NMR Chemical Shifts (δ, p.p.m. from TMS) and One-bond ^{13}C–^{1}H Coupling Constants (Hz) of some Simple Heterocyclic Cations (*cf.* pyridine, column 1)

Position	*Chemical shift* (*Coupling constant*)				
1	N	O^+	NH^+	NMe^+	NPh^+
2	150.3 (178)	169.3 (218)	148.3 (192)	145.8	145.3 (191)
3	124.3 (162)	127.7 (180)	128.6 (173)	128.5	129.5 (178)
4	136.4 (162)	161.2 (180)	142.2 (173)	145.8	147.8 (174)
Anion	—	ClO_4^-	$CF_3CO_2^-$	I^-	Cl^-
Solvent	DMSO-d_6	CD_3CN	D_2O	DMSO-d_6	D_2O
Ref.	70MI20100 76OMR(8)21	73OMR(5)251 77OMR(9)16	80CCC2766 70MI20100	76OMR(8)21	80CCC2766



Scheme 9 ^{13}C chemical shifts for *N*-oxides

The pyrones and thiinones show general ^{13}C NMR spectral characteristics similar to the pyridones which reflect charge distributions in the heterocyclic rings. Thus, carbon atoms α or γ to the heteroatom are deshielded relative to benzene, while those β are shielded. Substituent effects are in general as expected, although fewer detailed studies have been carried out in this area with the oxygen and sulfur heterocycles than with the azines. Chemical shift data for representative compounds are given in Scheme 10.



Scheme 10 ^{13}C chemical shifts for oxygen and sulfur systems

2.2.3.4.2 Aromatic systems: coupling constants

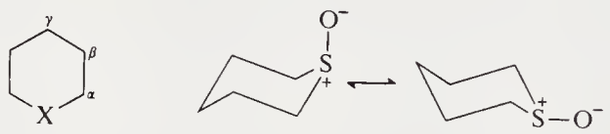
Single-bond ^{13}C–^{1}H coupling constants for six-membered heteroaromatic compounds lie in the approximate range 150–220 Hz, the magnitude varying with substituent electronegativity. Data for simple azines are summarized in Table 12. Longer range couplings are much smaller (up to *ca.* 12 Hz), and the values are difficult to predict.

Table 12 One-bond ^{13}C–^{1}H Coupling Constants (Hz) in the Simple Monocyclic Aromatic Azines (*cf.* 159 Hz for benzene)

	J (Hz) (Position of N atoms indicated)						
Position	*Pyridine*	*Pyridazine*	*Pyrimidine*	*Pyrazine*	*1,2,4-Triazine*	*1,3,5-Triazine*	*Tetrazine*
1	N	N	N	N	N	N	N
2	178	N	211	184	N	206	N
3	162	186	N	184	207	N	214
4	162	174	182	N	N	206	N
5	162	174	171	184	188	N	N
6	178	186	182	184	188	206	214

2.2.3.4.3 Saturated systems

Data are available on the ^{13}C spectra of saturated six-membered ring systems ⟨79MI20101⟩. The chemical shifts of the α-, β- and γ-methylene carbon atoms ⟨76JA3778⟩ of compounds of type (**40**) are summarized in Table 13.



(**40**) (**41**) (**42**)

Table 13 ^{13}C NMR Chemical Shifts (δ, p.p.m. from TMS) in Saturated Six-membered Rings (**40**)[a]

	Shift of C at position			
X in (40)	*2*	*3*	*4*	*Solvent*
CH_2	27.7	27.7	27.7	None
S	29.3	28.2	26.9	None
S—O (*ax*)	45.1	15.5	24.7	CD_2Cl_2
S—O (*eq*)	52.1	23.3	24.7	CD_2Cl_2
SO_2	52.6	25.1	24.3	CD_2Cl_2
NH	47.5	27.2	25.5	None
NMe	56.7	26.3	24.3	None
$NH_2^+ I^-$	45.6	23.2	22.5	H_2O
$NHMe^+ I^-$	55.6	23.9	21.8	H_2O
$NMe_2^+ I^-$	63.5	20.6	21.0	H_2O
NCOPh[b]	42.8, 48.5	25.5, 26.3	24.4	$CDCl_3$
N—NO[c]	39.0, 50.8	25.5, 27.2	24.7	None
O	68.0	26.6	23.6	None

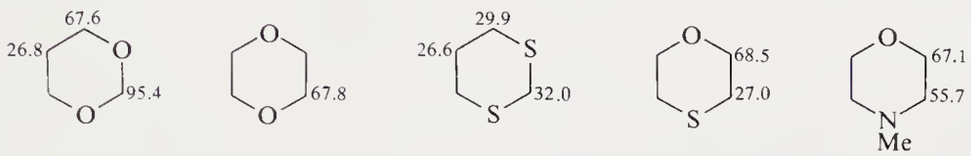
[a]From ⟨76JA3778⟩, unless otherwise indicated.
[b]⟨75JOC3547⟩.
[c]⟨74JCS(P2)1381⟩.

A sulfur (S^{II}) atom exerts only a very small effect on the chemical shifts of the carbon atoms in the ring: cyclohexane absorbs at δ 27.7, and the signals of the α, β and γ carbons of tetrahydrothiin (**40**; X = S) are all very close to this value. The corresponding sulfone (X = SO_2) shows a rather large shift of the α carbon (to δ 52.6), while the β and γ protons are moved slightly upfield. The sulfoxide group is variable in its effect, depending on whether the oxygen atom is axial (**41**) (the preferred conformation) or equatorial (**42**): an equatorial oxygen has considerably the more deshielded α and β carbons; in the axial conformer the β carbon absorbs at a field over 11 p.p.m. higher than cyclohexane.

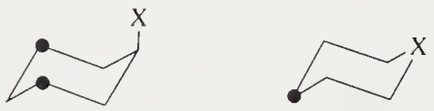
A nitrogen atom at X results in a variable downfield shift of the α carbons, depending in its extent on what else is attached to the nitrogen. In piperidine (**40**; X = NH) the α carbon signal is shifted by about 20 p.p.m., to *ca.* δ 47.7, while in *N*-methylpiperidine (**40**; X = Me) it appears at δ 56.7. Quaternization at nitrogen produces further effects similar to replacement of NH by *N*-alkyl, but simple protonation has only a small effect. *N*-Acylpiperidines show two distinct α carbon atoms, because of restricted rotation about the amide bond. The chemical shift separation is about 6 p.p.m., and the mean shift is close to that of the unsubstituted amine (**40**; X = NH). The nitroso compound (**40**; X = N—NO) is similar, but the shift separation of the two α carbons is somewhat greater (*ca.* 12 p.p.m.). The β and γ carbon atoms of piperidines, *N*-acylpiperidines and piperidinium salts are all upfield of the cyclohexane resonance, by 0–7 p.p.m.

The ether oxygen of tetrahydropyran (**40**; X = O) induces a large downfield shift of the α carbons, while the β and γ carbons move slightly upfield, the γ more noticeably.

When two heteroatoms are present in a saturated six-membered ring their effects are approximately additive to within 5 p.p.m. Observed shifts for a few representative examples are shown in structures (**43**)–(**47**).



Many studies have been made of substituent effects in saturated heterocyclic six-membered rings ⟨B-79MI20101⟩. The so-called 'γ-gauche effect' induces an upfield (screening) shift of the ^{13}C signal from a ring carbon *meta* to an axial substituent (**48**). The shielding experienced by the γ carbon atom caused by an electronegative heteroatom *para* to it (**49**) is also a manifestation of the γ-gauche effect.



The one-bond coupling ($^1J_{CH}$) for cyclohexane (an average of couplings to axial and equatorial protons) is 123 Hz, and is increased by substitution adjacent to the carbon by an electronegative element, as with the aromatic systems discussed above.

2.2.3.5 Nitrogen NMR Spectra ⟨B-73MI20100, B-79MI20102⟩

Some nitrogen chemical shifts relating to azines are given in Table 14.

The following trends are observed:

(1) A pyridine-type nitrogen absorbs at comparatively low field (+ 63 p.p.m. for pyridine itself, without solvent).

(2) Substituent effects are often considerable, particularly when strongly electron-donating effects (to the aza nitrogen) are present, when upfield shifts of up to 60 p.p.m. (2-NH_2) may be observed.

(3) Further aza substitution *ortho* or *para* in the same ring deshields the nitrogen; the effect is moderate for a *para*-, and large for an *ortho*-nitrogen. The latter is probably a special 'azo effect', since the nitrogens of a simple azo group absorb at still lower field (–130 p.p.m., in ether).

Table 14 ^{14}N and ^{15}N NMR Chemical Shifts of Typical Azines and their Derivatives[a]

Compound	*Solvent*	*N-shift*[b]	*^{14}N bandwidth at half height* (Hz)[c]
Pyridine	CCl_4	57	170
Pyridine	MeOH	83	
Pyridinium	HCl/H_2O	181	20
Pyridine 1-oxide	Acetone	85	66
1-Hydroxypyridinium	HCl/H_2O	133	570
1-Methylpyridinium	H_2O	174	(Narrow)
4-Nitropyridine	Acetone	35	490
4-Bromopyridine	None	56	1100
4-Methylpyridine	Acetone	74	480
4-Methoxypyridine	Acetone	90	1100
4-Aminopyridine	Acetone	105	680
4(1*H*)-Pyridone	Acetone	201	390
Pyridazine	$CHCl_3$	−20	410
Pyridazine	DMSO	−20.3	
Pyridazine 1-oxide	DMSO	55.1 (N-1), 33.6 (N-2)	
Pyrimidine	DMSO	84.8	
Pyrimidine 1-oxide	DMSO	90 (N-1), 80.3 (N-3)	
Pyrazine	DMSO	46.3	
Pyrazine 1-oxide	DMSO	75.7 (N-1), 70.4 (N-4)	
Quinoline	None	72	650
Isoquinoline	None	68	680
Cinnoline	DMSO	−44.6 (N-1), −41.3 (N-2)	
Phthalazine	Dioxane	11	800
Quinoxaline	Dioxane	46	950

[a]^{14}N data from ⟨B-73MI20100⟩; ^{15}N data from ⟨40HCA504⟩.
[b]Screening constants, p.p.m. upfield from $MeNO_2$.
[c]No entry in this column means data are from ^{15}N spectra.

(4) Hydrogen bonding to the nitrogen lone pair leads to an upfield shift, the extent of which depends on the proton-donor ability of the solvent, and the acceptor ability of the base: shifts of some 20 p.p.m. are commonly found.

(5) When the lone electron pair is protonated, the nitrogen chemical shift moves by *ca.* 100 p.p.m. to higher field. Large upfield shifts are also found when a compound exists in a tautomeric form with a proton on the nitrogen. The nitrogen NMR spectrum is often of considerable value in studies of tautomerism of this type.

(6) *N*-Oxidation of an azine nitrogen usually shifts the signal upfield by a smallish amount (10–30 p.p.m.). [In five-membered rings, however downfield shifts have been claimed ⟨78JOC2542⟩.]

Observation of the one-bond ^{13}C–^{15}N coupling in quaternized heterocycles containing specific labelling with ^{15}N has been used to identify the site of quaternization ⟨76JOC3051⟩.

2.2.3.6 UV and Related Spectra ⟨71PMH(3)67⟩

2.2.3.6.1 Features of UV spectra

The spectra of saturated heterocycles show amine $n\rightarrow\sigma^*$ absorptions and transitions associated with sulfur. Saturated ethers are usually transparent down to 210 nm.

The six-membered aza-aromatic compounds possess the basic π-electron systems of benzene and its homologues, and in addition there are non-bonding lone pairs of electrons on the nitrogen atoms. These lone pairs are responsible for weak transitions, denoted $n\rightarrow\pi^*$, at the long-wavelength end of the spectrum. These absorptions are usually weak, in comparison to the transitions ($\pi\rightarrow\pi^*$) of the π-electrons, and are frequently difficult to locate, except when two aza nitrogen atoms are adjacent. In these cases the two filled non-bonding orbitals interact (see Figure 1). The $n\rightarrow\pi^*$ bands are more obvious features of the spectra of compounds such as pyridazine, cinnoline and 1,2,4,5-tetrazine. In the last compound there are two $n\rightarrow\pi^*$ bands, a weak system near 320 nm, and a stronger one, giving a band at *ca.* 550 nm (ε 830), which is responsible for the red color. Table 15 gives the positions of the $n\rightarrow\pi^*$ absorptions of a number of the simpler aza-aromatics.

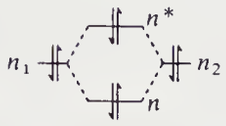


Figure 1 The splitting of the adjacent non-bonding orbitals in pyridazine

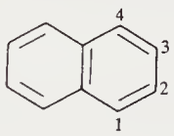
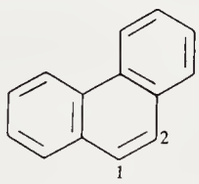
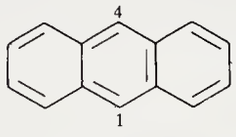
Table 15 UV Absorption Bands of the Simple Monocyclic Azines[a]

Compound	$\pi \rightarrow \pi^*$ *bands*	$n \rightarrow \pi^*$ *bands*
Benzene	203.5 (3.87), 254 (2.04)	—
Pyridine	251 (3.30)	*ca.* 270 (sh)
Pyridazine	246 (3.11)	340 (2.50)
Pyrimidine	243 (3.31)	298 (2.51)
Pyrazine	260 (3.75)	328 (3.02)
1,2,4-Triazine[b]	264 (3.71)	384 (2.72)
1,3,5-Triazine	222 (2.18)	272 (2.95)
1,2,4,5-Tetrazine	252 (3.33)	*ca.* 320 (w), 542 (2.92)

[a]Solvent cyclohexane; the positions of the peak maxima (nm) are given, with $\log_{10} \varepsilon$ values in parentheses; mainly from Mason ⟨59JCS1240, 1247⟩.
[b]Trimethyl derivative.

The transition energies from bonding to antibonding π-orbitals ($\pi \rightarrow \pi^*$) correspond fairly well in their levels to those of the isosteric hydrocarbons, although the band intensities are often very different. Thus, the spectra of naphthalene, quinoline, isoquinoline and the quinolizinium ion bear a remarkable similarity, except in the intensities of the long-wavelength bands. Cinnoline is slightly different, with long-wavelength peaks at 309 nm (log ε 3.29), 317 (3.25) and 322 (3.32) and the $n \rightarrow \pi^*$ band at 390 nm (log ε 2.43). The differences are probably a result of the pronounced asymmetry of the molecule, compared with naphthalene. Table 15 lists the principal bands in the spectra of some representative monocyclic systems, with those of benzene added for comparison. In the aza derivatives of the higher polyarenes, UV spectral comparisons have frequently been used as an indication of structural correspondence ⟨58HC(12)551⟩. For example, the spectra of the benzo, dibenzo, *etc.* derivatives of the quinolizinium ion bear similar qualitative relationships to those of the polycyclic hydrocarbons as does quinolizinium ion itself to naphthalene, *i.e.* a bathochromic shift accompanied by a pronounced intensification (see Table 16).

Table 16 UV Spectral Maxima (nm) for Benzazines[a] [λ_{max}(log ε)]

Position of nitrogen atom(s)	 *Neutral*	*Monocation*	 *Neutral*	*Monocation*	 *Neutral*	*Monocation*
—[b]	275 (4.0) 310 (2.81)	—	292 (4.30) 330 (2.54)	—	375 (4.88)	—
1	312 (3.52)	313 (3.79)	346 (3.24)	365 (3.56)	354 (4.02)	402 (3.48)
2	319 (3.47)	332 (3.63)	—	—	—	—
1,2	321 (3.44)	353 (3.40)	370 (3.2)	?	—	—
1,3	305 (3.38)	260 (3.91)	—	—	—	—
1,4	316 (3.79)	331 (3.93)	—	—	365 (4.2)	430 (3.2)
2,3	305 (3.11)	314 (3.45)	—	—	—	—

[a]Abstracted from ⟨71PMH(3)67⟩ which see for original references.
[b]Values in this row taken from E. S. Stern and C. J. Timmons, 'Electronic Absorption Spectroscopy in Organic Chemistry', Arnold, London, 1970, apply to the hydrocarbon species.

The effects of substituents on UV spectral maxima are illustrated in Table 17. The effects are greatest when conjugation is significantly increased, *e.g.* for strong electron donor substituents in the pyridinium cation.

The non-aromatic but fully conjugated 1,4-dioxin and its sulfur analogues show absorption at quite long wavelengths.

Table 17 UV Spectral Maxima (nm) of Substituted Azines[a]

Substituents		*Pyridine*	*Pyridine*	*Pyridine*			
Nature	*Position*	*(neutral)*	*(cation)*	*1-oxide*	*Pyridazine*	*Pyrimidine*	*Pyrazine*
—	—	257	256	265	300	243	261
Me	2	262	262	—	—	249	271
	3	263	262	254	310	252[b]	—
	4	255	252	256	292	245	—
Cl	2	264	271	—	—	—	268
	3	267	270	—	308	—	—
	4	258	257	265	—	—	—
OMe	2	269	279	249	—	264	292
	3	276	284	262	265	—	—
	4	245	236	261	254	248	—
NH_2	2	229	229	239	—	292	316
	3	231	250	—	—	298[b]	—
	4	241	263	215	249	268	—
NO_2	2	269	—	—	—	—	—
	3	241	—	—	—	237[b]	—
	4	286	—	328	—	—	—
CO_2H	2	264	265	259	—	246	—
	3	262	260	260	—	247[b]	—
	4	271	275	281	—	253	—
Ph	2	241	294	240	—	250	—
	3	244	—	249	254	256[b]	—
	4	256	286	293	—	275	—

[a]Abstracted from ⟨71PMH(3)67⟩ which see for original references.
[b]Refers to 5-substituted compound.

2.2.3.6.2 Applications of UV spectroscopy

(i) UV spectroscopy has been much used in determining ionization constants for both proton addition and proton loss. Conversely, it is important that the pH of a solution is known when a UV spectrum of a potentially basic or acidic compound is obtained.

(ii) UV spectroscopy has been particularly useful in studies of tautomeric compounds. Thus 2-pyridone has a spectrum very similar to 1-methyl-2-pyridone, and quite different from 2-methoxypyridine; this is illustrated in Figure 14 of CHEC 2.04.

(iii) UV absorption spectra are also very useful in the investigation of covalent hydration, important in polyaza six-membered heteroaromatics, especially when bicyclic (see Section 3.2.1.6.3).

(iv) UV-visible spectra demonstrate charge transfer complex formation, *e.g.* between polycyclic quinolizinium ions and polycyclic aromatic hydrocarbons.

2.2.3.7 IR and Raman Spectra ⟨63PMH(2)161, 71PMH(4)265⟩

Systematic studies of the IR spectra of substituted pyridines establish: (1) that substituents vibrate largely independently of the rings; (2) that the vibrational modes of the ring skeleton are related, and approximate in position, to those found in benzene derivatives; (3) that the bending modes of the ring hydrogen atoms are similar to those of the corresponding arrangements of adjacent hydrogen atoms on a benzene ring. Although it is reasonable to assume that these generalizations are applicable to all azines, other systems have not been examined in such detail as the pyridines.

Four ring-stretching modes for pyridines and pyrimidines are listed in Table 18, together with the corresponding bands of a monosubstituted benzene. Quinolines and isoquinolines show seven or eight bands in the region 1650–1350 cm^{-1}.

In six-membered aromatic rings the intensity of the ring-stretching mode near 1600 cm^{-1} is related to the square of the σ_R^0 parameter for the substituent and/or ring atoms. Such intensity measurements on 4-substituted pyridine *N*-oxides confirm the ability of the *N*-oxide group to both donate and withdraw electrons according to the nature of the 4-substituent.

Six-membered heteroaromatic rings show bands characteristic of in-plane CH bending in the region 1300–1000 cm^{-1} (Table 19), and of out-of-plane CH bending below 1000 cm^{-1} (Table 20).

Table 18 Approximate Positions of Ring-stretching Modes for Pyridines, Pyrimidines and Benzenes (cm^{-1})

Compounds	*Mode (see structures A–D)*			
	A	*B*	*C*	*D*
Monosubstituted benzene[a]	1610–1600	1590–1580	1520–1470	1460–1440
Pyridine[b]	1580	1572	1482	1439
4-Substituted pyridines[a]	1610–1595	1570–1550	1520–1480	1420–1410
Pyridine 1-oxides[a]	1645–1590	1585–1560	1540–1470	1440–1410
Pyrimidines[c]	1600–1545	1575–1540	1510–1410	1470–1330

[a]In $CHCl_3$. [b]Vapor phase. [c]Various media.

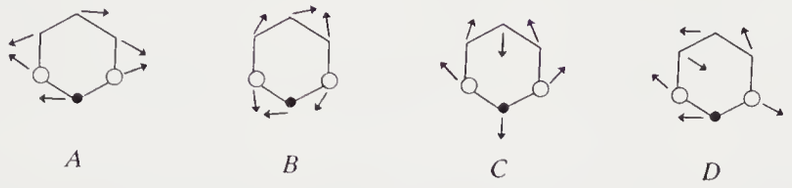


Table 19 Azines: Characteristic IR Bands (cm^{-1}) in the 1300–1000 cm^{-1} Region[a]

Compounds	*β CH modes*				*Ring modes*
2-Substituted pyridines	1293–1265	1150–1143	1097–1089	1053–1043	998–990
3-Substituted pyridines	1202–1182	1129–1119	1108–1098	1045–1031	1027–1023
4-Substituted pyridines	1232–1208	—	1070–1064	—	995–991
Pyridine 1-oxides	1158–1142	—	1130–1112	—	—
Pyrimidines	1280–1200	1210–1130	—	—	—
Pyridazines	—	1150–1100	—	—	1065–935

[a]Data taken from ⟨71PMH(4)265⟩ which see for references to the original literature.

Table 20 Azines: Characteristic IR Bands (cm^{-1}) below 1000 cm^{-1} [a]

Compounds					
2-Substituted pyridines	794–781[b]	752–746[b]	—	780–740[c]	—
3-Substituted pyridines	810–789[b]	715–712[b]	920–880[c]	820–770[c]	730–690[c]
4-Substituted pyridines	820–794[b]	775–709[b]	—	850–790[c]	*ca.* 725[c]
Pyridine 1-oxides	—	—	886–858	825–817	—
Pyrimidines	1010–960	—	850–780	—	—
Pyridazines	—	—	860–830	—	—

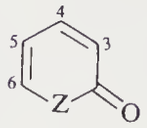
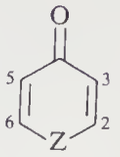
[a]Based on ⟨71PMH(4)265⟩ which see for references to the original literature.
[b]Alkyl substituents only.
[c]Other substituents.

In the IR spectra of six-membered heterocycles containing one or more carbonyl groups in the ring (pyridin-2- and -4-ones, the pyrones and pyrimidones) one of the higher-frequency bands in the 1700–1500 cm^{-1} region can usually be assigned to the carbonyl stretching vibration. However, this is by no means always the highest frequency band; solvent and isotopic substitution effects on the band positions have shown that there is a considerable degree of mixing of the ring and carbonyl modes in the pyridones. The assignments in Table 21 refer to the principal motion in these non-localized vibrations.

The position of the carbonyl group in the IR spectra of various pyranones and pyridones, *etc.*, is indicative of the C—O bond order, and therefore of the importance of the betaine structure. However, this criterion must be used with caution because of the non-localized nature of the vibrations just mentioned.

Assignments have been suggested for the absorptions of many of the saturated heterocyclic six-membered rings ⟨63PMH(2)240, 71PMH(4)339⟩. As expected, force constants between the atoms of the ring are much lower than in the aromatic rings, and the absorptions which are due to skeletal

Table 21 ν(C=O) Frequencies (cm^{-1}) for some Azinones[a]

Other structural features	*Bond*	 α-*Series*		 γ-*Series*	
		Z = NR	Z = O	Z = NR	Z = O
—	ν(C=O)	1666–1655	1736–1730	1577–1550	1634
	ring	1619–1570	1647–1612	1643–1624	1660
5,6-Benzo	ν(C=O)	1667–1633	1710–1700	1647–1620	1650
6-N	ν(C=O)	1681	—	1662	—
3-N	ν(C=O)	1670	—	1653	—

[a]Abstracted from ⟨63PMH(2)161⟩ and ⟨71PMH(4)265⟩ which see for references to the original literature.

modes are generally found below *ca.* 1200 cm^{-1}; bands in the region 1500–1200 cm^{-1} arise from the various deformation modes of the CH bands. The so-called Bohlmann bands at 2750 cm^{-1} are diagnostic of *trans*-fused quinolizidine structures.

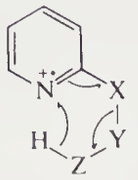
2.2.3.8 Mass Spectrometry ⟨B-67MI20100, 66AHC(7)301, 71PMH(3)223⟩

The behavior of the simple azines and their benzo analogues on electron impact under mass spectrometric conditions is complex. Extensive randomization of ring hydrogen atoms, which increases with increasing lifetime of the ions, takes place prior to fragmentation, as does independent scrambling of ring carbon atoms. Skeletal and Dimroth-type rearrangements (see Section 3.2.3.5.4.iii) are also common.

The mass spectra of the aromatic six-membered heterocycles and their benzo analogues reflect the stability of the ring systems, with the molecular ion in many cases also being the base peak. Fragmentation of the azines by loss of HCN (*M*–27) is the common pathway and for pyridine the *M*–27 ion is the only fragment of any significance in the spectrum apart from the molecular ion. Fragmentation by successive losses of molecules of HCN is cómmon in polyaza systems. Pyrimidine, for example, loses two molecules of HCN in succession to give the radical cation of acetylene, and pteridine fragments similarly to the dehydropyrazine radical cation. Loss of nitrogen from systems containing an—N=N— unit is also a common feature although the ease with which this occurs can vary substantially and, to some extent at least, predictably. It is, for example, very common with cinnolines and 1,2,3-benzotriazines but is of much less importance with phthalazines. There has been relatively little detailed study of the mass spectrometry of pyrylium and thiinium salts, due partly no doubt to the involatility of the compounds; elimination of CO or CS is the major fragmentation pathway.

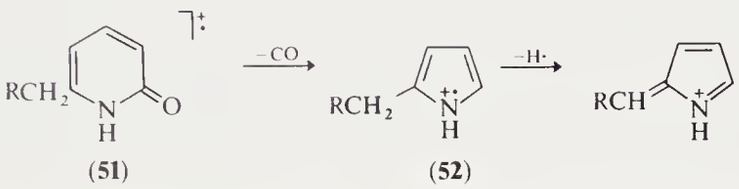
N-Oxides generally show an abundant *M*–16 peak which is sometimes the base peak and di-*N*-oxides show successive elimination of two atoms of oxygen. The intensity of the *M*–16 peak is often, however, reduced very substantially in compounds containing a substituent group α to the ring *N*-oxide which has at least one C—H bond, due to abstraction of a hydrogen atom by the oxygen of the *N*-oxide followed by elimination of a hydroxyl radical. The *M*–17 peak is then a correspondingly significant fragment. Methyl group substitution α to a ring nitrogen atom usually results in fragmentation *via* elimination of MeCN rather than HCN. In monomethyl polyazines both processes are observed, although which fragmentation occurs first appears to be determined by the position of the methyl group. 2-Methylazines also give rise to fragments formed by loss of both a hydrogen atom and a methyl radical. Unlike the general situation pertaining with benzenoid aromatics, where β-cleavage is the preferred fragmentation pathway, the decomposition mode of azines substituted with alkyl groups larger than methyl depends both on the nature of the substituent and on its position relative to the ring nitrogen atom. β-Cleavage occurs with all of the alkylpyridines, but the extent varies in the order 3 > 4 > 2, reflecting the relative electron densities at these positions. The resulting azabenzylic ions rearrange to the isomeric azatropylium ions, and these in turn fragment with loss of HCN or MeCN. γ-Cleavage of a carbon–hydrogen bond can also be important for 2-alkylazines and may even give rise to the base peak, but this form of

fragmentation is generally much less important than β-cleavage with the 3- and 4-isomers. McLafferty-type rearrangements are usually pronounced with 2-substituted azines, *e.g.* (**50**), and this is a general process.

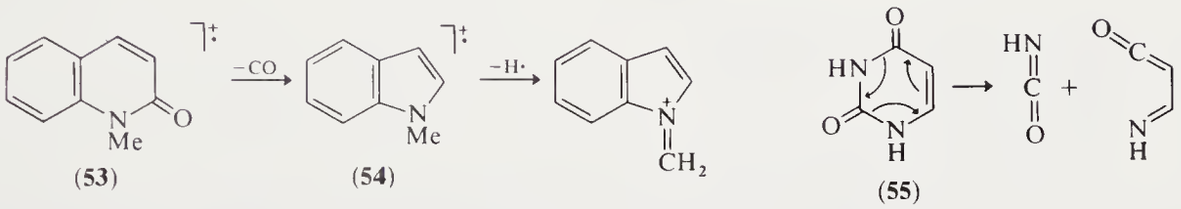


(**50**)

2-Pyridone undergoes fragmentation by loss of CO and formation of the pyrrole radical cation. 3-Hydroxypyridine, on the other hand, loses HCN to give the furan radical cation while 4-pyridone shows both modes of cleavage. The loss of CO from azinones is highly characteristic, *e.g.* (**51**)→(**52**) and (**53**)→(**54**), but with compounds such as uracils and their benzo analogues, the 1-substituted 4-quinazolinones and quinazolinediones, the retro-Diels–Alder fragmentation is favored, *e.g.* (**55**), followed by loss of CO, then HCN or a hydrogen atom, or both. Rather complex fragmentation is often observed with alkoxy-substituted azines, especially with quinolines and isoquinolines, and intramolecular transfer of a hydrogen atom from the ether alkyl group to a ring carbon atom appears to be common. Loss of the alkyl radical and formation of quinonoid intermediates, followed by loss of CO, also appear to be common. Amino groups are usually eliminated as HCN.



(**51**) (**52**)

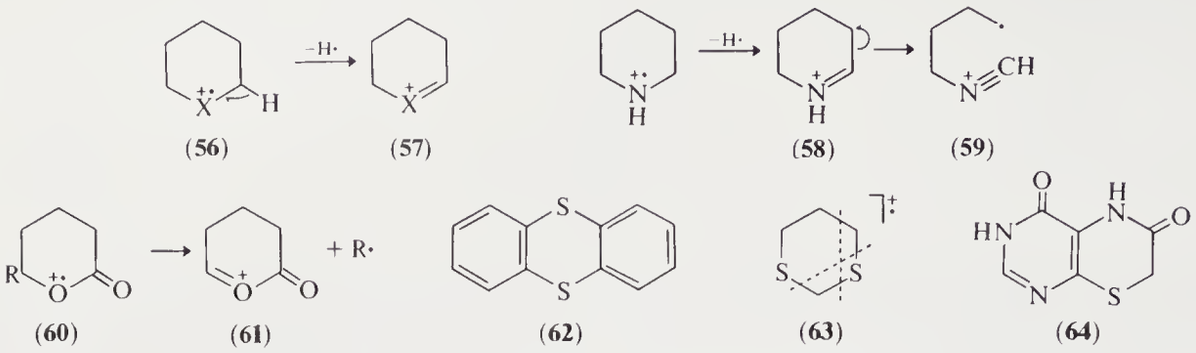


(**53**) (**54**) (**55**)

The mass spectrum of 2-pyrone shows an abundant molecular ion and a very prominent ion due to loss of CO and formation of the furan radical cation. Loss of CO from 4-pyrone, on the other hand, is almost negligible, and the retro-Diels–Alder fragmentation pathway dominates. In alkyl-substituted 2-pyrones loss of CO is followed by loss of a hydrogen atom from the alkyl substituent and ring expansion of the resultant cation to the very stable pyrylium cation. Similar trends are observed with the benzo analogues of the pyrones, although in some cases both modes of fragmentation are observed. Thus, coumarins, chromones, flavones and xanthones, for example, all show significant (*i.e.* >20% relative abundance) or dominant fragmentation by loss of CO, while the retro-Diels–Alder pathway is dominant or significant in the fragmentation of 4-hydroxy-coumarins, isocoumarins, chromones and flavones. Dihydrocoumarins fragment with loss of CO while the retro-Diels–Alder mode is important in the fragmentation of dihydrocoumarins, dihydrochromones, chromans, flavanones, isoflavanones and rotenoids. Not unexpectedly, the retro-Diels–Alder pathway also tends to dominate in the fragmentation of monocyclic dihydroheterocycles.

In the fully saturated heterocyclic systems loss of hydrogen atoms from α carbons, (**56**)→(**57**), and β-cleavage, (**58**)→(**59**) and (**60**)→(**61**), are common, but it is often impossible to discern clear trends in the later stages of fragmentation. Fragmentation of sulfur-containing heterocycles almost always proceeds with loss of sulfur atoms or of sulfur-containing fragments. Thianthrene (**62**) fragments by two successive losses of sulfur atoms to give the biphenylene radical cation, and two of the major fragments from 1,3-dithiane (**63**) are $(M-CH_2S)^+$ and $(M-C_3H_6S)^{+\cdot}$. Transfer of hydrogen atoms to sulfur is common: both thiane and 1,2-dithiane, for example, lose $H_2S\cdot$, in the latter case as a major fragment, while a third major fragment from 1,3-dithiane arises by loss of CH_3S, requiring a hydrogen migration. In other cases, loss of sulfur-containing fragments clearly

involves initial rearrangement; the pyrimidothiazinone (**64**), for instance, fragments with loss of COS. In cyclic sulfones loss of SO_2 is a major fragmentation process.



2.2.3.9 Photoelectron Spectroscopy

In the ultraviolet photoelectron spectrum, the most readily ionized level of pyridine is the non-bonding orbital (with contributions from the σ framework). The three diazines show two lone-pair levels, with the greatest splitting in the case of pyridazine but considerable also in pyrimidine and pyrazine. These long-distance splittings are attributed to both through-space and through-bond interactions, particularly the latter.

The energy levels corresponding to the second and subsequent ionization potentials of pyridine have been correlated with those in benzene.

PE spectroscopy offers a method of investigating the tautomeric structure of pyridones and other related compounds in the gas phase by comparison of ionization potentials of the potentially tautomeric compound with those of fixed models. This method is discussed in CHEC 2.04.

2.2.4 THERMODYNAMIC ASPECTS

2.2.4.1 Intermolecular Forces

2.2.4.1.1 Melting and boiling points (Table 22)

The introduction of a pyridine-like nitrogen into a benzene ring *tends* to make a derivative more crystalline and less volatile; this effect is greater for the diazines, especially pyridazine and pyrazine. When a hydrogen-bond donor substituent is also carried, the difference from the benzenoid compound becomes even more marked.

Examination of the effects of substituents on the melting and boiling points of the parent compounds is instructive.

(i) Methyl and ethyl groups attached to ring carbon atoms usually increase the boiling point by *ca.* 20–30 and *ca.* 50–60 °C, respectively.

Table 22 Melting and Boiling Points[a, b, c]

Ring system	*H*	*Me*	*Et*	*COMe*	*CO_2H*	*CO_2Et*	*$CONH_2$*	*CN*	*NH_2*	*OH*	*OMe*	*SH*	*SMe*	*Cl*	*Br*
Benzene	80	111	136	202	**122**	211	**130**	190	184	**43**	**37**	168	187	131	155
Pyridine-2	115	128	148	192	**137**	243	**107**	222	**57**	**107**	252	**128**	197	171	193
Pyridine-3	115	144	163	220	**235**	223	**129**	**50**	**65**	**125**	179d	**79**	—	150	173
Pyridine-4	115	145	171	211	**306**	219	**156**	**79**	**157**	**148**	**93**	**186**	**44**	147	174
Pyridazine-3	208	215	—	**90**	**200**	**68**	**182**	**44**	**169**	**103**	219	**170**	**38**	**35**	**73**
Pyridazine-4	208	225	—	—	**240**	255	**191**	**80**	**130**	**250**	**44**	**210d**	**45**	**76**	—
Pyrimidine-2	123	138	—	—	**270**	—	—	—	**127**	**320**	—	**230d**	218	**65**	—
Pyrimidine-4	123	141	—	—	**240**[d]	—	—	—	**151**	**164**	—	**187**	—	—	—
Pyrimidine-5	123	153	—	—	**270**	**38**	**212**	—	**170**	**210d**	—	—	—	**37**	**75**
Pyrazine-2	**57**	135	153	**77**	**229**[d]	**50**	**189**	**205**	**120**	**119**	**187**	**215**	**46**	160	180

[a]Melting points above 30 °C are given in bold; melting points below 30 °C are not included.
[b]Boiling points are given at atmospheric pressure to facilitate comparison; those reported at other than atmospheric pressure were converted using a nomogram (*Ind. Eng. Chem.*, 1957, **49**, 125).
[c]A dash indicates that the compound is unstable, unknown, or the data are not readily available.

(ii) Acids and amides are solids, as are amino and 'hydroxy' compounds. The latter generally exist in the tautomeric oxo structures. Strong hydrogen bonding is possible for all these classes of derivatives.

(iii) Methoxy, methylthio and dimethylamino derivatives are often liquids.

(iv) Chloro compounds usually have boiling points similar to those of the corresponding ethyl compounds. Bromo compounds boil approximately 25 °C higher than their chloro analogues.

2.2.4.1.2 Solubility (Table 23)

The solubility in water is much enhanced by the presence of a pyridine nitrogen atom due to the possibility of hydrogen bonding. However, if this possibility is increased sufficiently, then the compound will prefer intermolecular hydrogen bonding with itself, and this can decrease water solubility.

Introduction of amino groups into pteridine lowers the solubility in all solvents despite the fact that the amino group almost invariably increases the solubility in water of aliphatics and aromatics. The reduced solubility of aminopteridines is due to intermolecular hydrogen bonding.

Table 23 Solubilities in Water (parts soluble in 1 part of water) at 20 °C[a]

Parent monocyclic compounds		*Polycyclic derivatives*		*OH-Substituted derivatives*		*NH_2-Substituted derivatives*	
Benzene	0.0015	Naphthalene	0.00002	Phenol	0.07	Aniline	0.03
Pyridine	misc.[b]	Quinoline	0.007	2-Pyridone	1	2-Aminopyridine	1
Pyridazine	misc.	Isoquinoline	0.004	3-Hydroxypyridine	0.03	3-Aminopyridine	>1
Pyrimidine	>1	Quinoxaline	0.7	4-Pyridone	1	2,6-Diaminopyridine	0.1
Pyrazine	1.7	Pteridine	0.15	2-Pyrimidinone	0.5	2-Aminopteridine	0.0007

[a]Data abstracted from ⟨63PMH(1)177⟩.
[b]Misc. = miscible.

2.2.4.1.3 Gas–liquid chromatography

Typical operating conditions for the GLC separation of azines are shown in Table 24.

Table 24 Operating Conditions for the GLC Separation of Azines[a]

Compounds	*Conditions*
Pyridines	Diphenyl phthalate on 'Tide'
Quinolines	Silicone E-301
Pyrimidines	15% Hallcomid M-18 on firebrick
Pyrazines	Apiezon M and N or Reoplex 400
Piperazines	Flexol 8N8 on firebrick
Phenazines	SE-30 on Chromosorb W
s-Triazines	Ethylene glycol adibatic on glass beads

[a]Data abstracted from ⟨71PMH(3)297⟩ which see for original references and further information.

2.2.4.2 Fully Conjugated Rings

Heats of combustion can give useful comparative data on the thermodynamic stabilities of heterocyclic compounds ⟨74PMH(6)199⟩. The heats of formation of the isomeric diazines pyridazine, pyrimidine and pyrazine are respectively 4397.8, 4480.2 and 4480.6 kJ mol^{-1} ⟨62ACS916⟩; pyridazine is almost 83 kJ mol^{-1} less stable than the other two. Attempts to derive resonance energies for the aromatic heterocyclic systems are subject to a considerable degree of uncertainty. Table 25 records some of the rather divergent values reported.

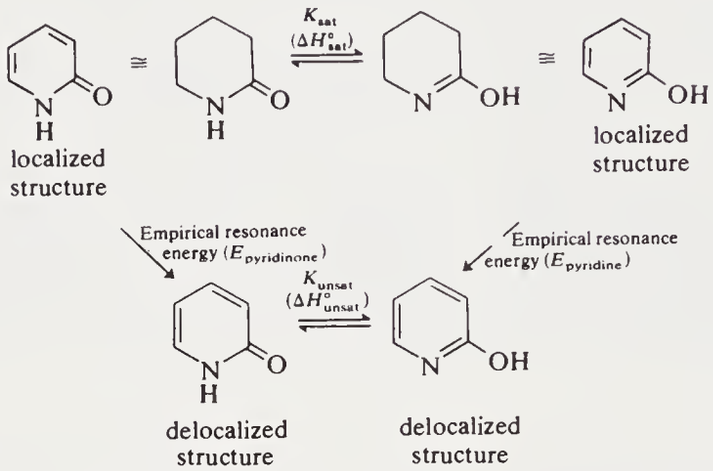
The concept of aromaticity has been linked to those of tautomerism and equilibrium by using K_T or an equilibrium constant as a measure of the binding energy difference between the pyridinoid

Table 25 Empirical Resonance Energy Data (kJ mol^{-1}) for Azines[a, b]

Compound	*A*[c]	*B*[d]	*C*[e]	*Compound*	*A*[c]
Benzene	151	171	92	Naphthalene	255
Pyridine	96	102	80	Quinoline	198
Pyridazine	—	52	42		
Pyrimidine	—	34	75		
Pyrazine	—	34	75		

[a]Adapted from ⟨74AHC(17)255⟩ which see for further details.
[b]4.2 kJ = 1 kcal.
[c]Derived from heat of combustion ⟨49CB358, 51CB916⟩.
[d]From other bonding data given in G. W. Wheland, 'Resonance in Organic Chemistry', Wiley, New York, 1955, p. 275.
[e]'Conjugation energy' ⟨63T1175⟩.

and pyridonoid form, and comparing this to the corresponding quantities for saturated derivatives (Scheme 11).



Scheme 11

In this way, pyridin-2-one and pyridin-4-one are calculated to be ~30 kJ mol^{-1} less aromatic than pyridine. In the bicyclic quinolone, the difference in aromaticity between the two forms is less. The precise degree of aromatic character possessed by 2- and 4-pyranone is not settled; various methods of estimation give divergent values.

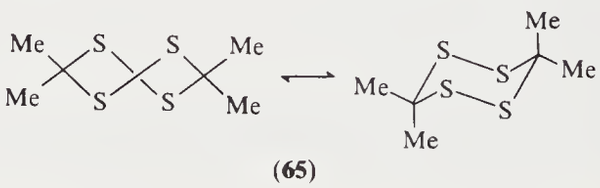
The predominant conformations of substituents such as CHO, CO_2Et, *etc.* in pyridine have been investigated by dipole moments and by IR intensities.

2.2.4.3 Partially and Fully Reduced Rings

The fully saturated rings share with cyclohexane the property of being able to adopt one or more conformations which are virtually free of torsion or bond angle strain.

Hetero-substituted cyclohexanes, with one or more CH_2 groups being replaced by O or NR, almost invariably exist predominantly in chair forms. Inclusion of a sulfur atom changes the geometry more significantly, because of the different bond lengths and angles, but again the overall shapes of the molecules are generally chair-like.

Exceptionally the tetrathiane (**65**) prefers the twist form in the solid phase. In CS_2 solution at 0 °C chair and twist forms coexist with a free energy difference of *ca.* 3.5 kJ between them ⟨67JA5978, 68JA2450⟩. Strain energies for several thianes have been derived from heats of formation.



(**65**)

Besides the shapes adopted by the rings, considerable attention has been paid to the conformational preferences of substituents, both on carbon and on the heteroatoms (nitrogen and sulfur):

(1) The sulfoxide group tends to occupy an axial rather than an equatorial position in the thiane *S*-oxides.

(2) An electronegative substituent adjacent to a ring oxygen atom also shows a preference for an axial orientation. This is known as the 'anomeric effect', and is particularly significant in the conformations of carbohydrates ⟨B-71MI20100, B-83MI20100⟩.

(3) Since a nitrogen freely undergoes 'umbrella' inversion, a substituent on that atom can exchange between axial and equatorial positions without interchange of the rest of the ring atoms. The inversion at nitrogen is usually faster than the ring inversion, unless an electronegative element is attached to it.

(4) The nitrogen lone pair is sterically undemanding and so usually occupies an axial site predominantly.

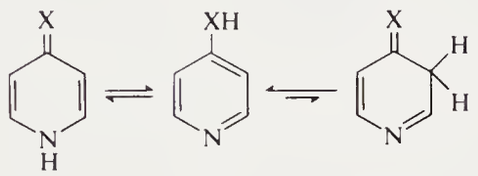
Hetero-substituted cyclohexenes, *e.g.* dihydropyrans, exist in half-chair conformations.

2.2.5 TAUTOMERISM ⟨76AHC(S1)71⟩

2.2.5.1 Prototropic Tautomerism of Substituent Groups

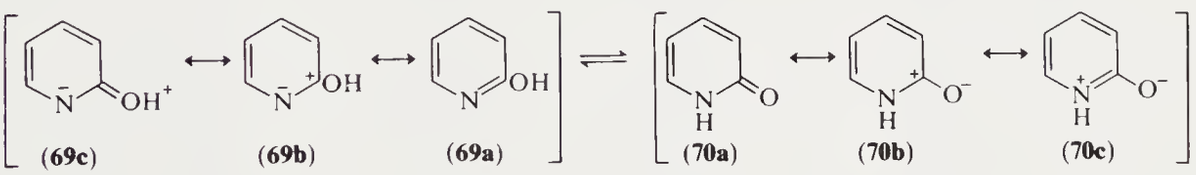
In the consideration of the tautomerism of pyridines and azines there is little need to consider the transfer of hydrogen to a ring carbon atom. In other words, in the set of formulae (**66**)–(**68**) the non-aromatic form (**68**) is not significantly populated. However, there are exceptions in, for example, polyhydroxy-pyridines and -azines.

Thus, the major area of consideration is tautomerism of the type between structures (**66**) and (**67**). Table 26 summarizes the main results on the tautomerism of mono-hydroxy-, -mercapto-, -amino- and -methyl-azines and their benzo derivatives for dilute solutions in water at *ca.* 20 °C.



(**66**) (**67**) (**68**)

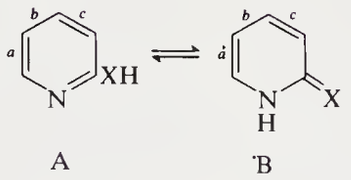
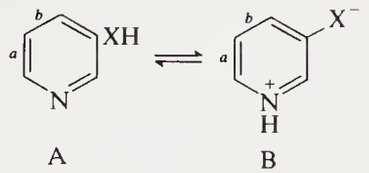
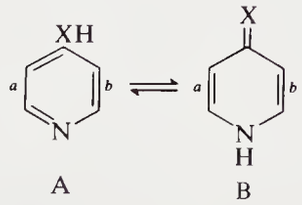
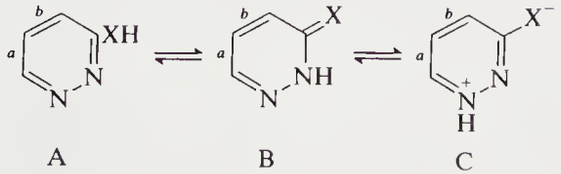
Of the important canonical forms of 2-hydroxypyridine (**69**) and 2-pyridone (**70**), the fact that positive charge prefers nitrogen and negative prefers oxygen indicates that charge-separated canonicals (**70c**) are more important than (**69c**). This partly explains the importance of the 2-pyridone tautomeric form. When the carbonyl oxygen of (**70**) is replaced by less electronegative atoms, as in the imine tautomers of amino heterocycles, or the methylene tautomers of methyl derivatives, the tendency toward polarization in forms corresponding to (**70b**) and (**70c**) is considerably less, and the amino and methyl tautomers are therefore favored in most instances.

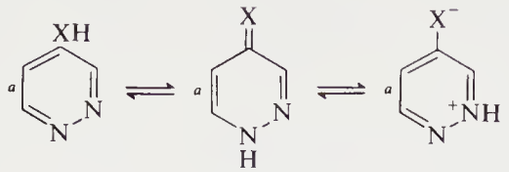
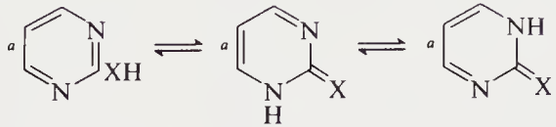
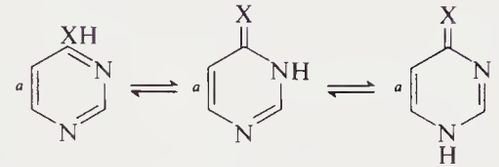
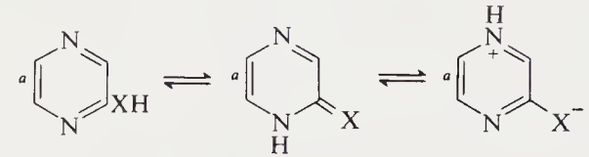


(**69c**) (**69b**) (**69a**) (**70a**) (**70b**) (**70c**)

Polar solvents stabilize polar forms. In the vapor phase at equilibrium both 2- and 4-hydroxypyridine exist as such, rather than as the pyridones. 3-Hydroxypyridine, which in water is an approximate 1:1 mixture of OH and NH forms, also exists as the OH form in the vapor phase. However, 2- and 4-quinolinones remain in the NH (oxo) forms, even in the vapor phase. Hydrocarbon or other solvents of very low polarity would be expected to give results similar to those in the vapor phase, but intermolecular association by hydrogen bonding often leads to a considerably greater proportion of polar tautomers being present than would otherwise have been predicted.

Table 26 Tautomeric Equilibria of some Monofunctional Azines and Benzazines[a]

	X =	O	S	NH	CH_2
 A ⇌ B	Parent	B (3.0)	B (4.7)	A (*ca.* 6)	A (13.3)
	Benzo[*a*]	B (3.9)	B (5.1)	A (4.3)	A (9.4)
	Benzo[*b*]	B (low)	B (3.0)	—	—
	Benzo[*c*]	B (4.8)	B (5.8)	A (3.8)	A (9.5)
	Dibenzo[*a*,*c*]	B (3.9)	—	A (2.8)	A (high)
 A ⇌ B	Parent	B (0.1)	B (2.2)	A	A
	Benzo[*a*]	A (*ca.* 1)	B (1.5)	A	A
	Benzo[*b*]	B (*ca.* 0.5)	—	A	A
 A ⇌ B	Parent	B (3.3)	B (4.6)	A (8.7)	A (13.4)
	Benzo[*a*]	B (4.2)	B (5.0)	A (3.2)	A
	Dibenzo[*a*,*b*]	B (7.0)	B (high)	A	A
 A ⇌ B ⇌ C	Parent	B (4.3)	B	A	
	Benzo[*a*]	B (2.6)	—	A (8.3 *vs.* B)	
	Benzo[*b*]	B	B	A	

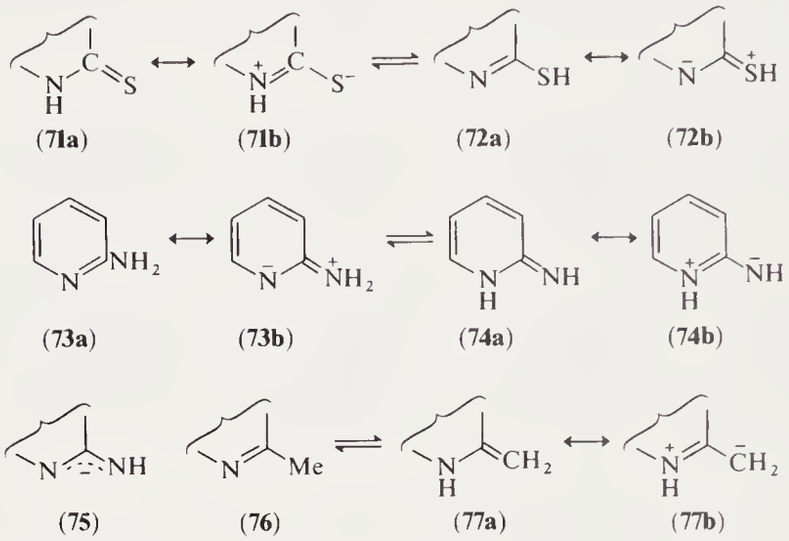
	X =	O	S	NH
 A B C	Parent	B (2.6)	B	A
	Benzo[*a*]	B (3.6)	B	A (4.1 *vs.* B)
 A B C	Parent	B ≡ C	B ≡ C	A (*ca.* 6 *vs.* B)
	Benzo[*a*]	B	—	—
 A B C	Parent	B (0.4 *vs.* C)	B	A (*ca.* 6 *vs.* B/C)
	Benzo[*a*]	B (0.85 *vs.* C)	B	A
 A B C	Parent	B	B	A
	Benzo[*a*]	B (> 1.6 *vs.* A)	B	A

[a] From ⟨76AHC(S1)206⟩; results are expressed as log([major form]/[minor form]); when a form is simply indicated, no quantitative data are available on the equilibrium.

Thiol–thione tautomerism in general parallels that of the corresponding hydroxy–oxo systems. Although a thiol group is in general more acidic than a hydroxy, the thioamide resonance (**71a**↔**71b**) is strongly polarized toward the form (**71b**), on account of the generally weak C=C π-bond in (**71b**). This tends to increase the acidity of the proton on the nitrogen atom, and as a result the thiol–thione equilibrium constants in heterocyclic systems carrying these functions favor the thione form over the thiol (**72**) to an extent only slightly greater than that found in the hydroxy–oxo equilibria. In the vapor phase, 2- and 4-pyridinethiols predominate over the thiones ⟨76JA171⟩.

In amine–imine systems (**73**⇌**74**) the mobile proton can in principle be located at either of the two basic nitrogen sites in the anion (**75**). Since the canonical form with aromatic (benzenoid) structure is polar in the imine (**74b**) and non-polar in the amine (**73a**), the amine structure should be and is favored, particularly in non-polar solvents.

The tautomerism of a methyl group α or γ to a ring nitrogen (**76**⇌**77**) is still less favorable than that of the amine; simple valence and electronegativity considerations of the type employed above suggest much reduced aromaticity associated with the methylene tautomer (**77**). These tautomers are therefore present to only a very small extent at equilibrium.



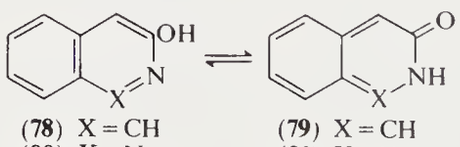
(**71a**) (**71b**) (**72a**) (**72b**)

(**73a**) (**73b**) (**74a**) (**74b**)

(**75**) (**76**) (**77a**) (**77b**)

The effects of other substituents on tautomeric equilibria can usually be predicted from general chemical principles. Thus, an electron-withdrawing group adjacent to a ring nitrogen atom tends to decrease its basicity, and so a tautomer with a proton at that nitrogen atom would be correspondingly destabilized, and the equilibrium displaced toward alternative forms. Substituents may also favor one tautomer or another by intramolecular hydrogen bonding. The effect of substituents on a group involved in the tautomerism (for instance, on an amino or methyl group) can be very profound, as, for instance, carbanion-stabilizing groups on the methyl group equilibrium (in structure **77b**).

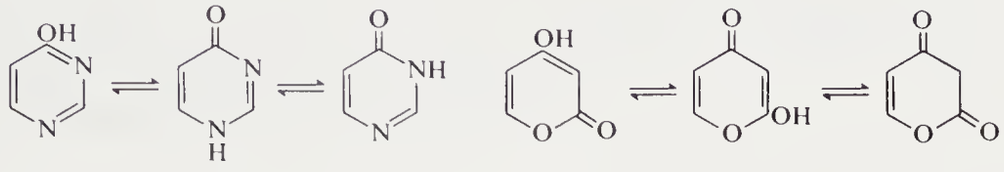
Benzo-fusion to a heterocyclic ring involved in tautomerism has the effect of steering the equilibrium in directions which tend to retain the full aromaticity of the benzene ring. Thus, while the 3-hydroxyisoquinoline–3-isoquinolinone equilibrium (**78**⇌**79**) and that of the cinnoline derivatives (**80**⇌**81**) favor the oxo forms (**79**, **81**), the proportion of hydroxy tautomers is considerably greater than in the corresponding unfused systems. The benzo-fusion in 2- and 4-quinolinone and in 1-isoquinolinone has the effect of reducing the aromaticity of the heterocyclic ring, and consequently of lowering the proportion of the hydroxy tautomers.



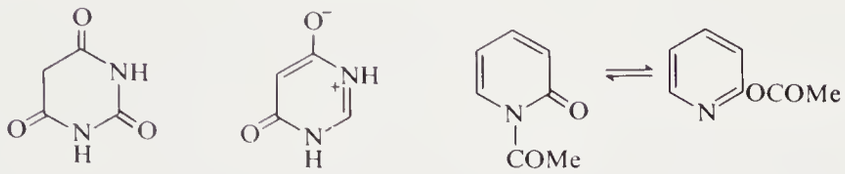
(**78**) X = CH (**79**) X = CH
(**80**) X = N (**81**) X = N

Extra nitrogen heteroatoms in the ring provide alternative sites for the tautomeric proton. 4-Hydroxypyrimidine, for instance, can exist as such (**82**), or in the 1*H*- (**83**) or 3*H*- (**84**) pyrimidone forms. In the hydroxypyrone (**85**), the 2-hydroxy form (**86**) is possible, and, since aromaticity is not

very strong in the pyrones, the diketo structure (**87**) may also be important. The general tendency in compounds of these types is for the forms with amide or ester groups (**84**, **85**) to be preferred over the vinylogous amides or esters (**83**, **86**). In compounds with several potential hydroxy groups, *e.g.* barbituric acid (**88**), non-aromatic structures, with interrupted cyclic conjugation, are commonly favored. In polar media the dipolar 4,6-pyrimidinedione molecule (**89**), with two CO—NH groups, is the predominant tautomer.



(**82**) (**83**) (**84**) (**85**) (**86**) (**87**)



(**88**) (**89**) (**90**) (**91**)

2.2.5.2 Tautomerism of Dihydro and Tetrahydro Compounds

There are manifold possibilities for tautomerism in partially saturated derivatives. As an example, dihydro-1,2,4,5-tetrazines have been formulated in the 1,2-, 1,4-, 1,6- and 3,6-dihydro structures, but the 1,4-dihydro structure is probably the most stable (see also Section 3.2.2.3.2).

2.2.5.3 Tautomerism of Other Substituents (Non-prototropic)

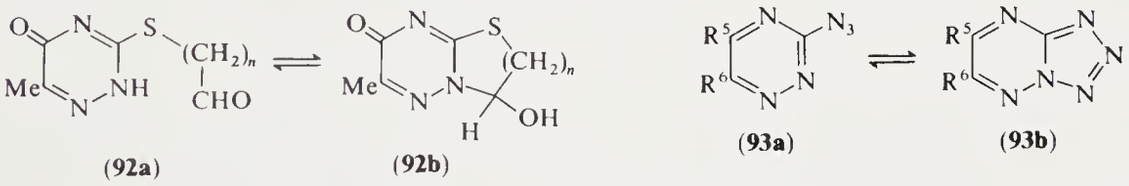
Like protons, acyl groups can occupy alternative positions, on a ring atom or a substituent (*e.g.* **90**⇌**91**), and their migration from one position to another is sometimes rapid enough for the system to be considered tautomeric.

2.2.5.4 Ring–Chain and Valence Bond Tautomerism

Ring–chain tautomerism can occur when a substituent group can interact with an NH group or nitrogen atom of a heterocyclic ring.

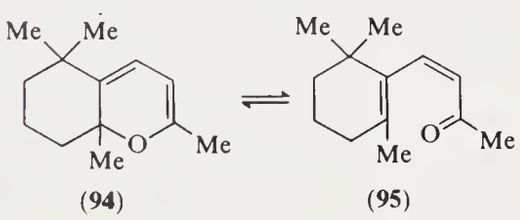
An example of the first case is provided by the 1,2,4-triazinone side-chain aldehydes (**92a**) and (**92b**) which exist in equilibrium with the cyclized forms.

The second possibility is illustrated by α-azidoazines which exist in equilibrium with tetrazole-fused systems: thus, 2-azido-1,2,4-triazines (**93a**) exist predominantly as the tetrazolotriazines (**93b**).



(**92a**) (**92b**) (**93a**) (**93b**)

The 2*H*-pyran (**94**) exists in valence bond tautomeric equilibrium with a small quantity of *cis*-β-ionone (**95**).



(**94**) (**95**)

2.3

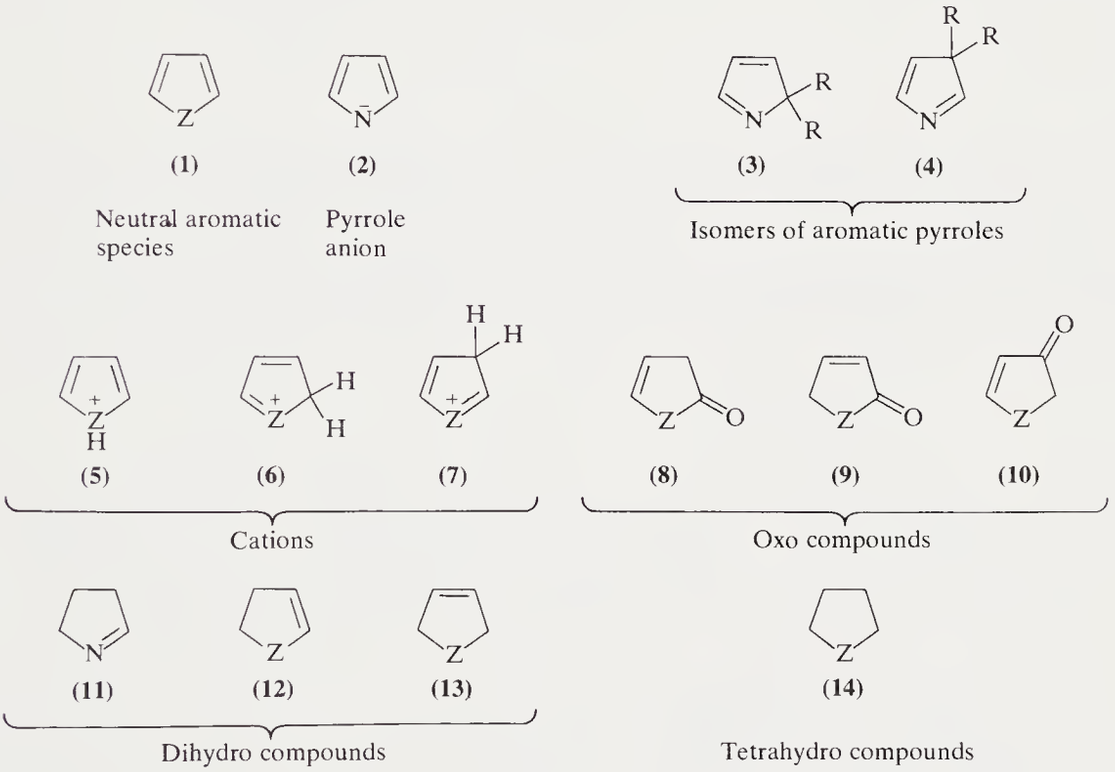
Structure of Five-membered Rings with One Heteroatom*

2.3.1 SURVEY OF POSSIBLE STRUCTURES

2.3.1.1 Monocyclic Compounds

Aromatic species include the neutral molecules pyrrole, furan and thiophene (**1**; Z=NH, O, S) and the pyrrole anion (**2**). The radicals derived from these rings are named pyrryl, furyl and thienyl. The 2-furylmethyl radical is called furfuryl. Compounds in which two pyrrole nuclei are joined by a CH_2 group are called 'dipyrromethanes'; when the linkage is by a CH group, they are named 'dipyrromethenes'. The 2- (**3**) and 3-pyrrolenines (**4**) are isomeric with the pyrroles, but are non-aromatic as the ring conjugation is broken by an sp^3-hybridized carbon atom.

Three types of cationic species exist (**5**–**7**); all are non-aromatic. The 2-oxo derivative exists in two tautomeric forms (**8** and **9**); the 3-oxo derivatives have a unique structure (**10**).



Three types of dihydropyrrole and two types of dihydro-furan and -thiophene exist (**11**–**13**), but only a single class of tetrahydro compounds (**14**).

Reduced thiophenes and furans are named systematically as 2,3-dihydro (**12**), 2,5-dihydro (**13**) and 2,3,4,5-tetrahydro compounds (**14**). Alternatively, *delta* (Δ) can be used to indicate the position of the remaining double bond. Thus (**12**) and (**13**) are named as Δ^2- and Δ^3-dihydro compounds, respectively; tetrahydrothiophene is also called thiophane.

*Based on Chapter 3.01 of 'Comprehensive Heterocyclic Chemistry', by C. W. Bird and G. W. H. Cheeseman, Queen Elizabeth College, University of London.

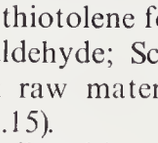
Reduced pyrroles have trivial names; the dihydro derivatives, of which there are three types, are designated as Δ^1- (**11**), Δ^2- and Δ^3-pyrrolines, and the tetrahydropyrroles are called pyrrolidines.

Reduced furan rings occur in many important anhydrides, lactones, hemiacetals and ethers. Maleic anhydride is frequently used as a dienophile in Diels–Alder reactions and it is a component of alkyd resins. Several unsaturated γ-lactones are natural products, while the furanose sugars are cyclic hemi-acetals.

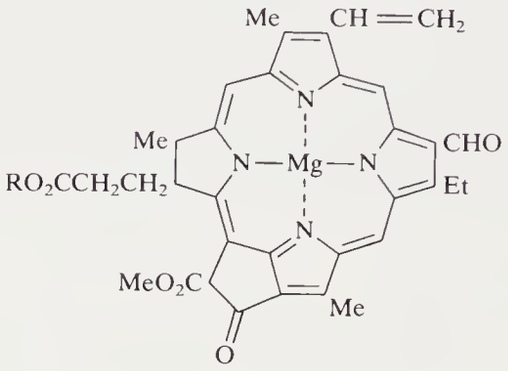
Thiophene and its homologues occur in coal-tar benzene, shale oil and crude petroleum. They show the indophenine test (Section 3.3.1.5.7.ii), and the discovery of thiophene followed the observation that pure benzene did not give this test. Thiophenes are sometimes named after the benzenoid analogues, *e.g.* thiotolene for methylthiophene, thiotenol for hydroxythiophene.

Furfural (furan-2-carbaldehyde; Scheme 1) arises from the decomposition of sugars and is a commercially important raw material used in furfural–phenol resins and as a synthetic intermediate (see CHEC 1.15).

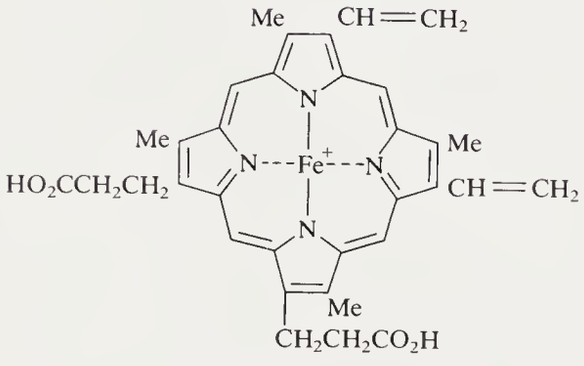
Pyrrole occurs in bone oil and imparts a bright red color to pine wood moistened with mineral acid; this characteristic behavior led to its discovery and is used as a qualitative test for pyrrole derivatives. The bile pigments are metabolic products having chains of four pyrrole rings. Their precursors are the porphyrins, which comprise the blood pigments, the chlorophylls and vitamin B_{12} and consist of four pyrrole units joined in a macro ring. The phthalocyanines are important synthetic pigments (see Scheme 1).



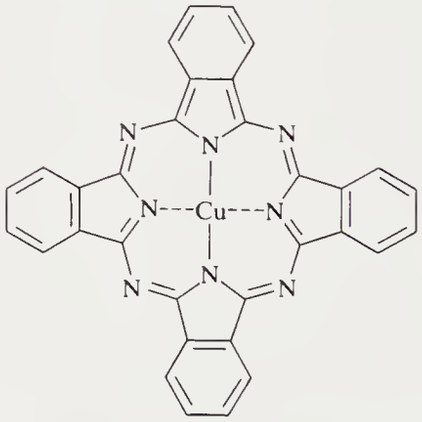
Furfural



Chlorophyll-*b*
R = phytyl, $C_{20}H_{34}$



Haemin (blood pigment)



Monastral blue (phthalocyanine pigment)

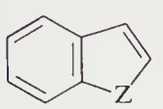
Scheme 1 Important derivatives

2.3.1.2 Benzo Derivatives

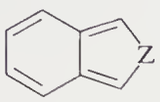
The benzo[*a*] (**19**), benzo[*b*] (**15**) and benzo[*c*] (**16**) fused heterocycles are heterocyclic analogues of naphthalene, with the dibenzo heterocycles (**17**) bearing a similar electronic relationship to phenanthrene. Some of these compounds are still known by their trivial names indole (**15**;

Z = NH), isoindole (**16**; Z = NH), carbazole (**18**) and indolizine (**19**). The names thianaphthene and pyrrocoline for (**15**; Z = S) and (**19**) respectively are now little used. Particular confusion can arise in consulting the literature on indolizine (**19**), where differing numbering systems have been used. Note that carbazole (**18**) is an exception to the IUPAC rules for numbering the other dibenzo heterocycles.

The non-aromatic isomers of indoles (**15**; Z = NH) are indolenines (**20**), which are stable only if R is not equal to H; however, isoindoles often exist as (**21**). Some of the carbonyl derivatives have trivial names: oxindole (**22**; Z = NH) coumarone (**22**; Z = O), indoxyl (**23**; Z = NH) and phthalide (**24**; Z = O). The common names indoline (**25**; Z = NH) and coumaran (**25**; Z = O) are used for the 2,3-dihydro derivatives of indole and benzofuran, respectively.



(15)



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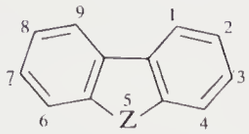

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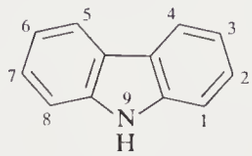

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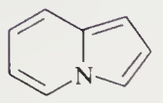

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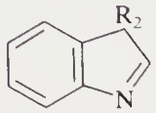

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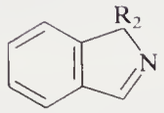

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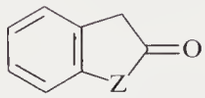

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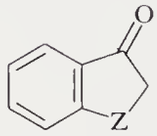

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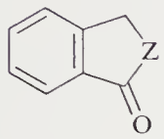

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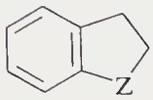

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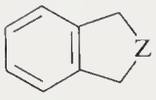
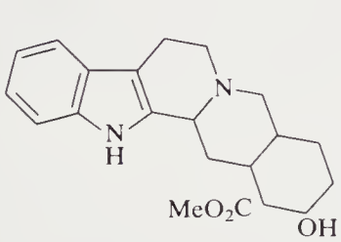
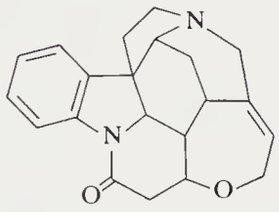


(26)

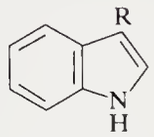
Important indole derivatives (see Scheme 2) include: (i) indigo, a vat dye known and widely used since antiquity, and originally obtained from indican, a β-glucoside of indoxyl which occurs in some plants. Indigo is now prepared synthetically. Tyrian purple, a natural dye used since classical times, is 6,6-dibromoindigo; (ii) the numerous indole alkaloids, with complex derivatives such as yohimbine and strychnine; (iii) tryptophan, an essential amino acid found in most proteins. Its metabolites include skatole and tryptamine; and (iv) 3-indoleacetic acid, which is important as a plant growth hormone.



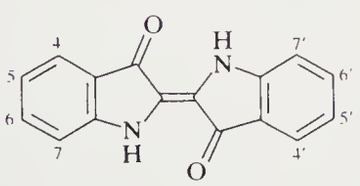
Yohimbine



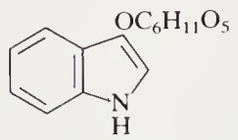
Strychnine



Tryptophan R = $CH_2CH(NH_2)CO_2H$
Skatole R = Me
Tryptamine R = $CH_2CH_2NH_2$
3-Indoleacetic acid R = CH_2CO_2H



Indigo



Indican

Scheme 2

2.3.2 THEORETICAL METHODS

The major object of the plethora of semi-empirical molecular orbital calculations on furan, thiophene and pyrrole has been to establish the suitability of various modes of parameterization for reproducing experimentally derivable parameters such as geometry, dipole moments and ionization potentials. Relatively recently, it has become practical to apply *ab initio* MO methods to these molecules, but these still require huge amounts of expensive computer time. Inclusion of sulfur 3*d*-orbitals in *ab initio* calculations on thiophene makes little difference to the total energy ⟨70CC319, 72MI30101⟩. Their principal role is to act as polarization functions rather than as an extra valence orbital. Thus the population of the 3*d*-orbital is very small but its introduction into the basis set causes considerable changes in the population of 3*s*- and 3*p*-orbitals so that electron density on sulfur is increased at the principal expense of the flanking carbon atoms. This conclusion has received experimental support ⟨76JCP(64)3021⟩ from analysis of fluorescent sulfur $L_{II,III}$ emission spectra, which supplies electronic populations of the 3*s* and 3*d* valence bands. A consequence of the inclusion of *d*-orbitals is that the calculated dipole moment is lowered from 0.96 to 0.62 D (*cf.* experimental value of 0.54 D). A similar effect has been observed upon the inclusion of selenium 4*d*-orbitals in calculations on selenophene ⟨75JCS(F2)1397⟩. These and other *ab initio* calculations ⟨74JCS(P2)420, 77JCP(67)5738⟩ have provided, *inter alia*, satisfactory dipole moments, second moments and ionization potentials for pyrrole, furan, thiophene and selenophene. Resonance energies have been calculated for pyrrole (149 kJ mol^{-1}), furan (89 kJ mol^{-1}) and thiophene (124 kJ mol^{-1}) ⟨75JCS(P2)974⟩.

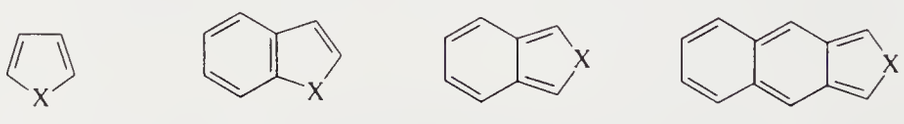
Extension of these calculations to thiophene *S,S*-dioxide has led to the deduction of an OSO bond angle of *ca.* 118° ⟨75JCS(P2)1223⟩, in close agreement with the angle of 120° found for dibenzothiophene *S,S*-dioxide, and an out-of-plane angle of 45° has been predicted for thiophene *S*-oxide with an estimated inversion barrier of 44 kJ mol^{-1}, which is of the same order of magnitude as that observed, 62 kJ mol^{-1}, for the 2,5-bis(2,2-dimethylhexyl) derivative. Out-of-plane angles of 28.4° and 75° have been computed for *O*-protonated furan and *S*-protonated thiophene respectively, with corresponding inversion barriers of 5.48 and 138 kJ mol^{-1} ⟨77G55⟩. These species may serve as models for *O*- and *S*-alkyl cations. Out-of-plane angles of 68.9° and 68.2° have been reported for the *S*-methyl cations of dibenzothiophene and naphtho[2,3-*b*]-thiophene ⟨81JA289⟩ and a similar geometry has been found for the 1,2,3,5-tetramethylbenzo[*b*]-thiophenium cation ⟨81JCS(P2)266⟩. The conformational preferences of 2- and 3-monosubstituted furans, pyrroles and thiophenes have been the subject also of *ab initio* calculations ⟨77JCS(P2)1601, 78JA3981, 79JA311⟩ and will be discussed in Section 2.3.4.3.1.

The MINDO/3 semi-empirical MO method provides ⟨75JA1302, 75JA1311, 79JOC374⟩ satisfactory geometries, heats of formation and ionization potentials for furan, thiophene and pyrrole, with somewhat less satisfactory dipole moments. Calculated vibrational frequencies for these heterocycles also agree well with experimental values, any errors tending to be systematic for a given vibration type ⟨77JA1685⟩.

The relative importance of through-bond (hyperconjugative) and through-space (homoconjugative) interactions between the heteroatom and the double bond in 2,5-dihydro-furan, -thiophene and -pyrrole has been the subject of a CNDO/S study ⟨76ZN(A)215⟩. This analysis concluded that the proportion of through-space interaction increased from 19% in the dihydrofuran and 20% for dihydrothiophene to 83% for the dihydropyrrole (*cf.* Section 2.3.3.9).

The less sophisticated PPP approximation has been shown to reproduce well the electronic spectral features not only of the monocyclic furan, pyrrole, thiophene, selenophene and tellurophene but also many of the benzo-fused derivatives as well ⟨79MI30101, 68JPC3975, 68MI30100⟩.

A useful predicative application of the relatively crude Hückel method to illustrate quantitatively the effect of benzenoid annelation on the resonance energies of furan and thiophene is summarized in Scheme 3. As expected, thiophenes are more stable than the corresponding furans and 3,4-fusion results in less stable compounds than 2,3-fusion ⟨77CR(C)(285)421⟩.



X = O	75 kJ mol^{-1}	188	138	201
X = S	121	222	184	251

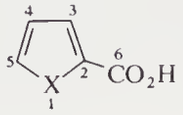
Scheme 3

2.3.3 STRUCTURAL METHODS

2.3.3.1 X-Ray Diffraction

Bond lengths and angles from X-ray structures of heterocyclic compounds through 1970 have been listed ⟨78PMH(5)1⟩. This compilation contains many examples, particularly of furans, thiophenes and pyrroles and their benzo derivatives; further examples are contained in the monograph chapters of CHEC. The dimensions in Table 1 for the 2-carboxylic acid derivatives of furan, thiophene, selenophene and tellurophene are generally in good accord with those obtained for the parent heterocycles (see Table 2). Further bond lengths are tabulated and discussed in Section 2.4.4.3.1 dealing with conformations of aromatic compounds.

Table 1 Bond Lengths and Angles of Heterocycle 2-Carboxylic Acids



Bond length (Å)	X = O	S	Se	Te
X—C(5)	1.312	1.701	1.850	2.047
X—C(2)	1.368	1.693	1.872	2.057
C(5)—C(4)	1.446	1.363	1.355	1.357
C(2)—C(3)	1.288	1.362	1.356	1.384
C(3)—C(4)	1.351	1.414	1.421	1.412
C(2)—C(6)	1.414	1.481	1.438	1.423
Bond angle (degrees)				
C(2)XC(5)	109	92.0	87.1	81.5
XC(5)C(4)	109	111.8	112.25	111.7
XC(2)C(3)	109	111.8	110.7	111.7
C(5)C(4)C(3)	105	111.9	114.2	118.8
C(4)C(3)C(2)	105	112.4	115.7	116.3
XC(2)C(6)	120	122.2	121.0	123.4
C(3)C(2)C(6)	131	125.9	128.3	124.8
Ref.	62AX919	62AX737	62AX737	72CSC273

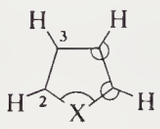
2.3.3.2 Microwave Spectroscopy

For some general remarks on microwave spectra see Section 2.4.3.2.

2.3.3.2.1 Molecular geometry

High accuracy molecular dimensions for the planar parent heterocycles in the gas phase have been obtained by microwave spectroscopy and are recorded in Table 2. Increasing size of the

Table 2 Comparison of Bond Lengths and Angles of Monoheterocycles



Bond length (Å)	X = NH	O	S	Se	Te
X—C(2)	1.370	1.362	1.714	1.855	2.055
C(2)—C(3)	1.382	1.361	1.370	1.369	1.375
C(3)—C(4)	1.417	1.430	1.423	1.433	1.423
C(2)—H	1.076	1.075	1.078	1.070	1.078
C(3)—H	1.077	1.077	1.081	1.079	1.081
Bond angle (degrees)					
C(2)XC(5)	109.8	106.5	92.17	87.76	82.53
XC(2)C(3)	107.7	110.65	111.47	111.56	110.81
C(2)C(3)C(4)	107.4	106.07	112.45	114.55	117.93
XC(2)H	121.5	115.98	119.85	121.73	124.59
C(2)C(3)H	125.5	127.83	123.28	122.59	121.04
Ref.	69JST(3)491	78JST(48)157	61JSP(7)58	69DOK(185)384	73MI30100

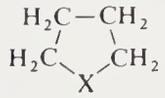
heteroatom results in lengthening of the X—C(2) bond and decrease of the C(2)XC(5) bond angle, so that the shape of the molecule is progressively elongated. Delocalization in the case of pyrrole brings the imino hydrogen into the plane of the other atoms with an N—H bond length of 0.996 Å.

The distortions caused by substitution are usually of small magnitude. Thus in 2-cyanopyrrole it has been found ⟨80JPC1767⟩ by microwave spectroscopy that the N—C(2) and C(2)—C(3) bond lengths are only shortened by 0.009 Å relative to those observed for pyrrole with consequent increases in the ring bond angles at N and C(3) of 0.1°. Distortions of the same magnitude have also been detected for the 2-cyano derivatives of furan and thiophene ⟨80JPC1767⟩, and for 3-cyanothiophene ⟨80ZN(A)770⟩.

2.3.3.2.2 Partially and fully saturated compounds

The determination of the bond lengths of the fully saturated heterocycles has been complicated by their conformational mobility, which is considered in Section 2.3.4.3.2. The data which have been provided by electron diffraction are listed in Table 3 and show the expected trends consonant with increasing size of heteroatom.

Table 3 Bond Lengths and Angles for Saturated Monoheterocycles



Bond lengths (Å)	X = O	S	Se
X—C	1.428	1.839	1.975
C—C	1.535	1.536	1.538
Bond angles (degrees)			
CXC	106.4–110.6	93.4	89.1
XCC	103.7–107.5	106.1	105.8
CCC	100.3–104.4	105.0	106.0
Ref.	69ACS2748, 69T3045	69ACS3534	70ACS1903

2.3.3.3 ^{1}H NMR Spectroscopy

2.3.3.3.1 Parent aromatic compounds

The ^{1}H NMR spectra of the parent heterocycles (Table 4) each consist of two multiplets, of which the one at lower field is assigned to the α-hydrogens.

Table 4 ^{1}H NMR Spectral Data for Monoheterocycles (in $CDCl_3$)[b]

	Pyrrole	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*	*Cyclopentadiene*
H-2	6.68	7.29	7.18	7.88	8.87	6.28
H-3	6.22	6.24	6.99	7.22	7.78	6.43
$J_{2,3}$	2.70	1.75	4.90	5.40	6.70	5.05
$J_{2,4}$	1.44	0.85	1.04	1.46	1.30	1.09
$J_{2,5}$	1.87	1.40	2.84	2.34	2.60	1.93
$J_{3,4}$	3.35	3.30	3.50	3.74	4.00	1.93
Ref.	[a]	65SA85	65SA85	65SA85	72JCS(P1)199	70JCP(53)2343

[a] Varian Catalog. [b] Units are p.p.m. and Hz.

Apart from pyrrole, the chemical shifts for the β-protons increase with decreasing electronegativity of the heteroatom. In contrast, the chemical shifts of the α-protons do not display any obvious regularity, probably due to paramagnetic shielding contributions which will become more important with increasing availability of *d*-orbitals. The chemical shift of the pyrrole N—H is solvent dependent.

In the case of pyrrole the ring protons are also coupled to the N—H with $J_{1,2} = J_{1,5} = 2.58$ Hz and $J_{1,3} = J_{1,4} = 2.46$ Hz, while satellites due to spin–spin coupling between the α-protons and the ring heteroatom are observed for selenophene, $J(^{77}Se, H) = 47.5$ Hz, and tellurophene, $J(^{125}Te, H) = 100.4$ Hz ⟨74ACS(B)175⟩.

The magnitudes of the vicinal vinylic proton coupling constants are much smaller than the 7.6 Hz observed for benzene and reflect in part the greater separation of the protons when attached to five-membered rings; however, factors such as electronegativity and double-bond character also affect coupling sizes: $J_{2,3}$ and $J_{3,4}$ increase systematically, *i.e.* O < NH < S < Se < Te. Comparison with the corresponding coupling constants for cyclopentadiene indicates the important role of heteroatom electronegativity in determining the magnitude of $J_{2,3}$. The much larger $J_{3,4}$ observed for all of the heterocycles emphasizes the greatly increased conjugative interaction between carbons 3 and 4 relative to that in cyclopentadiene. The longer range coupling constant $J_{2,4}$ is lower for all of the heterocycles than corresponding benzenoid *meta* coupling constants (*ca.* 2–3 Hz), whereas the $J_{2,5}$ couplings, which increase in the sequence O < NH < CH_2 < Se < Te < S, are larger than benzenoid *para* coupling constants (*ca.* 0–1 Hz).

2.3.3.3.2 Substituted aromatic compounds

As in benzenoid analogues, electron-withdrawing substituents deshield and electron-releasing groups shield the ring protons. Quantitative correlations between the ^{1}H NMR spectral properties of monosubstituted furans ⟨75CS(7)211⟩, thiophenes ⟨75CS(7)76⟩, selenophenes ⟨75CS(7)111⟩ and tellurophenes ⟨76ACS(B)605⟩ have been extensively explored and rationalizations offered in terms of inductive and mesomeric effects. Linear correlations exist (a) between the relative shifts of H-2 and H-3 in 3-substituted furans, thiophenes and selenophenes and (b) between heteroatom electronegativity and the shifts of H-5 in 2- and 3-substituted, and H-2 in 3-substituted, heterocycles.

Long-range couplings occur between ring protons and hydrogens attached to substituent atoms. For example, in heterocyclic 2-aldehydes couplings of the order of 1 Hz have been observed.

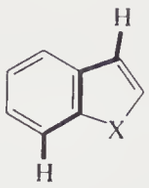
Annelation of a benzene ring on to the [*b*] face of the heterocyclic ring does not have any pronounced effect upon the chemical shifts of the heterocyclic protons (*cf.* Table 5). The chemical shift of the indole N—H is solvent dependent and as in pyrrole it is also coupled to the ring protons with $J_{1,2} = 2.4$ Hz and $J_{1,3} = 2.1$ Hz. The benzenoid protons H-4 and H-7 appear downfield from H-5 and H-6. Long-range coupling between H-3 and H-7 (*cf.* **27**) is of considerable diagnostic value in establishing the orientation of a substituent on the heterocyclic ring.

Table 5 ^{1}H NMR Spectral Data for Benzo[*b*] Heterocycles (in CCl_4)[b]

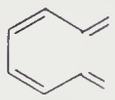
	Indole	*Benzofuran*	*Benzothiophene*	*Benzoselenophene*	*Benzotellurophene*
H-2	6.52 (7.27)[a]	7.52 (7.78)[a]	7.33	7.90	8.65
H-3	6.29 (6.45)	6.66 (6.76)	7.22	7.50	7.91
H-4	(7.55)	7.49 (7.63)	7.72	7.76	7.79
H-5	(7.00)	7.13 (7.23)	7.26	7.19–7.29	7.08–7.30
H-6	(7.08)	7.19 (7.30)	7.24	7.19–7.29	7.08–7.30
H-7	(7.40)	7.42 (7.51)	7.79	7.86	7.90
$J_{2,3}$	3.1	2.19	5.5	6.0	7.1
$J_{2,6}$	—	—	0.5	0.3	—
$J_{3,7}$	0.7	0.87	0.75	0.67	—
$J_{4,5}$	7.8	7.89	8.5	—	—
$J_{4,6}$	1.2	1.28	1.14	—	—
$J_{4,7}$	0.9	0.80	0.7	—	—
$J_{5,6}$	7.0	7.27	7.0–7.5	—	—
$J_{5,7}$	1.2	0.92	0.5–1.0	—	—
$J_{6,7}$	8.0	8.43	8.0–7.5	—	—
Ref.	64JCS981, 65AJC353	65AJC353	66BCJ2316	72BSF3193	72BSF3193

[a]Chemical shifts in parentheses are for acetone solutions. [b] Units are p.p.m. and Hz.

^{1}H NMR spectroscopy has provided useful structural information on the unstable benzo[*c*]-fused heterocycles (Table 6). The protons H-1 and H-3, adjacent to the heteroatom, are observed at lower field than are the corresponding ones in the parent heterocycles or their benzo[*b*] isomers.



(27)



(28)

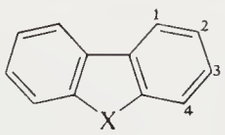
However, the same sequence of downfield shifts, namely NR < S < O < Se, is observed. Thus, at least the heterocyclic moiety appears to be aromatic. The ratio of the vicinal coupling constants $J_{5,6}/J_{4,5}$ (0.70–0.74) is significantly less than for compounds of the Kekulé series (*ca.* 0.9), much higher than observed for a polyenic π-system (cyclohexa-1,3-diene displays a value of 0.52), and close to the predicted value of 0.71 for the corresponding ratio for $J_{4,5}/J_{3,4}$ in octatetra-1,3,5,7-ene with conformation (**28**). NMR data for dibenzo heterocycles are given in Table 7.

Table 6 ^{1}H NMR Spectral Data for Benzo[*c*] Heterocycles[a]

	H-1, *H*-3	*H*-4, *H*-7	*H*-5, *H*-6	$J_{1,4}$	$J_{4,5}$	$J_{4,6}$	$J_{4,7}$	$J_{5,6}$	*Solvent*	*Ref.*
Isoindole	6.28	7.5	6.8	—	8.49	—	—	6.29	$(CD_3)_2CO$	73JCS(P1)1432
N-Methylisoindole	7.05	7.51	6.92	0.46	8.69	0.90	0.79	6.46	$CDCl_3$	76JCS(P2)81
Benzo[*c*]furan	7.99	7.38	6.84	0.64	8.52	1.01	0.57	6.22	$CDCl_3$	76JCS(P2)81
Benzo[*c*]thiophene	7.63	7.59	7.04	0.42	8.64	1.03	0.79	6.36	$CDCl_3$	76JCS(P2)81
Benzo[*c*]selenophene	8.40	7.33–7.54	6.77–7.02	—	9.16	—	—	6.79	$CDCl_3$	77JA8248, 76JA867

[a] Units are p.p.m. and Hz.

Table 7 ^{1}H NMR Spectral Data for Dibenzo Heterocycles (in Acetone)[b]



	Carbazole[a]	*Dibenzofuran*	*Dibenzothiophene*
H-1	7.49	7.61	7.95
H-2	7.36	7.51	7.50
H-3	7.16	7.37	7.49
H-4	8.08	8.07	8.29
$J_{1,2}$	8.21	8.42	8.07
$J_{1,3}$	0.89	0.72	1.11
$J_{1,4}$	0.67	0.57	0.70
$J_{2,3}$	7.17	7.56	7.23
$J_{2,4}$	1.18	1.36	1.17
$J_{3,4}$	7.80	7.87	8.06
Ref.	65AJC353	65AJC353	71AJC2293

[a] This is not the normal numbering system for carbazole. [b] Units are p.p.m. and Hz.

2.3.3.3.3 Saturated and partially saturated compounds

The α-hydrogen resonances for the fully saturated monocycles (Table 8) occur at lower fields than the β-hydrogen resonances. The chemical shifts of the β-hydrogens vary systematically with the electronegativity of the heteroatom, but the chemical shifts of the α-hydrogens do not.

Table 8 ^{1}H NMR Spectral Data (p.p.m.) for Tetrahydro Heterocycles (in CCl_4)

	H-2	*H*-3	*Ref.*
Pyrrolidine	2.77	1.63	72JA8854
Tetrahydrofuran	3.62	1.79	72JA8854
Tetrahydrothiophene	2.75	1.92	72JA8854
Tetrahydroselenophene	2.79	1.96	74JHC827
Tetrahydrotellurophene	3.10	2.03	74JHC827

The spectra of 2,5-dihydrofuran and 2,5-dihydrothiophene are simple, showing two singlets at 4.51 and 5.85 for the dihydrofuran, and 3.66 and 5.79 for the sulfur analogue; the lack of coupling is in accord with an almost planar conformation ⟨73JMR(12)244⟩.

2.3.3.4 ^{13}C NMR Spectroscopy

The ^{13}C NMR spectral properties of the parent heterocycles are summarized in Table 9. The signal for the pyrrole α-carbon is broadened as a result of coupling with the adjacent nitrogen-14 atom (*cf.* Section 2.3.3.5). While the frequencies observed for the β-carbon atoms show a fairly systematic upfield shift with increasing electronegativity of the heteroatom, the shifts for the α-carbon atoms vary irregularly. All the shifts are in the region of that for benzene, δ 128.7.

Table 9 ^{13}C NMR Spectral Data for Monoheterocycles (in Acetone)[a]

	Pyrrole	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*
C-2	118.2	143.6	125.6	131.0	127.3
C-3	107.2	110.4	127.3	129.8	138.0
$J_{C\text{-}2,H\text{-}2}$	184	201	185	189	183
$J_{C\text{-}3,H\text{-}3}$	170	175	168	166	159
$J_{C\text{-}2,H\text{-}3}$	(7.6)	14	7.35	7.0	—
$J_{C\text{-}2,H\text{-}4}$	(7.6)	5.8	10.0	10.0	—
$J_{C\text{-}2,H\text{-}5}$	(7.6)	7.0	5.15	3.5	—
$J_{C\text{-}3,H\text{-}2}$	7.8	7.0	4.7	4.5	—
$J_{C\text{-}3,H\text{-}4}$	4.6	4.0	5.9	6.0	—
$J_{C\text{-}3,H\text{-}5}$	7.8	10.8	9.5	10.4	—
Ref.	68JA3543	68JA3543, 65JA5333	68JA3543, 65JA5333	68JA3543, 74ACS(B)175	74ACS(B)175

[a] Units are p.p.m. and Hz.

The direct $J_{C\text{-}3,H\text{-}3}$ coupling constants decrease regularly along the series O > NH > S > Se > Te. The values for $J_{C\text{-}2,H\text{-}2}$ are appreciably larger than the 159 Hz observed for benzene and the 170 Hz for the alkenic protons of cyclopentadiene, while the $J_{C\text{-}3,H\text{-}3}$ coupling constants span this range.

Similar correlations have been observed ⟨75CS(7)211⟩ between the ^{13}C NMR spectra of monosubstituted furans, thiophenes, selenophenes and tellurophenes as with their ^{1}H NMR spectra (*cf.* Section 2.3.3.3). Thus for the 2-substituted compounds the Δ(C-3)/Δ(C-5) ratios decrease systematically in the series furan (2.58) > thiophene (1.34) = selenophene (1.34) > tellurophene (0.91). Extensive quantitative correlations have been established between the shifts of the corresponding carbon atoms in the different heterocycles ⟨75CS(7)211⟩. In most cases $^{1}J_{(C,H\beta)}$ in both 2- and 3-substituted heterocycles can be linearly correlated with the electronegativity of the heteroatom, with the couplings being largest for the furans.

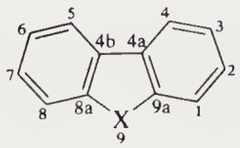
The signal for C-2 of indole, benzo[*b*]furan and benzo[*b*]thiophene (Table 10) is shifted to lower field than C-3. However, the shifts for C-2 (O, 144.8; Se, 128.8; S, 126.1; NH, 124.7; Te, 120.8) and C-7a (O, 155.0; Se, 141.3; S, 139.6; NH, 135.7; Te, 133.0) in the benzo[*b*] heterocycles vary irregularly ⟨80OMR(13)319⟩, and the sequence is different to that observed for C-2 in the parent heterocycles, namely O > Se > Te > S > NH. Also noteworthy is the upfield position of C-7,

Table 10 ^{13}C NMR Spectral Data (p.p.m.) for Benzo[*b*] Heterocycles

	Indole	*Benzofuran*	*Benzothiophene*
C-2	124.67	145.1	126.21
C-3	102.14	106.9	123.79
C-4	120.76	121.6	123.57
C-5	121.81	123.2	124.10
C-6	119.76	124.6	124.17
C-7	111.35	111.8	122.44
C-7a	135.65	155.5	139.71
C-3a	128.26	127.9	139.57
Solvent	dioxane	CS_2	$CDCl_3$
Ref.	70JOC996, 75JOC3720	74BCJ1263	76OMR(8)252

especially in indole and benzofuran, relative to the other benzenoid carbons at positions 4, 5 and 6. In the dibenzo heterocycles (Table 11), C-1 and C-8 are shifted upfield in carbazole and dibenzofuran relative to the corresponding carbons in dibenzothiophene and fluorene, and similar, though smaller, shifts can be discerned for C-3 and C-6 in the former compounds.

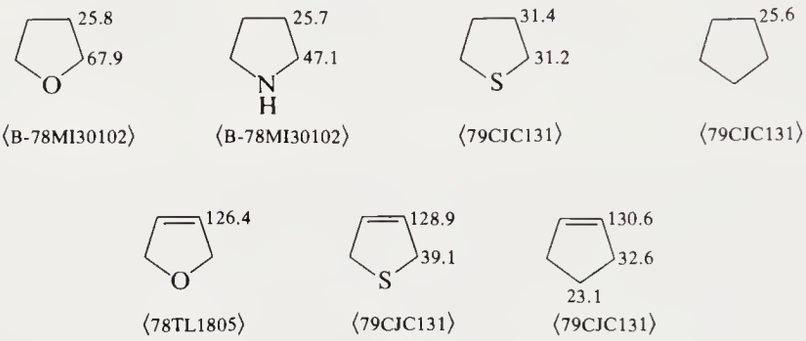
Table 11 ^{13}C NMR Spectral Data (p.p.m.) for Dibenzo Heterocycles (in DMSO-d_6) ⟨79OMR(12)647⟩



	Carbazole	*Dibenzofuran*[a]	*Dibenzothiophene*[a]	*Fluorene*
C-1,8	110.8	111.6	122.9	125.0
C-2,7	125.4	127.5	127.0	126.7
C-3,6	118.4	123.0	124.6	126.7
C-4,5	120.0	121.1	121.9	119.9
C-4a,4b	122.6	123.5	134.9	141.0
C-8a,9a	139.6	155.4	138.5	142.8

[a] This is not the normal numbering system for these molecules.

Information on partially and fully saturated heterocycles is much more limited and is summarized in Scheme 4. As would be expected, the downfield shift of the α-carbon atom decreases with decreasing electronegativity of the heteroatom in the sequence $O < NH < S < CH_2$.



Scheme 4

2.3.3.5 Heteroatom NMR Spectroscopy

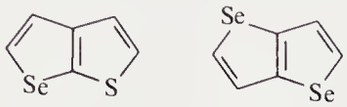
All of the heteroatoms possess at least one naturally occurring isotope with a magnetic moment (Table 12). The electric quadrupole of ^{14}N, ^{17}O and ^{33}S broadens the NMR signals so that line widths may be 50–1000 Hz or even wider. To some extent this problem is offset by the more extensive chemical shifts that are observed. The low natural abundances and/or sensitivities have necessitated the use of accumulation techniques for all of these heteroatoms. ^{14}N and ^{15}N chemical shifts are interchangeable.

Table 12 Magnetic Properties of Heteronuclei

Isotope	*Natural abundance* (%)	*Nuclear spin*	*Electric quadrupole moment*[a]	*NMR frequency for a 23.5 kG field* (MHz)	*Relative sensitivity*
^{1}H	99.98	$\frac{1}{2}$	—	100	1
^{13}C	1.11	$\frac{1}{2}$	—	25.19	0.016
^{14}N	99.635	1	2.0	7.224	0.00101
^{15}N	0.365	$\frac{1}{2}$	—	10.133	0.00104
^{17}O	0.037	$\frac{5}{2}$	−0.4	13.56	0.029
^{33}S	0.74	$\frac{3}{2}$	−6.4	7.67	0.0023
^{77}Se	7.58	$\frac{1}{2}$	—	19.135	0.00693
^{125}Te	7	$\frac{1}{2}$	—	30.6	0.032

[a] $e \times 10^{-26}$ cm^2.

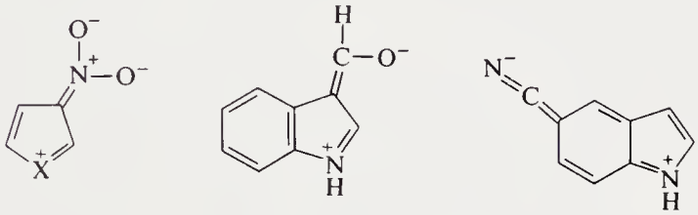
A ^{17}O downfield shift of 222 p.p.m. is observed on the formal aromatization of tetrahydrofuran to furan ⟨61HCA865⟩. Similar downfield shifts have been observed for ^{33}S (tetrahydrothiophene→thiophene 309 p.p.m.) ⟨72JA6579⟩ and ^{14}N (pyrrolidine→pyrrole 106 p.p.m.) ⟨71TL1653⟩, and a very much larger one can be anticipated for tetrahydroselenophene to selenophene ⟨76OMR(8)354, 72JCS(D)1397⟩. Benzoannelation of pyrrole causes *ca.* 10–20 p.p.m. upfield shift per benzene ring. Much larger upfield shifts are observed in proceeding from selenophene→benzoselenophene (79 p.p.m.)→dibenzoselenophene (75 p.p.m.) ⟨76OMR(8)354⟩. Similar upfield shifts of 65 p.p.m. and 56 p.p.m. respectively are observed on annelation with a thiophene ring or selenophene ring to give the selenolothiophene (**29**) ⟨76OMR(8)354⟩ and the selenoloselenophene (**30**) ⟨74CS(5)236⟩.



(**29**) (**30**)

The effects of 2- and 3-substituents on the ^{77}Se NMR chemical shifts in selenophene and benzo[*b*]selenophene have been investigated in detail ⟨75CS(8)8, 81OMR(16)14⟩. The ^{125}Te shifts in 2-substituted tellurophenes exactly parallel the ^{77}Se shifts in similarly substituted selenophenes ⟨76CS(10)139⟩.

The relatively modest shifts observed for substituted pyrroles are more suitably probed by ^{15}N rather than ^{14}N NMR and seem to parallel the ^{77}Se and ^{125}Te behaviors. Electron withdrawing groups such as 2-nitro, 2-formyl and 2-acetyl cause downfield ^{15}N shifts ⟨76OMR(8)208⟩. Perhaps unexpected is the much larger downfield shift found for 3-nitropyrrole than its 2-nitro isomer. Similar disparities with electron accepting groups also arise with selenophenes, and may be accounted for in terms of an important contribution to the hybrid from the resonance structure (**31**). Similar considerations apply to the relatively large ^{15}N downfield shifts observed when such groups are present at positions 3 or 5 of the indole nucleus, the relevant exemplary resonance structures being (**32**) and (**33**) respectively ⟨76OMR(8)117⟩.



(**31**) (**32**) (**33**)

2.3.3.6 UV Spectroscopy

The parent heterocycles (Table 13) display a strong band near 220 nm with one additional band at longer wavelengths for thiophene and selenophene, and two for tellurophene. Analogous weak bands reported in the older literature for furan and pyrrole are now generally accepted as arising from autoxidation products.

The cyclopentadiene anion is a carbocyclic analogue of these heterocycles. Simple theoretical treatment shows that, in contrast to the iso-π-electronic molecule benzene, there is no breaking of the degeneracy of the low-energy forbidden transitions or the high-energy allowed ones as a result of the lower symmetry of the anion. The absorption spectrum of the cyclopentadienyl anion and its hetero analogues is thus expected to consist of a moderate intensity band followed at shorter wavelengths by a high intensity band. Bands arising from promotion of an electron from the lone-pair orbital of a heteroatom to a π-orbital of the heterocyclic ring ($n \rightarrow \pi^*$) would not be expected for pyrrole, where the nitrogen lone pair is involved in the π-bonding. For the other heterocycles where additional heteroatom lone pairs are available they have yet to be identified, even by electron impact studies ⟨76JCP(64)1315, 76MI30100⟩. These did, however, show singlet→triplet transitions at 3.99 eV (311 nm) and 5.22 eV (238 nm) in furan, 3.75 eV (331 nm) and 4.62 eV (268 nm) in thiophene and 4.21 eV (294 nm) in pyrrole. The positions and energy splitting are analogous to the lowest $\pi \rightarrow \pi^*$ transitions in benzene and very different to those anticipated for conjugated dienes.

The marked progressive shift of absorption to longer wavelengths in the sequence furan < pyrrole < thiophene < selenophene < tellurophene is also observed with their 2-substituted

Table 13 UV Spectra (nm) of Monosubstituted Heterocycles

	λ_{max} (log ε)				
Substituent	*O*	*NH*	*S*	*Se*	*Te*
None	208 (3.90)	210 (4.20)	215 (3.8) 231 (3.87)	232 (3.56) 249 (3.75)	209 (3.57) 241 (3.36) 279 (3.93)
2-CO_2H	214sh (3.58) 243 (4.03)	222sh (3.65) 258 (4.10)	246 (3.96) 260 (3.84)	258 (3.94) 282 (3.70)	—
2-CO_2Me	252 (4.13)	238sh (3.63) 263 (4.14)	248 (3.97) 268 (3.86)	260 (4.0) 284 (3.80)	—
2-COMe	226 (3.38) 270 (4.15)	250sh (3.70) 287 (4.21)	260 (4.01) 283 (3.87)	271 (4.02) 302 (3.70)	211 (3.93) 282 (3.87) 346 (3.58)
2-CHO	227 (3.48) 272 (4.12)	251 (3.49) 287 (4.12)	260 (4.04) 286 (3.86)	271 (4.07) 304 (3.71)	—
2-NO_2	225 (3.53) 315 (3.91)	231 (3.61) 335 (4.23)	270 (3.80) 296 (3.78)	—	—
3-CO_2H	200 (3.85) 235 (3.39)	223 (3.89) 245 (3.71)	241 (3.92)	—	—
3-CO_2Me	238 (3.40)	224 (3.90) 247 (3.73)	241 (3.95)	—	—
3-COMe	—	243 (3.97) 270sh (3.66)	250 (4.08)	—	—
3-CHO	—	243 (3.97) 270 (3.66)	251 (4.12)	—	—
Solvent *Ref.*	EtOH 71PMH(3)79	EtOH, MeOH 71PMH(3)79, 71T245	EtOH 58AK(13)239, 58SA350	EtOH 58G453	*n*-hexane 72JCS(P1)199

derivatives. Increasing conjugating powers of 2-substituents result in displacement of absorption bands to longer wavelength in the expected sequence $CO_2H < COMe < CHO < NO_2$. Smaller bathochromic shifts occur when conjugating substituents are introduced into position 3, but now pyrrole displays larger shifts than thiophene.

Annelation increases the complexity of the spectra just as it does in the carbocyclic series, and the spectra are not unlike those of the aromatic carbocycle obtained by formally replacing the heteroatom by two aromatic carbon atoms (—CH=CH—). Although quantitatively less marked, the same trend for the longest wavelength band to undergo a bathochromic shift in the heteroatom sequence O < NH < S < Se < Te is discernible in the spectra of the benzo[*b*] heterocycles (Table 14). As might perhaps have been anticipated, the effect of the fusion of a second benzenoid ring on to these heterocycles is to reduce further the differences in their spectroscopic properties (*cf.* Table 15). The absorption of the benzo[*c*]heterocycles (Table 16) at longer wavelengths than their benzo-[*b*] counterparts is a reflection of the lower aromaticity of the former compounds and the consequential differences in the energies of the highest occupied molecular orbitals.

Whereas none of furan, pyrrole or thiophene fluoresce or phosphoresce, indole and carbazole both fluoresce and phosphoresce strongly (CHEC 3.04.4.4) ⟨74PMH(6)166⟩. The characteristic fluorescence of indoles has found extensive application in the detection and estimation of naturally occurring derivatives. The fluorescence maximum of indole observed at 297 nm in cyclohexane undergoes dramatic shifts in hydrogen-bonding solvents, possibly due to strong interactions between the solvent and the lowest excited singlet state of the indole. The wavelength of phosphorescence of benzothiophene (λ_p 416 nm) is somewhat longer than for indole (λ_p404 nm), reflecting the effect of the higher energy $3p_\pi$ orbital of sulfur on the energy of the highest occupied MO as opposed to the nitrogen $2p_\pi$ one. The effect is less marked in the case of dibenzothiophene (λ_p 411 nm), relative to dibenzofuran (λ_p 408 nm) and carbazole (λ_p 407 nm).

2.3.3.7 IR Spectroscopy

2.3.3.7.1 Ring vibrations

The literature concerning the IR spectra of these heterocycles has been extensively surveyed ⟨63PMH(2)165, 71PMH(4)265⟩.

The vibrational assignments for the parent heterocycles are summarized in Table 17. These have been derived from IR and Raman spectra of both the parent heterocycles and deuterated

Table 14 UV Spectra of Benzo[*b*] Heterocycles (in Heptane)

Compound	λ_{max} (nm) (log ε)							*Ref.*
Benzofuran	—	239.5 (4.03)	240.5 (4.03)	244.5 (4.04)	250.5 (3.91)	269 (3.23) 275 (3.40)	271 (3.25) 281 (3.49)	57ACH(11)365
Indole	215 (4.38)	261 (3.69)	266.5 (3.70)	277sh (3.58)	279 (3.62)	287 (3.51)	—	57ACH(11)365
Benzothiophene	228 (4.45)	263sh (3.71)	258 (3.76)	281 (3.19)	288.5 (3.33)	290.5 (3.33)	297 (3.52)	57ACH(11)365
Benzoselenophene	236 (4.45)	260 (3.70)	270sh (3.52)	296 (3.56)	298 (3.54)	305 (3.79)	—	57ACH(11)365
Benzotellurophene	214 (4.43)	251 (4.43)	—	312sh (4.15)	318 (4.2)	—	—	71BSB521

Table 15 UV Spectra of Dibenzo Heterocycles (in EtOH) ⟨58AC(R)738⟩

Compound	*Zone A*	*Zone B*	*Zone C*
Dibenzofuran	218 (4.51), 227sh (4.31), 241 (4.04), 244 (4.04), 249 (4.26)	275sh (4.09), 280 (4.22), 286 (4.19)	296 (3.95), 300sh (3.65)
Carbazole	211 (4.43), 227sh (4.53), 233 (4.57), 243 (4.38), 253 (4.25)	282sh (3.99), 291 (4.14)	322 (3.52), 334 (3.44)
Dibenzothiophene	237 (4.57), 258 (4.12), 264 (3.99)	280sh (3.75), 289 (4.05)	317 (3.28), 328 (3.39)
Dibenzoselenophene	238 (4.77), 260sh (4.14)	278 (3.84), 286 (3.98)	316 (3.37), 326 (3.46)
Dibenzotellurophene	212 (4.39), 232sh (4.93), 235 (4.93), 255 (4.32), 263 (4.20)	280sh (3.99), 286 (4.24)	303 (3.45), 312 (3.53), 325 (3.63)

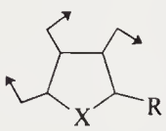
Table 16 UV Spectra of Benzo[*c*] Heterocycles (in Hexane)

Compound	λ_{max} (nm) (log ε)	*Ref.*
Benzo[*c*]indole	263.5, 268.5, 275, 286.5, 294sh, 300, 306.5, 312.5, 320, 326.5, 335	73JCS(P1)1432
Benzo[*c*]furan	215 (4.17), 244 (3.4), 249 (3.37), 254 (3.35), 261 (3.12), 292sh (3.35), 299sh (3.47), 305sh (3.56), 313 (3.7), 319 (3.7), 327 (3.87), 334 (3.66), 343 (3.79)	71TL2337
Benzo[*c*]thiophene (in MeOH)	215 (4.84) 257sh (4.04), 272 (3.94), 278 (3.94), 283sh (3.93), 290 (3.97), 295 (3.96), 298sh (3.94), 305 (4.06), 313 (3.89), 318 (3.90), 322 (3.88), 328 (3.91), 333 (3.90), 343 (3.79)	63JPR(20)244
Benzo[*c*]selenophene	273, 286, 291, 298, 302sh, 305sh, 312, 323, 328, 336sh, 340, 344sh, 353, 357, 362sh	76JA867

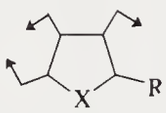
derivatives. In the case of the vibrations of A_1 symmetry, these have been further supported by photoelectron spectroscopic studies ⟨71SA(A)2525⟩. The variety of factors responsible for the observed differences precludes a complete rationalization as they may variously operate in concert or in opposition. Pertinent factors include the mass and electronegativity of the heteroatom, π-electron delocalization, ring geometry and vibrational coupling of normal modes. The ring modes permit the best qualitative comparison, especially as the interaction of the C—H and N—H in-plane deformation modes of pyrrole precludes direct comparisons of its β-CH vibrations with those of the other heterocycles. The increase in frequency of the ν_5 mode, which is associated with the symmetric stretching of the double bonds, occurs in the sequence thiophene < selenophene < tellurophene < pyrrole < furan and may be related to increasing localization of double bonds attendant upon decreasing aromaticity. The large decreases in frequency of the ν_3 and ν_{17} modes, which depend upon symmetric and antisymmetric C—X—C stretching respectively, and the ring deformation modes ν_8, ν_{18} and ν_{21} have been attributed to mass and geometry effects.

In the case of 2- and 3-substituted heterocycles, bands attributed to three ring stretching modes are generally observed (*cf.* Table 18) with frequencies decreasing in the order furan > pyrrole > selenophene ≥ thiophene > tellurophene. The intensities of these bands are frequently increased by increasing electron withdrawing capabilitics of substituents. The effect of this increased electron withdrawal will be to cause tighter conjugation, steeper charge gradients, and hence larger dipole moment changes during the vibrations. As a consequence of the occurrence of hydrogen bonding, either between molecules in concentrated solution or between molecules and solvent, the stretching frequency of the pyrrole N—H is subject to considerable variation ⟨70SA(A)269⟩. In the absence of association the NH stretching vibration is also very susceptible to the electronic character of ring substituents. This is particularly noticeable with electron-withdrawing groups such as ethoxycarbonyl, acetyl, benzoyl and cyano, and the effect of an α-substituent is always greater than that of a β-analogue ⟨65SA295, 66AJC107, 70MI30100⟩.

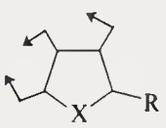
Three β-CH modes corresponding to in-plane C—H deformations are also observed (Table 19) and are probably best depicted as in (**34**), (**35**) and (**36**), although those for pyrrole will be modified as a result of interaction with the in-plane N—H deformation. The skeletal ring breathing mode (**37**) observed at *ca.* 1137 cm^{-1} for 2-substituted pyrroles and at 1015 cm^{-1} for 2-substituted furans is displaced to the 800 cm^{-1} region for thiophenes and presumably to even lower wavelengths for selenophene and tellurophene derivatives. The NH deformation mode of substituted pyrroles is responsible for a band at *ca.* 1120 cm^{-1} ⟨63AJC93⟩.



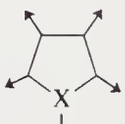
(**34**)



(**35**)

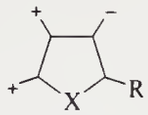


(**36**)

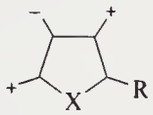


(**37**)

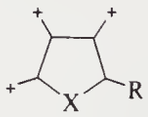
The γ-CH modes arising from out-of-plane CH deformations characterize the substitution pattern, and the observed frequencies are summarized in Table 20. For 2-substituted compounds these may be assigned as (**38**), (**39**) and (**40**). Additional characteristic bands for 2-substituted thiophenes are observed at 870–840m and 740–690s cm^{-1} ⟨67RTC37⟩.



(**38**)



(**39**)



(**40**)

2.3.3.7.2 Substituent vibrations

In most cases the frequencies of substituent groups attached to these heterocycles differ little from those observed for their benzenoid counterparts. The only notable exception is the spectral behavior of carbonyl groups attached to position 2. These have attracted much attention as they frequently give rise to doublets, and occasionally multiplets. In the case of (**41**), (**42**) ⟨76JCS(P2)1⟩ and (**43**) ⟨76JCS(P2)597⟩ the doublets arise from the presence of two conformers (*cf.* Section

Table 17 Fundamental Vibrational Frequencies (cm^{-1}) of Parent Heterocycles

Vibration[a]	*Approximate description*[a]	C_{2v}	*Pyrrole*[b]	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*
ν_1	C—H stretch	A_1	3133	3159	3110	3110	3084
ν_2	C—H stretch		3108	3128	3086	3063	3045
ν_5	Ring stretch		1466	1483	1408	1419	1432
ν_4	Ring stretch		1384	1380	1360	1341	1316
ν_6	C—H def. i.p.		—	1140	1081	1080	1079
ν_7	C—H def. i.p.		1076	1061	1033	1010	984
ν_3	Ring stretch		—	986	833	758	687
ν_8	Ring def. i.p.		—	873	606	456	380
ν_9	C—H def. o.o.p.	A_2	869	863	900	905	912
ν_{10}	C—H def. o.o.p.		—	728	686	685	690
ν_{11}	Ring def. o.o.p.		—	613	565	541	507
ν_{12}	C—H stretch	B_1	3133	3148	3110	3100	3084
ν_{13}	C—H stretch		3108	3120	3073	3054	3030
ν_{14}	Ring stretch		1531	1556	1506	1515	1516
ν_{15}	C—H def. i.p.		1047	1270	1250	1243	1246
ν_{16}	C—H def. i.p.		1015	1171	1081	1080	1079
ν_{17}	Ring (def. + stretch)			1040	871	820	797
ν_{18}	Ring def. i.p.		652	873	750	623	552
ν_{20}	C—H def. o.o.p.	B_2	1047	839	864	870	884
ν_{19}	C—H def. o.o.p.		768	745	712	700	674
ν_{21}	Ring def. o.o.p.		649	601	453	394	354
	Ref.		B-77MI30100	67JSP(24)133	65SA689	70AHC(12)1	76SA(A)1089

[a] Numbering and approximate description from ⟨67JSP(24)133⟩.
[b] Also 3410 N—H (A_1) stretch, 1146 NH in-plane def. (B_1), 561 NH out-of-plane def. (B_2), 1418 ring stretch (B_1).

Table 18 Monosubstituted Heterocycles: Ring Stretching Bands in the 1600–1300 cm^{-1} Region

Heterocycle	*Substituent*	*Phase*		*β-CH modes*		*Ring breathing*	*Ref.*
			(cm^{-1}) (ε_A)	(cm^{-1}) (ε_A)	(cm^{-1}) (ε_A)	(cm^{-1}) (ε_A)	
Pyrrole	1-	$CHCl_3$	1549 ± 3 (15–25)	1477 ± 7 (25–185)	—	1394 ± 10 (15–35)	66AJC289
Furan	2-	$CHCl_3$	1585 ± 26 (10–145)	1498 ± 28 (20–290)	1391 ± 14 (5–115)	—	59JCS657
Thiophene	2-	$CHCl_3$	1523 ± 9 (3–110)	1422 ± 12 (20–280)	1354 ± 7 (15–150)	1231 ± 10	59JCS3500, 70SA(A)1651
Selenophene	2-	$CHCl_3$	1532 ± 28 (5–213)	1432 ± 28 (13–290)	1332 ± 28 (6–65)	—	75JST(27)195
Tellurophene	2-deutero	liquid	1505	1423	1300	1224	76SA(A)1089
Pyrrole	2-	$CHCl_3$	1558 ± 9 (20–80)	1471 ± 3 (20–70)	1415 ± 8 (20–325)	—	63AJC93
Furan	3-	liquid	*ca.* 1562	*ca.* 1512	—	—	59G913, 58T(4)68
Thiophene	3-	$CHCl_3$	1512 ± 17 (90–240)	1413 ± 15 (65–135)	1365 ± 11 (5–45)	1210 ± 12	63JCS3881
Selenophene	3-	$CHCl_3$	1532 ± 28 (6–307)	1432 ± 28 (12–139)	1332 ± 28 (9–360)	—	75JST(27)195
Pyrrole	3-	$CHCl_3$	1549 ± 7 (20–180)	1491 ± 9 (55–195)	1427 ± 4 (60–160)	—	71PMH(4)265

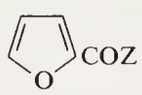
Table 19 Monosubstituted Heterocycles: Characteristic Bands in the 1300–1000 cm^{-1} Region

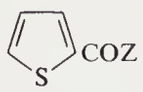
Heterocycle	*Substituent*	*Phase*	*β*-CH (**34**) (cm^{-1})	*β*-CH (**35**) (cm^{-1}) (ε_A)	*β*-CH (**36**) (cm^{-1}) (ε_A)	*Ring breathing* (**37**) (cm^{-1}) (ε_A)	*Ref.*
Pyrrole	1-	$CHCl_3$	—	1069 ± 6 (100–240)	1027 ± 9 (35–135)	—	66AJC289
Furan	2-	$CHCl_3$	1220 ± 20	1158 ± 7 (70–120)	1076 ± 3 (25–65)	1015 ± 4 (60–280)	59JCS657
Thiophene	2-	$CHCl_3$	—	1081 ± 3 (5–15)	1043 ± 7 (15–95)	—	59JCS3500, 70SA(A)1651
Pyrrole	2-	$CHCl_3$	—	1088 ± 18 (25–450)	1033 ± 13 (40–400)	1137 ± 8 (25–130)	63AJC93
Selenophene	2-deutero	liquid	—	1027	1083	—	70AHC(12)1
Tellurophene	2-deutero	liquid	—	1079	1021	—	76SA(A)1089
Furan	3-	liquid	—	*ca.* 1156	—	—	59G913
Selenophene	3-deutero	liquid	—	1013	1076	—	70AHC(12)1
Pyrrole	3-	$CHCl_3$	—	1077 ± 3 (60–100)	1041 ± 4 (30–150)	—	B-71MI30100

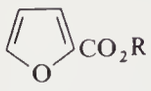
Table 20 Monosubstituted Heterocycles: Characteristic Bands in the 1000–600 cm^{-1} Region

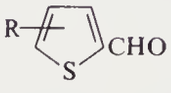
Heterocycle	*Substituent*	*Phase*	*γ-CH or β-ring modes* (cm^{-1}) (ε_A)				*Ref.*
Pyrrole	1-	$CHCl_3$	—	926 ± 4 (20–140)	722 ± 2 (375–475)	—	—	66AJC289
Furan	2-	$CHCl_3$	—	925 ± 9	884 ± 2	808 ± 28	—	59JCS657
Thiophene	2-	$CHCl_3$	—	925 ± 8 (5–15)	853 ± 7 (50–100)	823 ± 20 (30–70)	752 ± 16	59JCS3500, 70SA(A)1651
Selenophene	2-deutero	liquid	—	873	785	845	612	70AHC(12)1
Tellurophene	2-deutero	liquid	—	910	856	855	748	76SA(A)1089
Pyrrole	2-	—	961 ± 8 (15–45)	929 ± 3 (10–75)	882 ± 4 (10–120)	—	—	63AJC93
Furan	3-	liquid	—	—	878 ± 8	—	741	59G913, 58T(4)68
Thiophene	3-	liquid	—	—	—	—	755s	57AK(12)239
Selenophene	3-deutero	liquid	—	852	810	794	609	70AHC(12)1
Pyrrole	3-	—	953 ± 4 (30–110)	—	886 ± 2 (10–20)	—	—	B-77MI30100

2.3.4.2.2), whereas for the aldehydes (**44**) the doublets are attributed to Fermi resonance ⟨75JCS(P2)604⟩. This phenomenon has also been found to occur with several compounds of types (**41**), (**42**) and (**43**), causing the observance of multiple peaks. Fermi resonance is also responsible for the splitting of the —C≡N stretching band of some cyanopyrroles ⟨70JCS(B)79⟩. In concentrated solutions 2-acylpyrroles and pyrrole-2-carboxylic esters exist as NH---O=C bonded dimers with a consequent lowering of the carbonyl stretching frequency. In dilute solution the spectra of the monomeric species show a carbonyl frequency for the 2-substituted pyrroles some 20–30 cm^{-1} lower than displayed by the 3-isomers ⟨66AJC107, 65SA1011, 65T2197⟩. The carbonyl frequencies of 1-acyl- and 1-alkoxycarbonyl-pyrroles are some 70 cm^{-1} higher than those of the corresponding 2- or 3-substituted compounds ⟨65T2197, 66AJC289⟩.

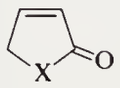
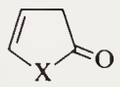
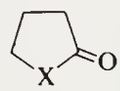
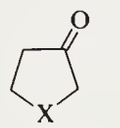
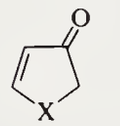

(**41**) Z = F, Cl


(**42**) Z = F, Cl


(**43**)


(**44**)

IR spectroscopy has been particularly helpful in detecting the presence of keto tautomers of the hydroxy heterocycles discussed in CHEC 3.01.6. Some typical frequencies for such compounds are indicated in Scheme 5. Here again the doublets observed for some of the carbonyl stretching frequencies have been ascribed to Fermi resonance.

	X = NH	O	S
	1690, 1660 ⟨57LA(604)178⟩ (1638)	1785, 1755 ⟨64CRV353⟩ (1630–1620)	1678–1670 ⟨60AK(15)499⟩ (1607)
	—	1800 ⟨64CRV353⟩	1715 ⟨60AK(15)499⟩ (1639)
	1695 ⟨57CB975⟩	1770 ⟨57CB975⟩	—
	1757 ⟨58BSF350⟩	1770 ⟨64T1763⟩	—
	1675 ⟨63CJC625⟩	1712 ⟨63HCA1259⟩	1680 ⟨64CRV353⟩

Scheme 5 IR frequencies (cm^{-1}) for keto heterocycles (carbonyl stretching frequencies; bracketed frequencies are for C=C stretches)

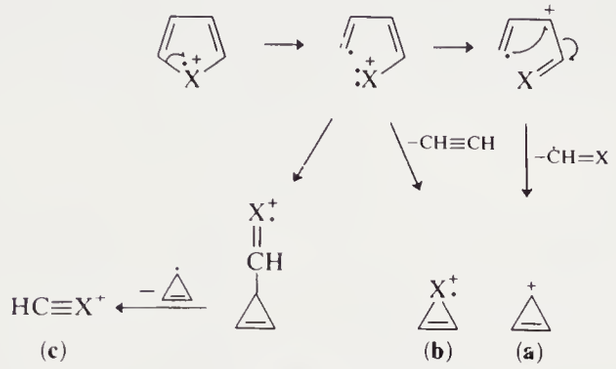
2.3.3.8 Mass Spectrometry

In contrast to the other heteroatoms under consideration here, the uneven valence and the even atomic weight of the principal isotope, ^{14}N, of nitrogen ensure that pyrroles always display a molecular ion of uneven mass unless bearing a nitrogen-containing substituent. Like nitrogen, oxygen has only one principal naturally occurring isotope but sulfur with a natural isotope distribution $^{32}S/^{34}S$ of 25:1 ensures that thiophenes have two molecular ions, two mass units apart, of appropriate intensity ratio. A far more complex situation arises with selenium and tellurium, which each has a number of naturally occurring isotopes, namely ^{76}Se (9.1%), ^{77}Se (7.5%), ^{78}Se (23.6%), ^{80}Se (50%), ^{82}Se (8.8%) and ^{122}Te (2.5%), ^{123}Te (0.9%), ^{124}Te (4.7%), ^{125}Te (7%), ^{126}Te (18.7%), ^{128}Te (31.8%), ^{130}Te (34.8%).

2.3.3.8.1 Parent monocycles

The principal fragmentation pathways encountered for pyrrole ⟨64JCS1949⟩, furan ⟨60BSB449⟩, thiophene ⟨59CCC1602⟩, selenophene ⟨78JHC137⟩ and tellurophene ⟨78JHC137⟩ are indicated in

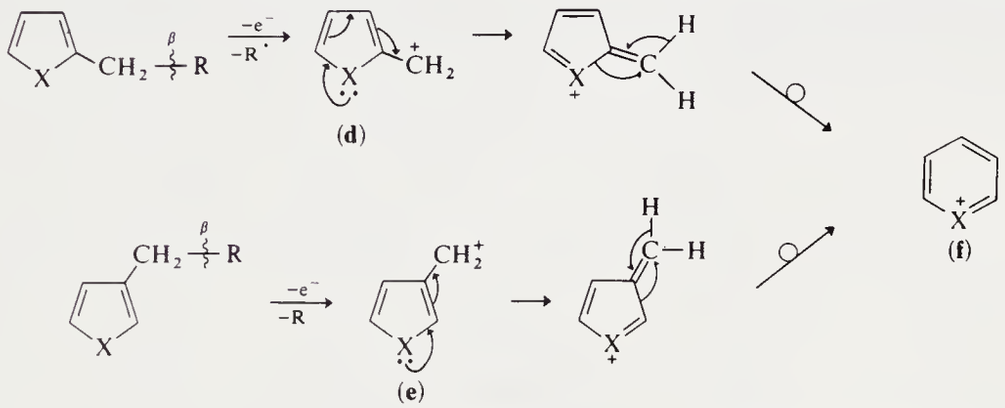
Scheme 6. The molecular ions are the base peaks in their respective spectra, for all except furan where the molecular ion is the strongest peak (70%) after the cyclopropenyl cation. The cyclopropenyl ion is also an important feature of the spectrum of pyrrole but much less important in the fragmentation of thiophene and selenophene, and apparently not observed for tellurophene. Another important ion in the spectra of pyrrole, thiophene and selenophene, but of low abundance for tellurophene and absent from the spectrum of furan, is (**b**) formed by loss of acetylene from the molecular ion. The ion (**c**) is much less abundant with furan and selenophene than for pyrrole or thiophene and only just detectable for tellurophene. In keeping with the much weaker nature of the carbon–tellurium and carbon–selenium bonds the spectrum of tellurophene contains ions corresponding to *M*–Te and *M*–HTe, and that of selenophene less abundant *M*–Se and *M*–HSe ions. The spectrum of tellurophene contains a very intense Te^+ ion and the one for selenophene a weaker Se^+ ion.



Scheme 6

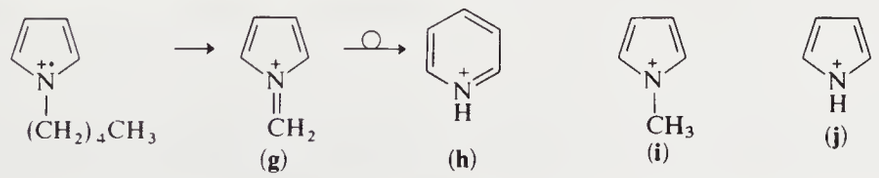
2.3.3.8.2 Substituted monocycles

Similar mass spectra are obtained for 2- and 3-alkyl derivatives of furan ⟨66T2223⟩, thiophene ⟨59CCC1602⟩ or pyrrole ⟨64JCS1949⟩. Apart from modest contributions from ions corresponding to (**a**), (**b**) and (**c**) above, a major fragmentation pathway is initiated by *β*-cleavage of the alkyl substituent (Scheme 7). The resulting ions (**d**) and (**e**) are believed to rearrange to the common ion



Scheme 7

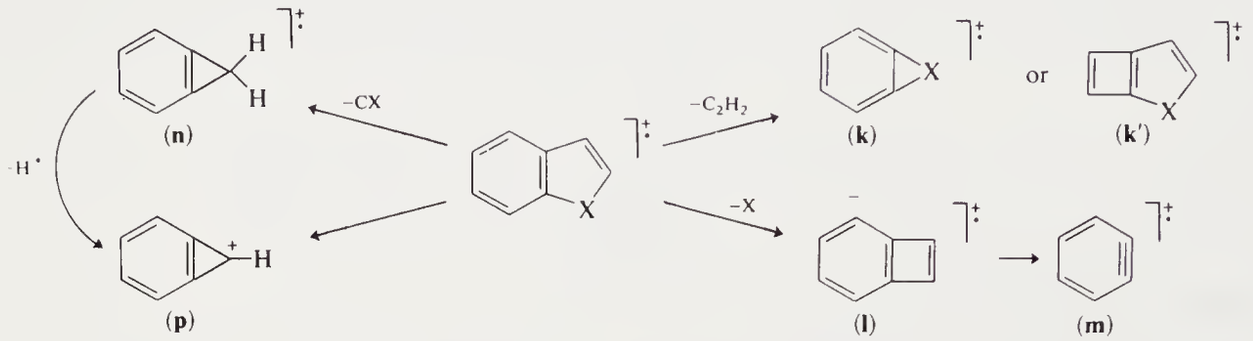
(**f**) which is generally the base peak. *N*-Alkylpyrroles ⟨64JCS1949⟩ fragment in a somewhat different fashion, typified by *N*-pentylpyrrole. Apart from *β*-cleavage of the alkyl groups yielding the ion (**g**) (Scheme 8), which is believed to rearrange to the pyridinium ion (**h**) as it subsequently undergoes the characteristic fragmentation of elimination of HCN, the molecular ion also generates the *N*-methylpyrrole cation (**i**) which is the base peak. Deuterium labelling experiments ⟨65JA805⟩ indicate that the hydrogen transferred in the formation of (**i**) comes mainly (78%) from C-3 of the alkyl chain with the remainder supplied by C-4. A lesser amount of the pyrrole cation (**j**) is also formed with the N—H being mainly derived from C-2 and C-4.



Scheme 8

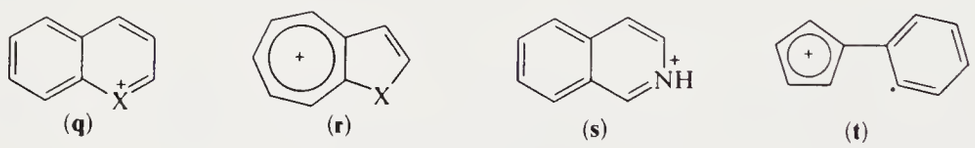
2.3.3.8.3 *Benzo derivatives*

The fragmentation pathways displayed by the benzo[*b*]-fused analogues of these heterocycles parallel those of the monocyclic compounds (X = NH ⟨68AJC997⟩, O ⟨64AJC975⟩, S ⟨67AJC103⟩, Se ⟨69JCS(B)971⟩, Te ⟨70JHC219⟩) (Scheme 9). As befits aromatic molecules, the molecular ion is also the base peak except for benzotellurophene. The fragment **k** (or **k′**) has only been noted as a minor ion in the spectra of benzo[*b*]thiophene and benzo[*b*]tellurophene. The elimination of the heteroatom resulting in the formation of the benzocyclobutadiene cation radical (**l**) is most prevalent with benzotellurophene where it provides the base peak, less important with benzoselenophene and only just detectable for benzothiophene. Finally, the ions (**n**) and (**p**) are prominent in the spectra of all of the benzo[*b*] heterocycles apart from benzotellurophene. As with the monocyclic series, 2- and/or 3-alkyl derivatives undergo *β*-fission of the alkyl group and rearrangement of the initial resulting radical ion to the cation radical (**q**) (Scheme 10). A similar cleavage occurs when the alkyl group is attached to the benzene ring but the resulting ion is probably the isomeric tropylium one (**r**). The fragmentation of 1-metholindolyl proceeds *via* (**s**).



Scheme 9

The only notable fragments derived from the very stable molecular ions of carbazole ⟨64JA3729⟩, dibenzofuran ⟨64AJC975⟩ and dibenzothiophene ⟨68T3255⟩ are at *m/e* 140 ($C_{11}H_8$) and 139 ($C_{11}H_7$), corresponding to loss of CX and HCX respectively; structure (**t**) has been suggested.

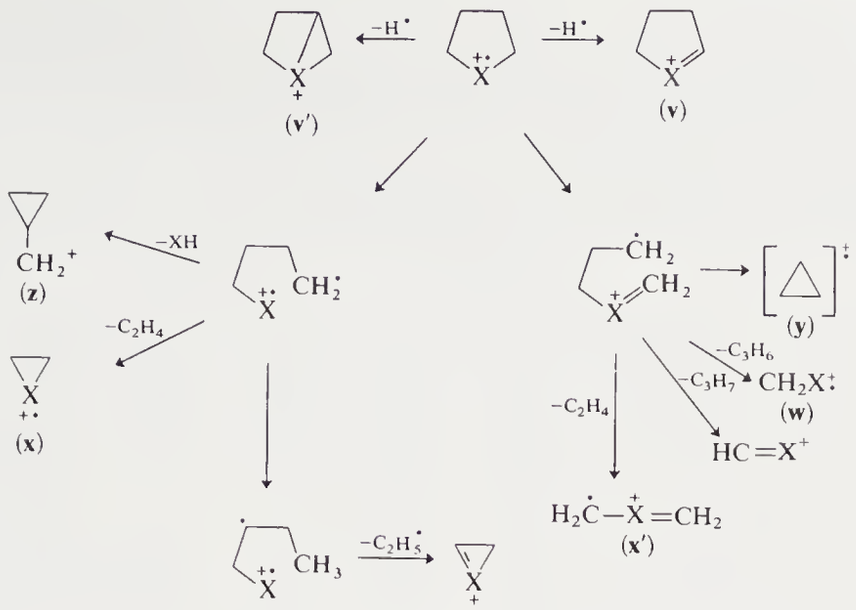


Scheme 10

2.3.3.8.4 *Saturated compounds*

The mass spectral fragmentations of the fully saturated parent heterocycles ⟨65JA2920⟩ are indicated in Scheme 11. All exhibit appreciable molecular ions. The $M-1$ ions (**v**) from pyrrolidine, tetrahydrofuran and tetrahydrothiophene are formed by the predominant loss of an *α*-hydrogen atom (94%, 70% and 65% respectively), while tetrahydroselenophene loses only a *β*-hydrogen. The percentage total ionization of the $M-1$ species decreases in the order NH > O > S > Se > Te. Ions (**x**, **x′**) corresponding to loss of C_2H_4 were generally abundant with a notable exception in the case of tetrahydrofuran.

The ions (**w**) resulting from loss of cyclopropane from the molecular ions were only observed for the sulfur, selenium and tellurium analogues. The alternative mode of fragmentation in which the hydrocarbon fragment (**y**) carries the charge provides the base peak for the tetrahydrofuran spectrum, but is only a minor feature of the spectra of the selenium and tellurium analogues. The hydrocarbon ion $C_4H_7^+$ (**z**) is a minor feature of the tetrahydrothiophene spectrum but provides the base peak of the spectra of the selenium and tellurium analogues.



Scheme 11

2.3.3.9 Photoelectron Spectroscopy

2.3.3.9.1 Parent monocycles

The He(Iα) photoelectron spectra of the parent heterocycles are compared in Table 21. The assignments are based upon comparisons with the spectra of the reduced heterocycles, the effect of ring substituents and comparisons with results of MO calculations. In the case of pyrrole, furan and thiophene the assignments have been further supported by measurements of photoelectron angular distribution which permit evaluation of the asymmetry factors, thereby providing a useful criterion for distinguishing between π- and σ-orbitals ⟨79MI30100⟩. Even so, the third π-orbital cannot be unambiguously assigned. The three π-molecular orbitals can be depicted as in Scheme 12. The energy of the π_3-orbital which extends exclusively over the carbocyclic part of the molecules is almost constant for the chalcogen heterocycles, whereas the π_2-orbital energy depends markedly on the heteroatom and increases as the electronegativity decreases. As expected, the values for π_3 are close to the ionization potentials determined by electron impact. There is also excellent agreement with the energies of the π_3- and π_2-orbitals obtained from the charge transfer spectra of these heterocycles with tetracyanoethylene ⟨75JCS(F1)2045⟩.

Table 21 Vertical Ionization Energies (eV) of π-Molecular Orbitals of Parent Heterocycles

Molecular orbital	*Pyrrole*	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*
π_3	8.2	8.89	8.87	8.92	8.88
π_2	9.2	10.32	9.49	9.18	8.40
π_1		14.4	12.1	12.0	11.8
Ref.	79MI30100	73MI30101	73MI30101	73MI30101	73MI30101

Scheme 12

2.3.3.9.2 Substituted compounds

Vertical ionization energies are available ⟨76JCS(P2)276⟩ for a range of α-substituted heterocycles (Table 22). Excellent linear correlations of unitary slope are obtained between corresponding π-orbital energies of the different α-substituted heterocycles, such as π_3 for thiophenes *versus* π_3 for

tellurophenes. α-Methyl substitution increases the separation of π_2 and π_3 in furan, thiophene and selenophene, in agreement with the expectation that electron-releasing substituents in the α-position would exert a more pronounced destabilizing effect on the energy of the π_3-orbital than on the π_2 one.

Table 22 Vertical Ionization Energies (eV) of π_3 and π_2 Molecular Orbitals of 2-Substituted Heterocycles ⟨76JCS(P2)276⟩

Substituent	*Furan*		*Thiophene*		*Selenophene*		*Tellurophene*	
	π_3	π_2	π_3	π_2	π_3	π_2	π_3	π_2
Me	8.37	10.13	8.43	9.23	8.40	8.96	8.20	8.43
H	8.89	10.31	8.87	9.49	8.92	9.18	8.40	8.88
$CONMe_2$	8.86	10.41	8.84	9.40	8.85	9.10	8.39	8.89
Cl	—	—	8.89	9.63	8.83	9.34	8.68	8.89
Br	—	—	8.82	9.58	—	—	8.59	8.84
I	—	—	8.52	9.47	—	—	8.34	8.52
CO_2H	9.16	10.72	9.14	9.73	9.19	9.45	8.62	9.15
CO_2Me	9.00	10.56	8.98	9.61	9.05	9.26	8.51	9.00
NO_2	9.75	11.13	9.73	10.21	9.64	9.88	—	—
CH_2Cl	—	—	8.89	9.49	—	—	—	—
CHO	—	—	9.37	9.87	—	—	—	—
CN	9.47	10.99	—	—	—	—	—	—
SMe	8.58	10.32	8.63	9.37	—	—	—	—

The spectra of the halogen-containing compounds show two bands due to the halogen lone pairs which are non-equivalent due to the different interaction of the p_x- and p_y-orbitals with the aromatic π-electron system. The peak at lower ionization energy has been assigned to the electrons occupying the p_x-orbital coplanar with the ring. The band at higher energy is thus due to electrons in the p_y-orbital which is perpendicular to the plane of the ring and overlaps the ring π-orbitals. Linear relationships are observed between the energies of the lone pair orbitals of Cl, Br and I and their corresponding Pauling electronegativities for 2-halo-thiophenes and -tellurophenes ⟨76JCS(P2)276⟩. The ionization energies of the halogen lone pairs vary with the ring decreasing in the series furan > thiophene > selenophene > tellurophene.

The energy separation between the lone pairs of a particular halogen is constant (Cl 0.38, Br 0.53, I 0.68 eV) and independent of the heteroatom. This is consistent with the p_y-orbital interacting with the π_3-orbital whose energy is constant for these chalcogen heterocycles. These energy separations are similar to those observed for halobenzenes, namely Cl 0.34, Br 0.55, I 0.84 eV. The effect of benzenoid annelation is to lower ionization potentials (Table 23). Perhaps the most noteworthy feature is that the ionization potentials of the benzo[*c*] heterocycles are lower than those of the benzo[*b*] isomers.

Table 23 The Lowest Vertical Ionization Potentials (eV) of Benzo Annelated Heterocycles

	Benzo[b]	*Benzo[c]*	*Dibenzo*
Pyrrole	7.76[a]	6.93[c,e]	7.60[d]
	8.38	8.60	7.99
	9.78	9.61	9.06
Furan	8.37[a]	7.63[c]	8.09[d]
	8.99	9.81	8.48
	10.40	10.30	9.35
Thiophene	8.13[a]	7.50[c]	7.93[d]
	8.73	8.95	8.34
	10.02	10.20	9.26
Selenophene	8.03[b]	—	—
	8.64		
	9.86		
Tellurophene	7.76[b]	—	—
	8.52		
	9.54		

[a] ⟨76ZN(A)1051⟩. [b] ⟨75HCA2646⟩. [c] ⟨76JCS(P2)81⟩. [d] ⟨78ZN(A)1006⟩.
[e] These values are for *N*-methylisoindole.

2.3.3.9.3 Reduced compounds

Ionization energies for fully reduced heterocycles are recorded in Table 24. Interpretation is based on a local C_{2v} symmetry of the —CH_2—X—CH_2— fragment. Mixing of the non-bonding electrons of the heteroatoms (O, S, Se, Te) with the σ-system is highest for tetrahydrofuran and gradually decreases down to tetrahydrotellurophene. Transannular interaction between the heteroatom and the double bond in 2,5-dihydro-furans and -thiophene is indicated as 'through-bond' rather than 'through-space' ⟨78H(11)443, 74CB725, 73TL1437⟩.

Table 24 Vertical Ionization Potentials (eV) of Tetrahydro Heterocycles

	n_π (b_1)	C_2X (a_1)	C_2X (b_2)	*Ref.*
Pyrrolidine	8.82	—	—	78MI30100
Tetrahydrofuran	9.53 9.65	11.4	13.0±0.5	74MI30100
Tetrahydrothiophene	8.42	10.9	≥11.9	74MI30100
Tetrahydroselenophene	8.14	10.5	≥11.9	74MI30100
Tetrahydrotellurophene	7.73	10.0	10.7	74MI30100

2.3.3.9.4 Core ionization energies

Available core ionization energies for the parent heterocycles and some of their tetrahydro derivatives are listed in Table 25. The main C_{1s} band of these compounds consists of two overlapping signals about 1 eV apart ⟨77JCP(67)2596, 72MI30100⟩ due to the non-equivalent carbon atoms. The core ionization energy of the heteroatom in the aromatic compounds is higher than that for the corresponding tetrahydro derivatives. Conversely the averaged C_{1s} ionization energies of the aromatic compounds are lower than for the corresponding tetrahydro derivatives. These trends are due to the net drift of charge from the heteroatoms toward the carbon atoms which occurs on going from the tetrahydro derivative to the aromatic compound.

Table 25 Core Ionization and Shake-up Energies (eV) for Some Heterocycles ⟨73MI30102⟩

	Ionization energy		*Shake-up energy*	
	Heteroatom	*Carbon (1s) (average)*	*Heteroatom*	*Carbon (1s)*
Tetrahydrofuran	533.1 (O_{1s})	285.9	—	—
Furan	534.3 (O_{1s})	285.0	8.6 (O_{1s})	7.7
Pyrrolidine	399.7 (N_{1s})	285.7	—	—
Pyrrole	400.4 (N_{1s})	284.8	8.0 (N_{1s})	7.2
Tetrahydrothiophene	163.2 ($S_{2p^{3/2}}$)	285.1	—	—
Thiophene	163.8 ($S_{2p^{3/2}}$)	284.3	7.5±0.5 (S_{2p})	5.7

2.3.4 THERMODYNAMIC ASPECTS

2.3.4.1 Intermolecular Forces

2.3.4.1.1 Melting and boiling points

A selection of these physical constants for pyrroles, furans and thiophenes is included in Table 32 of Chapter 2.4 and trends are discussed there (Section 2.4.4.1.1), together with data for five-membered rings containing two or more heteroatoms.

2.3.4.1.2 Solubility ⟨63PMH(1)177⟩

Pyrrole, furan and thiophene have only limited solubility in water, decreasing in the order cited (6, 3 and 0.1%). The hydrogen donor property of the NH site of pyrrole and the hydrogen acceptor property of the oxygen atom of furan probably account for the much greater solubility of the first two over that of thiophene.

2.3.4.1.3 Gas chromatography ⟨71PMH(3)297⟩

Hydrogen bonding with polar phases (tristearine, tween, polyethylene glycol 1000) by pyrrole lengthens its retention time. Thus, *N*-methylpyrrole on these stationary phases has a shorter retention time. Ethyl or larger alkyl groups at the 2-position sterically hinder such bonding and also shorten the time. 3-Alkylpyrroles therefore have a longer retention time than the 2-isomers.

Furans have been separated on columns using tricresyl phosphate, triethylene glycol and dinonyl phthalate stationary phases, often with Chromosorb as a support.

Stationary phases used for thiophenes include: pentaerythritol benzoate, polyethylene glycol adipate, tricresyl phosphate and benzyldiphenyl. Celite 545 is a useful support.

2.3.4.2 Stability and Stabilization

2.3.4.2.1 Thermochemistry and conformation of saturated heterocycles

Strain energies of 23.5, 24.8 and 8.3 kJ mol^{-1} were estimated for tetrahydrofuran, pyrrolidine and tetrahydrothiophene respectively ⟨74PMH(6)199⟩. The larger sulfur covalent radius of 1.04 Å lowers angular strain.

The effect on strain energy of introducing unsaturation into these rings has been evaluated in the cases of 2,3- and 2,5-dihydrothiophene, where the additional values are 18 and 15.8 kJ mol^{-1}.

2.3.4.2.2 Aromaticity

All of the parent heterocycles possess some degree of aromaticity, as based upon chemical behavior such as their proclivity to undergo substitution reactions with electrophilic reagents. Quantification of the relative aromaticities of these heterocycles is less easily resolved. The wide range of potential criteria available for this purpose has been surveyed ⟨74AHC(17)256⟩.

A widely employed criterion for the quantitative assessment of aromaticity is the resonance energy. Pertinent information for pyrrole, furan and thiophene has been obtained mainly from heats of combustion and heats of hydrogenation. Considerable uncertainties arise in the calculation of the thermochemical data for the localized model. Typical resonance energies are compared in Table 26.

Resonance energies of *ca.* 90, 182 and 330 kJ mol^{-1} have been estimated for pyrrole, indole and carbazole respectively by comparing their protonation constants with those for selected model compounds ⟨72CI(L)335, 72TL5019⟩.

The modified definition of resonance energy introduced by Dewar ⟨66T75, 69JA6321⟩ has as the reference point the corresponding open-chain polyene. Values obtained using a semi-empirical SCF-MO method ('Dewar Resonance Energies') are listed in Table 27.

All estimates of resonance energies indicate a decrease in aromaticity in the sequence benzene > thiophene > pyrrole > furan. Similar sequences are also found for the benzo[*b*] and dibenzo analogues. A somewhat different sequence is found for the benzo[*c*]-fused heterocycles with isoindole > benzo[*c*]thiophene > benzo[*c*]furan. As would be anticipated, the resonance energies for the benzo[*c*] heterocycles are substantially lower than those for their benzo[*b*] isomers.

Aromaticity indices for the parent heterocycles based upon structural or magnetic properties are summarized in Table 28. The similarity of the bond orders of formally non-equivalent bonds should provide a measure of ring aromaticity. This can most simply be assessed in terms of the ratio of the C-2—C-3 to C-3—C-4 bond lengths, but does not of course allow for any incidental effects imposed by the differing sizes of the heteroatoms or their electronegativities. More sophisticated indices are the sum of the differences in bond orders of the three non-equivalent bonds, $\Sigma\Delta N$, and the Julg aromaticity index A_1, which measures the degree of averaging of the peripheral bonds in the aromatic ring ⟨67MI30100⟩.

Table 26 Empirical Resonance Energies (kJ mol^{-1})

Compound	*Heats of combustion*							*Heats of hydrogenation*
Benzene	150.2	150.6	154.8	150.6	152.3	150.6	92.0	—
Furan	67.8	71.1	96.2	66.1	92.9	96.2	33.5	62.3[a]
Thiophene	121.8	100.8	129.7	120.1	115.9	129.7	66.9	71.6
Pyrrole	90.4	58.6	129.7	88.7	102.5	113.0	62.8	77.4
Indole	213.4	—	225.9	196.6	205.0	225.1	—	—
Carbazole	365.7	—	380.7	309.6	313.8	375.3	—	—
Ref.	49CB358	51CB916	33JCP(1)606	B-55MI30100	B-55MI30100	50JA4278	63T1175	B-62MI30100

[a] Values of 88.3 and 72.0 are reported in refs. ⟨51CB916⟩ and ⟨B-55MI30100⟩ respectively.

Table 27 Dewar Resonance Energies (kJ mol^{-1})

Benzene[a]	94.6[e]	Naphthalene[a]	140.6	—		—	
Furan[b]	18.0[e]	Benzo[*b*]furan[a,d]	84.9	Benzo[*c*]furan[d]	10.0	Dibenzofuran[a,d]	166.9
Thiophene[c]	27.2	Benzo[*b*]thiophene[c]	103.8	Benzo[*c*]thiophene[c]	38.9	Dibenzothiophene[c]	186.6
Pyrrole[b]	22.2[e]	Indole[d]	99.6	Isoindole[d]	48.5	Carbazole[d]	171.1

[a] ⟨69JA6321⟩. [b] ⟨70MI30101⟩. [c] ⟨70JA1453⟩. [d] ⟨70T4505⟩.
[e] Modified values for benzene (83.8), furan (6.7) and pyrrole (35.7 kJ mol^{-1}) have been proposed subsequently ⟨70MI30101⟩.

Table 28 Aromaticity Indices for Parent Heterocycles

	Bond alternation[a]	A_1[b]	A[c]	$\Sigma\Delta N$[d]	μ_m[e]	$\delta_\alpha - \delta_b$[f]	*Dilution shift, g*	*Solvent shift(s)*[h]	B[i]	Λ[j]	$\Delta\chi$[k]
Benzene	1	1	1	0	0	0	13.93	1	5.0	13.7	58
Thiophene	0.963	0.93	0.67	0.90	1.38	0.19	11.56	0.745	3.85	13.0	50.1
Selenophene	0.955	0.91	—	1.02	1.29	0.66	10.44	—	2.94	—	51.0
Pyrrole	0.959	0.91	0.38	1.04	3.48	0.46	—	0.82	2.94	10.2	42.4
Tellurophene	0.966	0.88	—	1.30	1.17	1.09	8.50	—	1.85	—	—
Furan	0.952	0.87	0.06	1.42	1.04	1.05	7.67	0.42	1.72	8.9	38.7
Cyclopentadiene	0.912	—	—	1.25	0.42	−0.15	—	0.39	—	6.5	34.2

[a] Ratio of C(2)—C(3)/C(3)—C(4) bond lengths taken from Table 2.
[b] ⟨67MI30100⟩.
[c] ⟨B-71MI30101⟩.
[d] From ⟨74JCS(P2)332⟩ except the newly calculated value for pyrrole.
[e] From Table 1 of CHEC 3.01 (in D).
[f] Derived from values listed in Table 4.
[g] ⟨74JCS(P2)332⟩.
[h] ⟨71JA556⟩.
[i] ⟨74JCS(P2)332⟩. The value for pyrrole has been calculated using data from ⟨63JOC3052⟩.
[j] ⟨B-71MI30102⟩; units of $-4\pi\ 10^{-12}\ m^3\ mol^{-1}$.
[k] Units of $-4\pi\ 10^{-12}\ m^3\ mol^{-1}$; values from ⟨69AJC1415, 70JA7523, 69JA4063, 69JA6895, 72ZN(A)1691⟩.

NMR has been widely invoked in assessing aromaticity. Comparison of the chemical shift of furan, H-2 7.46 and H-3 6.41, with those observed for 4,5-dihydrofuran, H-2 6.31 and H-3 4.95 ⟨66JCS(B)127⟩, indicates that there is *ca.* 1–1.5 p.p.m. downfield shift attributable to the presence of an aromatic ring current in furan. The same effect is observed for thiophene, H-2 7.35 and H-3 7.13, and 4,5-dihydrothiophene, H-2 6.17 and H-3 5.63. The similar range of chemical shifts observed for all of the parent heterocycles may be compared with that for benzene, 7.27 δ, and further attests to their possessing appreciable ring currents.

The validity of using chemical shifts as a quantitative measure of ring currents has frequently been questioned ⟨*e.g.* 66JCS(B)127⟩. As with other approaches to assessment of aromaticity, a major difficulty is the selection of appropriate non-aromatic models. However, the order of decreasing aromaticity arrived at in the present case, namely benzene 1, thiophene 0.75, pyrrole 0.59 and furan 0.46 ⟨65CC160, 65T515⟩ is in keeping with that derived by other means.

Several methods based on NMR spectroscopy have been devised which attempt to assess the relative magnetic susceptibilities of aromatic molecules, parallel and perpendicular to the plane of the ring. Values of the dilution shift parameter ($\delta\Delta V_{m3}^{2}$) ⟨74JCS(P2)332⟩ gave an excellent linear correlation with the Pauling resonance energies ⟨33JCP(1)606⟩ for benzene, thiophene and furan and permitted the estimation of resonance energies for selenophene and tellurophene of 121.3 and 104.6 kJ mol^{-1} respectively.

The solvent shift parameter, S, is based on the chemical shift differences between the protons of a mixture of acetonitrile and cyclohexane, in solvent cyclohexane and in the putative aromatic compound as solvent ⟨71JA556⟩. The values relative to benzene, $S = 1.0$, are listed in Table 28, and show reasonable agreement with the diamagnetic susceptibilities.

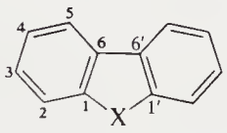
In summary, most of the presently available criteria point to an order of decreasing aromaticity of benzene > thiophene > selenophene ≈ pyrrole > tellurophene > furan.

2.3.4.3 Conformation

2.3.4.3.1 Aromatic compounds

Comparison of the data in Table 29 with that in Table 2 shows that the internal bond angles of the heterocyclic ring do not change appreciably on annelation. However, the bond lengths are increased and this is particularly noticeable in the case of the C—X bond (*cf.* Table 30). It may be noted, however, that in no case does the length of the C(6)—C(6′) bond reach the 1.497 Å length

Table 29 Comparison of Bond Lengths and Angles of Dibenzo Heterocycles



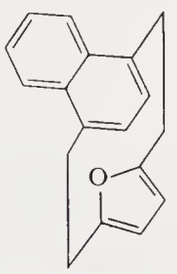
Bond length (Å)	X = NH	O	S	Se	Te
C(1)—C(2)	1.403	1.385	1.384	1.395	1.397
C(2)—C(3)	1.372	1.388	1.384	1.371	1.381
C(3)—C(4)	1.393	1.385	1.385	1.377	1.386
C(4)—C(5)	1.392	1.389	1.370	1.380	1.375
C(5)—C(6)	1.391	1.384	1.392	1.395	1.403
C(6)—C(6′)	1.477	1.481	1.441	1.453	1.460
C(1)—C(6)	1.408	1.393	1.409	1.398	1.394
C(1)—X	1.393	1.404	1.740	1.899	2.087
X—H	1.02	—	—	—	—
Bond angle (degrees)					
C(1)XC(1′)	108.3	104.1	91.5	86.6	81.7
XC(1)C(6)	109.7	112.3	112.3	112.4	112.1
C(1)C(2)C(3)	115.6	116.7	117.8	118.7	119.1
C(2)C(3)C(4)	123.9	120.9	121.6	121.1	120.6
C(3)C(4)C(5)	120.1	121.9	120.5	120.6	120.1
C(4)C(5)C(6)	117.9	117.9	120.0	120.3	120.9
C(5)C(6)C(1)	120.6	119.6	118.7	118.1	118.0
C(6)C(1)C(2)	121.9	123.0	121.6	121.6	121.3
C(1)C(6)C(6′)	106.1	105.3	111.9	114.3	117.1
Ref.	69BCJ2174	72AX(B)1002	70JCS(A)1561	70AX(B)628	75IC2639

Table 30 Comparison of C—X Bond Lengths for Parent Heterocycles and their Dibenzo Derivatives

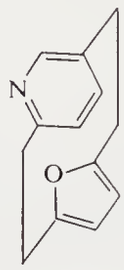
X	*Parent heterocycle* C—X (Å)	*Dibenzo derivative* C—X (Å)
NH	1.383	1.414
O	1.362	1.404
S	1.714	1.740
Se	1.855	1.899
Te	2.055	2.087

⟨61MI30100⟩ of the interannular bond of biphenyl, implying that the central heterocyclic ring retains some modicum of aromaticity. A most intriguing feature of these molecules is that they adopt a slightly bow-shaped configuration with small dihedral angles between the planes of the five-membered and benzenoid rings. The observed values are carbazole 1.0°, dibenzofuran 1.12°, dibenzothiophene 0.4–1.2°, and dibenzoselenophene 0.5–1.2°.

Large distortions of the heterocyclic ring are encountered in [2,2]heterophanes. In the furanonaphthalenophane (**45**) the furan ring is completely planar but the extra annular bonds are directed about 7° out of the plane of the furan ring ⟨78T1641⟩. While the non-bridged portion of the naphthalenoid ring is planar, the portion which is bridged to the furanoid ring through its 1 and 4 carbon atoms is puckered and boat shaped. A similar situation obtains in the furanopyridophane (**46**), where the furan ring is again effectively planar with the 2 and 5 carbon atoms displaced by only 0.022 Å from the plane occupied by the remaining ring atoms. The pyridine ring is puckered to the same extent as the bridged half of the naphthalenoid ring in (**45**) and the pyridine 2 and 5 carbon atoms are displaced by 0.172 Å from planarity ⟨75JHC433⟩.

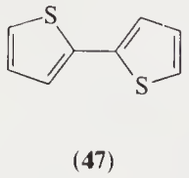


(**45**)

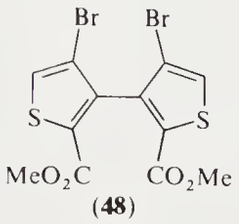


(**46**)

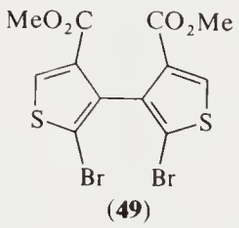
X-Ray crystallographic studies show that the three isomeric bithienyls are planar in the solid state ⟨68AX(B)467⟩. However, in the vapor phase the principal conformation of 2,2′-bithienyl is indicated by electron diffraction to be a non-planar one with an angle of twist of 34° ⟨58ACS1671⟩ relative to the planar *transoid* conformation (**47**) adopted in the solid state. However, 2-(2-furyl)pyrrole and 2-(2-thienyl)pyrrole preferentially adopt a *cis* planar conformation in solution ⟨81JCS(P2)127⟩. Bulky substituents in the positions adjacent to the interannular bond permit the separation of the resulting stereoisomers. Typical examples are provided by (**48**) and (**49**) ⟨75CS(7)173⟩, whose X-ray structures ⟨75CS(7)204, 76CS(9)66)⟩ show that *cis* skew conformations are adopted in the solid state. Circular dichroism spectra of these compounds in solution and the solid



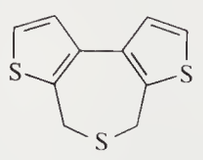
(**47**)



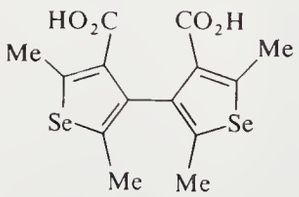
(**48**)



(**49**)



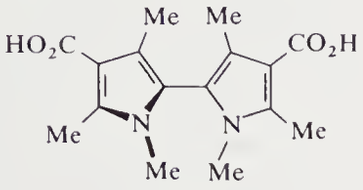
(**50**)



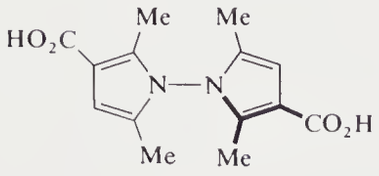
(**51**)

state are very similar and comparable with those of the necessarily *cisoid* dithienothiepins (**50**) ⟨76CS(10)120⟩. Analogous behavior has been observed for 3,3′-biselenienyls where both (**51**) and its thiophene analogue have been resolved ⟨75CS(7)131⟩.

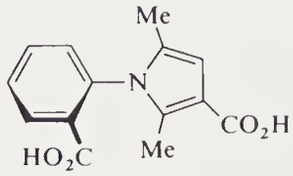
Comparable examples of restricted rotation involving pyrroles were encountered much earlier and resolutions effected, amongst others, of compounds (**52**) ⟨53JOC1413⟩, (**53**) ⟨31JA2353⟩ and (**54**) ⟨31JA3519⟩. A consequence of the greater separation of adjacent substituents on these five-membered rings relative to six-membered ones is a lower barrier to rotation (see Scheme 13, p. 82). Thus the rotational barrier for pentaarylpyrroles is about 75 kJ mol^{-1} lower than for the corresponding hexaarylbenzenes ⟨81JOC1499⟩.



(**52**)

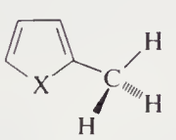


(**53**)

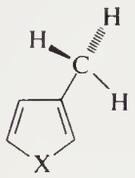


(**54**)

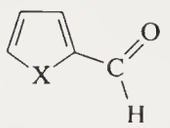
The conformational preferences of 2- and 3-monosubstituted derivatives of furans, thiophenes and pyrroles have been the subject of *ab initio* MO studies ⟨77JCS(P2)1601, 78JA3981, 79JA311⟩. Of the systems considered, experimental information from microwave spectroscopy is available for 2- and 3-methyl derivatives of furan ⟨69JCP(51)403, 70ZN(A)570, 71BCJ2344⟩ and thiophene ⟨70MI30100, 74JSP(42)38⟩ and agrees with prediction. The preferred conformations are (**55**), (**57**), (**56**) and (**58**) with barriers to rotation of 5.0, 4.6, 2.3 and 3.1 kJ mol^{-1} respectively, which are somewhat higher than those calculated. The experimentally established conformational preferences in solution for a variety of other 2-substituted heterocycles are summarized in Table 31. Most of these conclusions have been deduced either from dipole moment measurements in benzene or by the use of lanthanide induced shifts for chloroform solutions. The aforementioned MO studies correctly predict the preferred conformations, (**59**) or (**60**), of pyrrole-2-carbaldehyde, thiophene-2-carbaldehyde and furfural in the gas phase. In the latter case the calculated preference of 4.1 kJ mol^{-1} for the *anti* isomer and a barrier to rotation of *ca.* 24.7 kJ mol^{-1} compare favorably with the values that have been estimated from microwave spectra, 3.1 and 36 kJ mol^{-1} ⟨66ZN(A)1633⟩, and from far-IR spectroscopy, 8.5 and 25 kJ mol^{-1} respectively ⟨67SA(A)891⟩. These conformational effects have also been rationalized by MINDO/3 calculations, which also took solvent effects into account ⟨81JHC1055⟩. The presence of other ring substituents would be expected to modify the *syn–anti* preference *inter alia* by modifying the dipole moment of the ring, and this aspect has been extensively studied for pyrrole-2-carbaldehyde ⟨75JCS(P2)333, 75JCS(P2)337⟩.



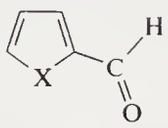
(**55**) X = O
(**56**) X = S



(**57**) X = O
(**58**) X = S



(**59**)



(**60**)

Table 31 Conformational Preference of 2-Substituted Five-membered Heterocycles

Substituent	*Pyrrole*	*Percent of* syn *form* (**60**) *Furan*	*Thiophene*	*Selenophene*	*Tellurophene*	*Phase*
CHO	Mainly[a]	Minor[c]	Mainly[f]	—	—	Vapor
	100[b]	83[d]	100[d]	80[d]	72[d]	C_6H_6
		70–75[e,i]	99[e,i]	98[e]	96[e]	$CDCl_3$
COMe	100[b]	51[d]	92[d]	70[d]	47[d]	C_6H_6
		53[e]	79[e]	87[e]	90[e]	$CDCl_3$
$CONMe_2$	—	11[d]	56[d]	33[d]	11[d]	C_6H_6
		5[e]	2[e]	5[e]	—	$CDCl_3$
CO_2Me	Predominates[g]	55[d,h]	33[d]	59[d]	42[d]	C_6H_6
SMe	—	48[d,h]	51[d]	59[d]	65[d]	C_6H_6

[a] ⟨74JST(23)93⟩. [b] ⟨74JCS(P2)1318⟩. [c] ⟨66ZN(A)1633⟩. [d] ⟨77JCS(P2)775⟩. [e] ⟨74T4129⟩. [f] ⟨73JST(17)161⟩.
[g] ⟨80JCS(P2)1631⟩. [h] ⟨80SA(A)633⟩. [i] ⟨82T1485⟩.

In the 2-carboxylic acids the oxygen of the OH group faces the heteroatom in all cases except furoic acid. Progressive shortening of the C(2)—C(CO_2H) bond, presumably indicating an increase in conjugative interaction, occurs in the sequence thiophene > selenophene > tellurophene > furan, which corresponds to the order of decreasing heterocyclic aromaticity.

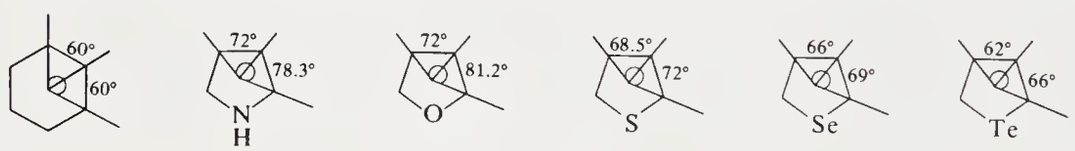
Although the same theoretical studies indicate very small energy differences between the *syn* and *anti* conformers of the 3-carbaldehydes of furan, thiophene and pyrrole with a slight preference for the *syn* conformer, in chloroform solution the furan- and thiophene-3-carbaldehydes adopt the *anti* conformers to the extent of 100 and 80% respectively ⟨82T3245⟩. However, *N*-substituted 3-(trifluoroacetyl)pyrroles exist in solution as mixtures of rotational isomers ⟨80JCR(S)42⟩.

NMR-evaluated free energies of activation for rotation about the C(O)—N bond in furan-, pyrrole- and thiophene-2- and -3-*N,N*-dimethylcarboxamides ⟨76JOC3591, 77T1337⟩ are summarized in Table 32. The barrier to rotation arises from resonance interaction between the lone pair of electrons on the nitrogen atom and the electronegative oxygen of the carbonyl group. An electron donor attached to this carbonyl group will reduce this interaction and hence lower the rotational barrier. As expected, the values show that the order of electron donation is pyrrolyl > thienyl > furyl, and that donation is greater from the 2- than the 3-position. All are electron donating compared with benzene.

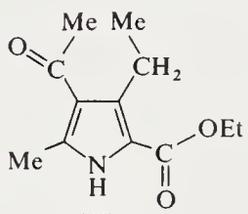
Table 32 Free Energies of Activation (kJ mol^{-1}) for Rotation of Five-membered Heterocyclic *N,N*-Dimethylcarboxamides

Ring	*Substituent position* 2	3
Furan	63.1	63.5
Thiophene	60.6	—
Pyrrole	60.2	61.0
Benzene	66.5	

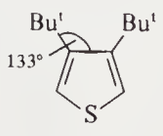
Inspection of Scheme 13 shows that, in contrast to benzene, *ortho* substituents should experience less steric interference in these five-membered heterocycles and for any individual ring system this will be smaller for 2,3- rather than 3-4-disubstitution. The tetrasubstituted pyrrole (**61**) has a planar ring but most substituent atoms deviate significantly from this plane ⟨72JCS(P2)902⟩. The acetyl group is twisted about 15° out of the ring plane whereas the ester group is only twisted 1°. Distortions of the ring are also obviously present in 3,4-di-*t*-butylthiophene (**62**) ⟨80CC922⟩, where in particular the C(3)—C(4) bond length is 1.667 Å in contrast to 1.423 Å in the parent heterocycle, and the indicated bond angles are increased to 133° from their preferred value of 124°. No appreciable distortions of the thiophene ring are observed for (**63**) ⟨78CSC703⟩, the overcrowding being relieved by the nitro groups being twisted out of the plane of the ring by 37° and 44° and the C—N bonds being displaced out of the plane of the ring by 5.3° and 6.7° in opposite directions.



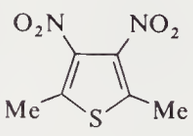
Scheme 13



(**61**)



(**62**)



(**63**)

2.3.4.3.2 Reduced ring compounds

Some reduced heterocyclic rings are non-planar. In 2,3-dihydrofuran and 2,3-dihydrothiophene the C-2 methylene group is out of the plane of the other ring atoms with barriers to ring inversion

of about 1 and 4 kJ mol^{-1} respectively ⟨72JCP(56)5692, 73JCP(59)2249⟩. The higher barrier for the sulfur compound is presumably due to a decrease in the ring strain forces relative to those in the dihydrofuran. Torsional forces are comparable for both molecules and tend to overcome the lower ring strain forces of the dihydrothiophene and pucker the ring to a larger degree. 2,5-Dihydrofuran ⟨67JCP(47)4042⟩ and 2,5-dihydrothiophene ⟨69SA(A)723⟩ are planar, but 2,5-dihydropyrrole is non-planar with an asymmetric double minimum potential on account of the axial–equatorial conversion of the N—H bond by ring inversion ⟨72MI30102⟩. The equatorial form is favored energetically.

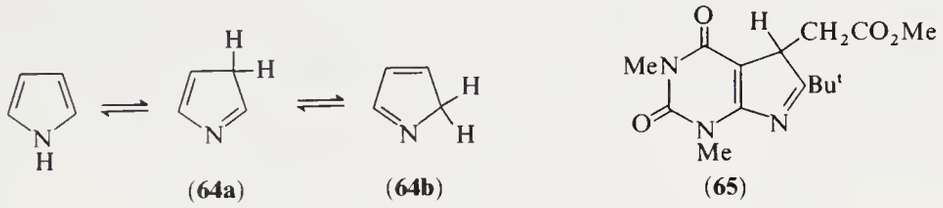
The fully reduced ring systems are also non-planar. For tetrahydrofuran, analysis of IR ⟨69JCP(50)124⟩, dipole moment, microwave ⟨69JCP(50)2446⟩ and ^{1}H NMR ⟨74JMR(16)136⟩ data, together with *ab initio* MO calculations ⟨75JA1358⟩, indicates a freely pseudorotating system with 10 twist and 10 envelope conformations. In the envelope conformation, one of the ring atoms is out of the plane of the other four atoms. Intermediate between these envelope conformations are half-chair twist conformations (only three adjacent ring atoms coplanar), slightly more stable than the envelope and with a barrier to pseudorotation of about 0.7 kJ mol^{-1}. Similarly, pyrrolidine is a free or only slightly restricted pseudorotator ⟨58JCP(29)966⟩, but the appreciably increased size of the heteroatom in tetrahydrothiophene ⟨79MI30102, 80CJC2340, 80OMR(13)282⟩ and tetrahydroselenophene ⟨78JCP(69)3714, 79JMR(36)113⟩ results in higher barriers to pseudorotation and these molecules preferentially adopt twisted conformations.

2.3.5 TAUTOMERISM

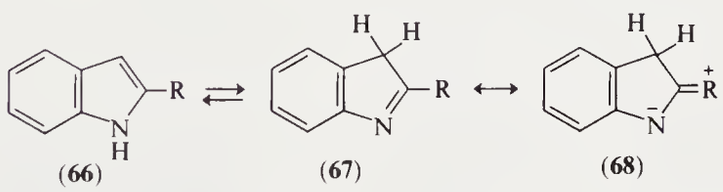
All tautomeric equilibria of these heterocycles involve one or more non-aromatic tautomers. An important factor in determining the extent to which such non-aromatic tautomers are involved is the magnitude of the potential loss of resonance energy.

2.3.5.1 Annular Tautomerism

Tautomerism not involving a functional group can only occur with pyrroles. There is no authenticated case of a non-annelated pyrrolenine tautomeric form (**64a**) or (**64b**) predominating, but the pyrrolopyrimidinedione (**65**) adopts the tautomeric form shown ⟨77JOC1919⟩, possibly because this minimizes steric repulsions between the adjacent *t*-butyl and acetate groups. The potential loss of resonance energy is much less for tautomerism of an indole to the corresponding indolenine (**67**). Even so, most indoles exist in the indole form but the introduction of a strong electron donating group at C-2 can tip the balance. Thus the equilibrium is progressively shifted from (**66**) to (**67**) as the substituent is changed from —SEt to —OEt to —NC_5H_{10}, due to increasing electron donating ability as implied by the zwitterionic canonical form (**68**) ⟨70T4491, 71T775⟩.

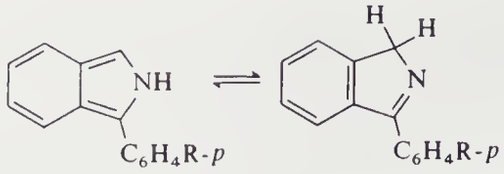


(**64a**) (**64b**) (**65**)



(**66**) (**67**) (**68**)

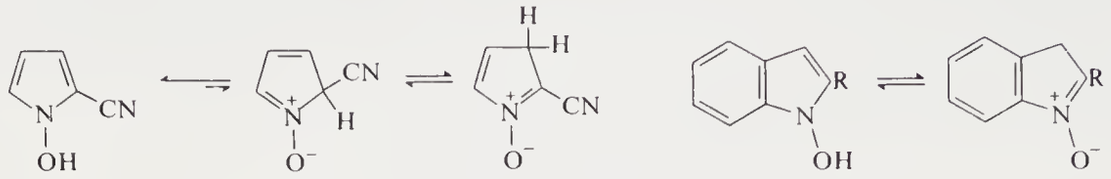
Although isoindole itself exists preferentially as such ⟨73JCS(P1)1432⟩, in accord with predictions of MO calculations ⟨64JA4152, 67TL3669⟩, the lower resonance energy of isoindole often results in the isoindole–isoindolenine equilibrium favoring the latter species in substituted derivatives. Thus the presence of an aryl group at C-1 capable of conjugating with C=N results in increasing proportions of the isoindolenine tautomer (**69**) as the *p*-substituent (R) is changed from hydrogen (9%) to methoxy (31%) to dimethylamino (50%) in $CDCl_3$ ⟨64JA4152⟩.



(69)

2.3.5.2 Compounds with a Potential Hydroxy Group

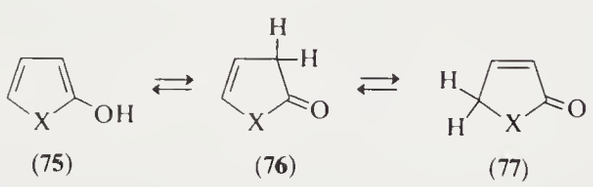
Although *N*-hydroxypyrroles possess in principle three tautomeric forms, *i.e.* (**70**), (**71**) and (**72**), only the *N*-hydroxy form (**70**) has been observed for 1-hydroxy-2-cyanopyrrole ⟨73JOC173⟩. In the case of 1-hydroxyindoles, where the potential loss of aromatic resonance energy will be much less, both tautomers (**73**) and (**74**) coexist in solution with the relative proportions being dependent on the solvent ⟨67BSF1296⟩.



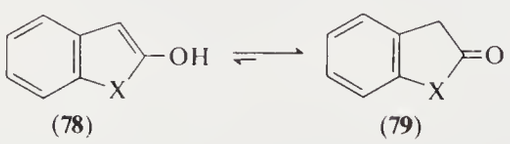
(70) (71) (72) (73) (74)

Potential *C*-hydroxy compounds usually exist as the oxo tautomers, unless the hydroxy tautomer is appreciably stabilized by electron withdrawing or chelating substituents. The tendency for enolic hydroxy compounds to revert to the oxo form is easily comprehended by reference to simple aliphatic ketones where the keto–enol tautomeric equilibrium constants are of the order of 10^8. In the heterocycles under consideration this tendency will be in opposition to the attendant loss of aromatic conjugation energy which will increase in the order furan $\ll$ thiophene $\leqslant$ pyrrole. For the 2-hydroxy compounds (**75**) some extra stabilization of the oxo tautomers (**76**) and (**77**) will come from the resonance energy of the —X—C(=O)— group, which by analogy with open-chain groups should increase in the sequence thiolester $\leqslant$ ester $\ll$ amide.

Variation in tautomeric behavior is observed with change of heteroatom. Thus 2-hydroxyfurans exist predominantly as the tautomer (**77**) although the energy of activation for the conversion of (**76**) to (**77**) is sufficiently high to permit the isolation of (**76**) ⟨64CRV353⟩. 2-Hydroxypyrroles behave similarly but equilibration between (**76**) and the more stable (**77**) occurs in polar solvents at room temperature ⟨65JOC3824, 71OMR(3)7, 80HCA121⟩. For thiophenes the ratio of (**76**) to (**77**) depends upon the substitution at C-5 ⟨63T1867, 64AK(22)211, 67T3737, 69AK(29)427⟩. Whereas (**77**) predominates in the parent molecule the introduction of a 5-aryl group causes the equilibrium to shift largely toward (**76**) in the solid state or carbon tetrachloride solution, and in methanol (**76**) is accompanied by some 25–30% of the hydroxy tautomer (**75**). Tautomer (**77**) also predominates in the case of 2-hydroxyselenophene ⟨71BSF3547⟩. In the benzo[*b*] (**78**) and benzo[*c*] heterocycles (**80**), where the loss of heterocycle ring resonance energy on tautomerism to (**79**) and (**81**) will be much less than for the non-annelated heterocycle, the latter oxo tautomers are preferred.

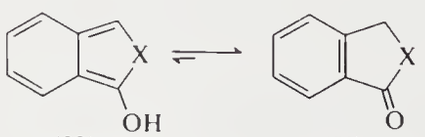


(75) (76) (77)



(78) (79)

X = O ⟨69JOC4164⟩
X = S ⟨70JCS(C)1926⟩
X = Se ⟨76JCS(P1)2452⟩
X = NH ⟨68T6093⟩

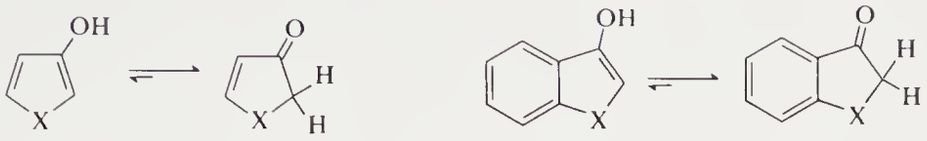


(80) (81)

X = O, S, Se ⟨70JA4447⟩
X = NH ⟨71PMH(4)265, p. 289⟩

Most 3-hydroxyfurans ⟨65HCA1322, 76CS(10)126⟩, pyrroles ⟨70LA(736)1⟩ and selenophenes ⟨76CS(10)126, 71BSF3547⟩ exist preferentially as the oxo tautomer (**83**), but introduction of an acyl function into position 2 of furan ⟨65HCA1322⟩ or pyrrole ⟨67AJC935⟩ causes the equilibrium to favor the hydroxy tautomer (**82**), a consequence of intramolecular hydrogen bonding between the hydroxy and acyl groups and of their mesomeric interaction. The importance of the latter factor is indicated by the existence of the potential 3-hydroxy-4-acyl analogues in the oxo form. The 3-hydroxy form is considerably more favored in the more aromatic thiophene system. For simple alkyl and aryl derivatives both hydroxy (**82**) and oxo (**83**) forms generally coexist ⟨72CS(2)9⟩, but electron withdrawing groups such as alkoxycarbonyl generally cause the hydroxy form to predominate ⟨65T3331⟩.

A closely similar pattern of behavior is also found for the corresponding benzo-annelated derivatives. Thus 3-hydroxybenzofuran ⟨66CB3076⟩ and 3-hydroxyindoles ⟨58JCS1217⟩ adopt the oxo form (**85**), but enolize to (**84**) when an acetyl group is present at position 2 ⟨65T3331, 60JA1187⟩.

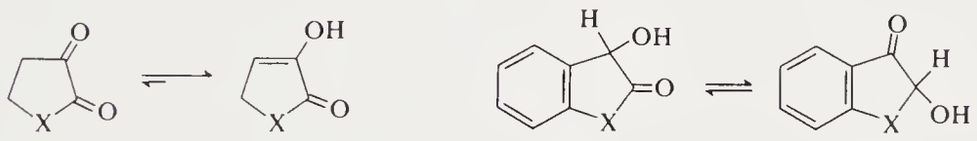


(**82**) (**83**) (**84**) (**85**)

Generally speaking, increasing solvent polarity favors the hydroxy tautomer (**84**) which becomes the almost exclusive species in 2-acetyl ⟨65T3331⟩ and 2-aryl ⟨76CS(9)216⟩ derivatives even in non-polar media.

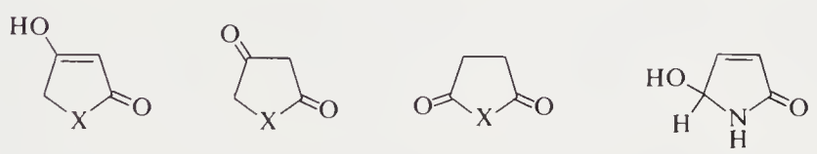
2.3.5.3 Compounds with Two Potential Hydroxy Groups

2,3-Dihydroxy-furan ⟨71T3839⟩, -pyrrole ⟨53JOC382, 69JOC3279⟩ and -thiophene ⟨71T3839⟩ all adopt the tautomeric structure (**87**) rather than (**86**). 2,3-Dihydroxyindole adopts the structure (**88**) whereas the behavior of 2,3-dihydroxybenzofuran is strongly temperature dependent. At 20 °C it exists solely as the tautomer (**89**) but as the temperature is raised the equilibrium is shifted progressively toward (**88**) whose proportion reaches 95% at 100 °C ⟨68M2223⟩.



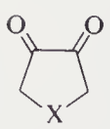
(**86**) (**87**) (**88**) (**89**)

The potentially 2,4-dihydroxy derivatives of furan and thiophene exist in the solid state and in polar solvents as the monoenols (**90**) ⟨71T3839⟩. However, in non-polar solvents the furan derivatives exist predominantly in the dioxo form (**91**). The 2,5-dioxo structure (**92**) is well established for X = O, NR, S and Se ⟨71BSF3547⟩ and there is no evidence for intervention of any enolic species. The formal tautomer (**93**) of succinimide has been prepared and is reasonably stable ⟨62CI(L)1576⟩.



(**90**) (**91**) (**92**) (**93**)

Examples of the potential 3,4-dihydroxy heterocycles are presently restricted to furan and thiophene. Although the parent 3,4-dihydroxyfuran apparently exists as the dioxo tautomer (**94**), derivatives bearing 2-alkyl or 2,5-dialkyl substituents prefer the keto-enol structure (**95**) ⟨71T3839, 73HCA1882⟩. The thiophene analogues also prefer the tautomeric structure (**95**), except in the case of the 2,5-diethoxycarbonyl derivative which has the fully aromatic structure (**96**) ⟨71T3839⟩.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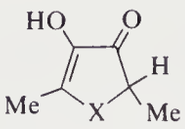
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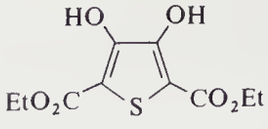
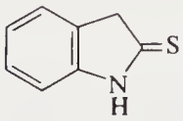

(96)

2.3.5.4 Compounds with Potential Mercapto Groups

The mercapto form is much more strongly favored than is the hydroxy form for the corresponding oxygen compounds. A pertinent comparison in this respect is the greatly reduced inclination of enethiols to tautomerize to the corresponding thiocarbonyl compounds, in contrast to the facile ketonization of vinyl alcohols.

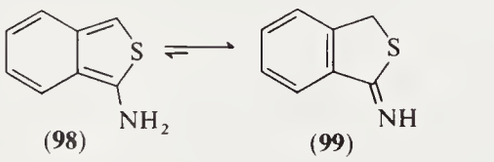
2-Mercapto derivatives of furan, thiophene, selenophene ⟨77ACS(B)198⟩ and pyrrole ⟨72AJC985⟩ all exist predominantly in the thiol form. 2-Mercaptobenzothiophene is also a thiol ⟨70JCS(C)2431⟩ whereas 2-mercaptoindole is mainly indoline-2-thione (**97**) ⟨69CPB550⟩. This is not due solely to the greater resonance energy associated with thioamides since *N*-alkylation (which disallows hydrogen bonding) shifts the tautomeric equilibrium back to the thiol form.

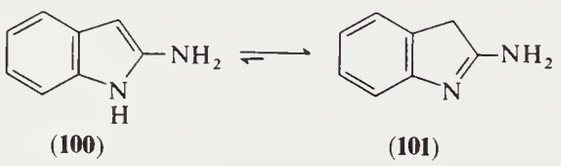

(97)

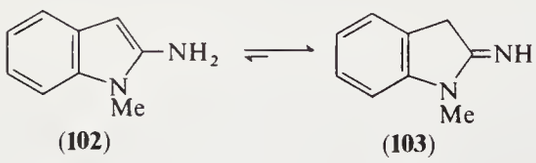
The known 3-mercapto derivatives of furan, thiophene, selenophene ⟨77ACS(B)198⟩, benzothiophene ⟨70JCS(C)2431⟩ and indole ⟨69TL4465⟩ all exist as the 3-thiol tautomers.

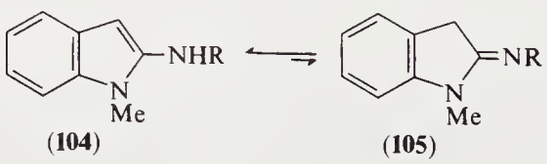
2.3.5.5 Compounds with Potential Amino Groups

MO calculations predict that 2- and 3-amino derivatives of furan and pyrrole will preferentially exist as such rather than adopt tautomeric imino forms ⟨70JA2929⟩. These conclusions appear to be borne out for 2-aminofurans ⟨66CB1002⟩, as well as 2-amino- ⟨54HCA1256⟩ and 3-amino-pyrroles ⟨64UP30100, 70JCS(C)1658⟩. 3-Aminofuran still eludes isolation but its *N*-acyl derivatives are 3-acylaminofurans ⟨82T2783⟩. The preference for the amino form is also observed for 2-amino- ⟨69JHC147, 71T5873⟩ and 3-amino-thiophene ⟨73JHC1067⟩, 2-amino-3-ethoxycarbonyl- ⟨71T5873⟩ and 3-amino-benzofurans ⟨73JPR779⟩, 2-aminobenzo[*b*]thiophene ⟨65JOC4074⟩, 3-aminoindoles ⟨69BSF2004⟩ and 1-aminoindolizines ⟨65JCS2948⟩. Among the few well-established exceptions is the aminobenzo[*c*]thiophene (**98**) which preferentially exists as the imine (**99**) ⟨64JOC607⟩. The existence of 2-aminoindole (**100**) as the tautomer (**101**)⟨56HCA116, 71T775⟩ has been mentioned earlier and is a consequence of the appreciable resonance energy of the amidine group and the low resonance energy of the indole pyrrole ring. In the corresponding *N*-methyl compound (**102**) the equilibrium is displaced toward (**103**) and this displacement increases with increasing solvent polarity; however, replacement of the 2-amino group by an *N*-alkylamino causes (**104**) to predominate over (**105**).


(98) (99)


(100) (101)


(102) (103)


(104) (105)

2.4

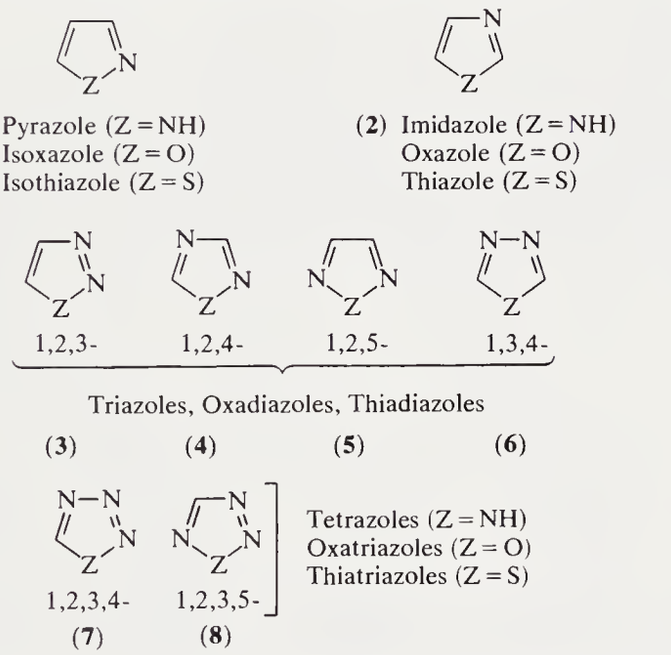
Structure of Five-membered Rings with Two or More Heteroatoms*

2.4.1 SURVEY OF POSSIBLE STRUCTURES

We classify compounds as aromatic, if there is continuous conjugation around the ring, or non-aromatic. Aromatic compounds are further subdivided into those without exocyclic double bonds and those in which canonical forms containing exocyclic double bonds contribute.

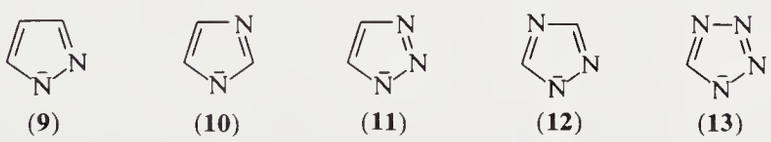
2.4.1.1 Aromatic Systems without Exocyclic Conjugation

The neutral aromatic azole systems (without exocyclic conjugation) are shown in Scheme 1; throughout, Z is O, S or NR. There are, thus, 24 possible systems; however, for NR = NH, tautomerism renders (**3**) ≡ (**5**), (**4**) ≡ (**6**), and (**7**) ≡ (**8**). Ring-fused derivatives without a bridgehead nitrogen atom are possible for systems (**1**), (**2**), (**3**) and (**5**). Ring-fused derivatives with a bridgehead nitrogen atom can be derived from all except (**5**) and (**8**).



Scheme 1 Neutral aromatic azoles (no exocyclic double bonds) (Z = O, S or NR)

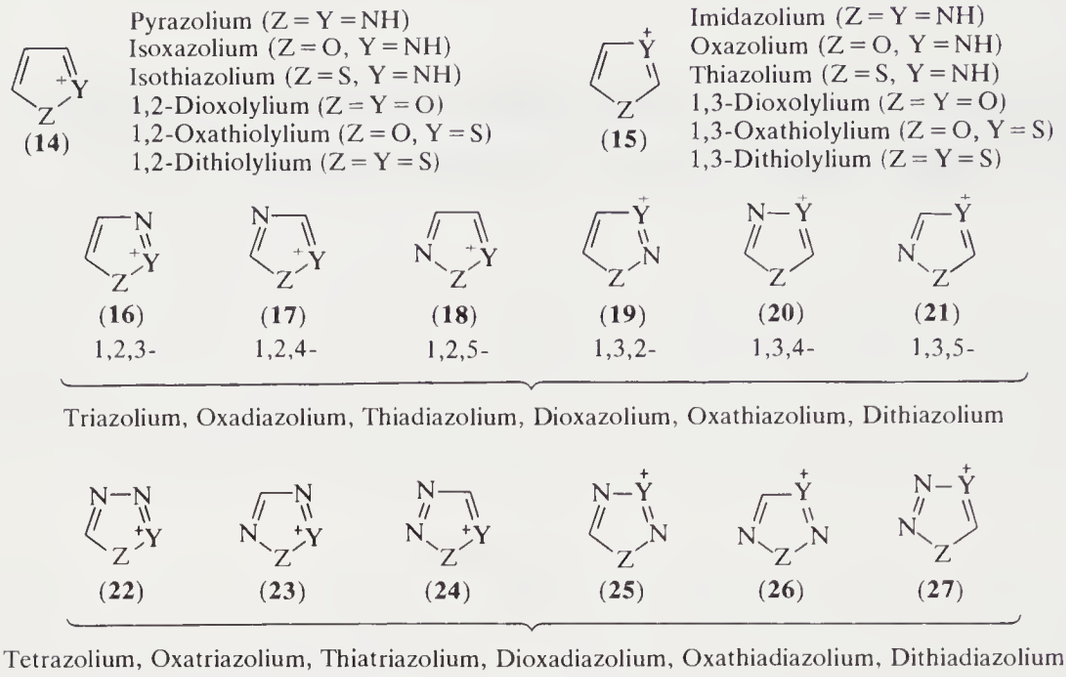
The five possible azole monoanions are shown (one canonical form only) in Scheme 2; all heteroatoms are now nitrogens.



Scheme 2 Monoanionic aromatic azoles

*Chapter 4.01 of 'Comprehensive Heterocyclic Chemistry', by A. R. Katritzky, University of Florida, and J. M. Lagowski, The University of Texas at Austin.

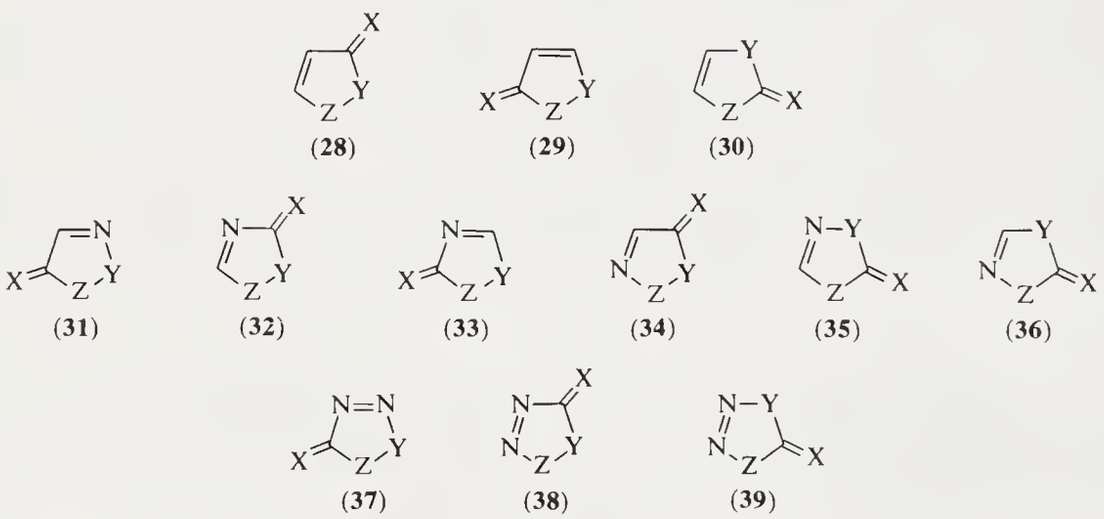
The aromatic azole monocations are given in Scheme 3; here Z and Y are both O, S or NR; there are therefore three mixed sets. If Z = Y, then (**16**) ≡ (**18**), (**20**) ≡ (**21**), (**22**) ≡ (**24**), and (**25**) ≡ (**26**). Hence there are (3 × 14) + (3 × 10) = 72 possible systems.



Scheme 3 Monocationic azoles

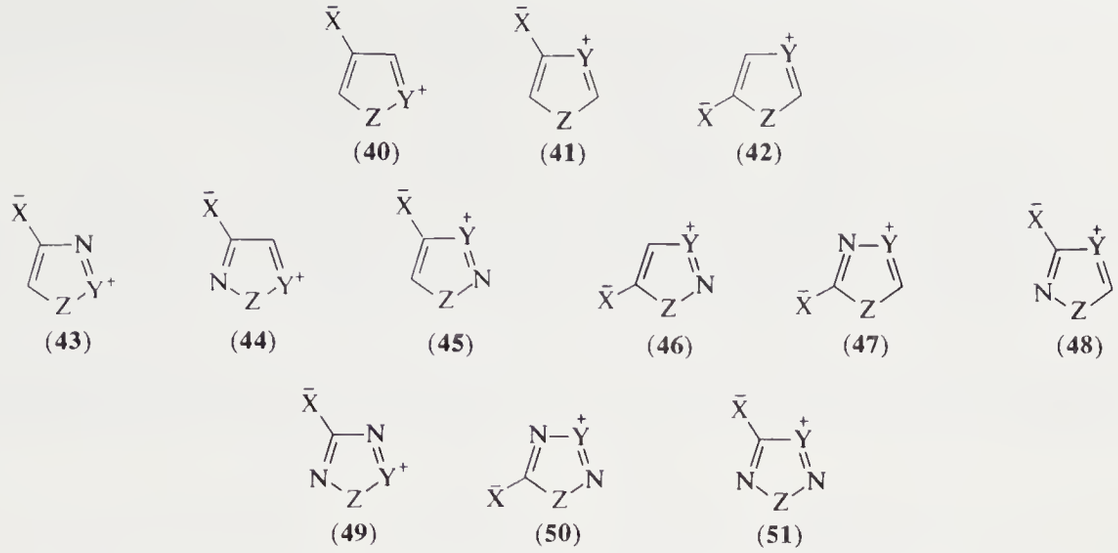
2.4.1.2 Aromatic Systems with Exocyclic Conjugation

Each of the aromatic monocationic systems (**14**)–(**27**) can be converted into a neutral system by substitution of an anionic O, S or NR group on to a ring carbon atom. However, (**14**) and (**15**) each give three such systems, (**16**)–(**21**) two each, and (**22**)–(**27**) one each. The resulting 24 systems can be divided into two groups: 12 systems for the azolinones and related compounds (Scheme 4) and 12 systems for the mesoionic (betaine) compounds (Scheme 5).



Scheme 4 Azolinones and related compounds (X = O, azolinones; X = S, azolinethiones; X = NR, azolinimines)

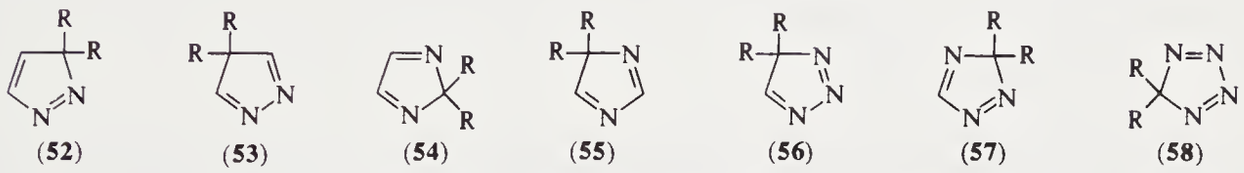
Of the mesoionic systems, (**40**) and its aza derivatives (**43**), (**44**) and (**49**) have been designated as Class B by Ollis ⟨76AHC(19)1⟩, including compounds with X = CRR′; there are 88 total systems. Class A mesoionic compounds include (**41**), (**42**) and their aza derivatives (**45**)–(**48**), (**50**) and (**51**), giving a total of 144 systems. Members of the latter group contain 1,3-dipoles, often reflected in their pronounced ability to undergo cycloaddition reactions.



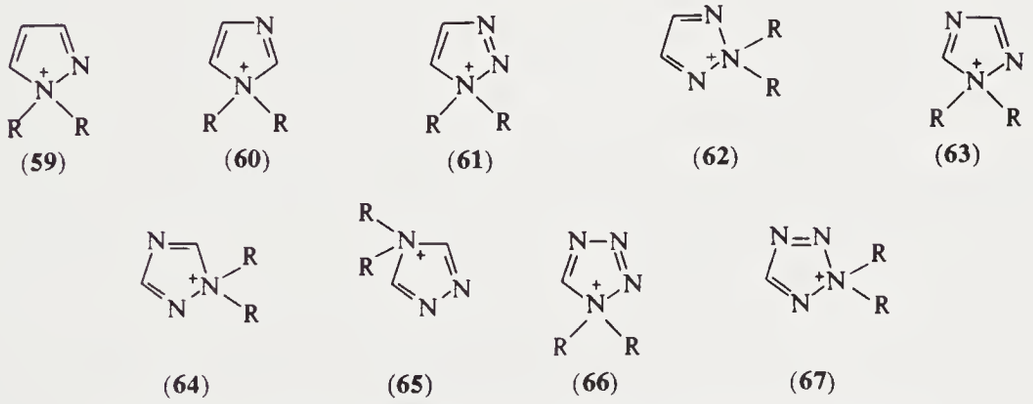
Scheme 5 Mesoionic compounds (Z = O, S or NR; X = O, S, NR or CR_2)

2.4.1.3 Non-aromatic Systems

These are subdivided into: (a) compounds isomeric with aromatic compounds in which the ring contains two double bonds but also an sp^3-hybridized carbon (7 systems; Scheme 6) or a quaternary nitrogen atom (9 systems; Scheme 7).

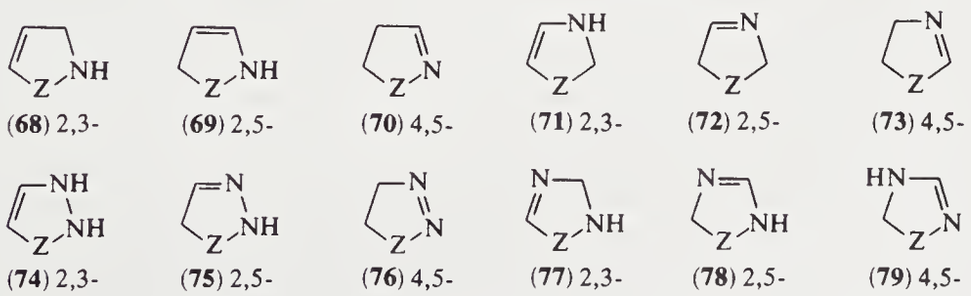


Scheme 6 Isomers of aromatic compounds with an sp^3-hybridized carbon atom

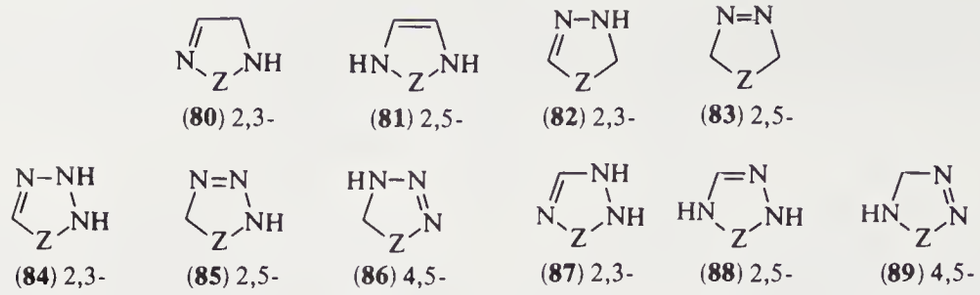


Scheme 7 Isomers of aromatic compounds with a quaternary nitrogen atom

(b) Dihydro compounds in which the ring contains one double bond (66 systems; Scheme 8).

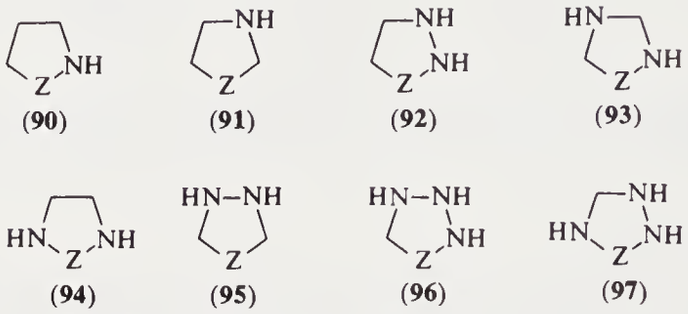


Scheme 8 Dihydroazoles (Z = O, S or NR)



Scheme 8 Dihydroazoles (Z = O, S or NR)

(c) Tetrahydro compounds in which the ring contains no double bonds (24 systems; Scheme 9).



Scheme 9 Tetrahydro compounds (Z = O, S or NR)

2.4.2 THEORETICAL METHODS

2.4.2.1 The MO Approximation

In the simpler MO approximations the π-electrons are assumed to move independently in MOs that can be represented as linear combinations of the atomic *p*-orbitals. When these MOs are used as the basis for an approximate wave mechanical calculation, the energy of the MOs and the distribution of the π-electrons in each depend on the values of certain integrals. These integrals are of two types, termed Coulomb integrals and resonance integrals; both are negative and have the dimensions of energy. The Coulomb integrals are characteristic of an atomic π-orbital in a given molecular environment and are a measure of the effective electronegativity of that atom toward π-electrons. The resonance integrals are characteristic of a π-bond between two atoms and are a measure of the stability that a localized π-bond would have if formed between them. Neither the Coulomb integrals nor the resonance integrals are usually directly evaluated by integration; the calculations are based on certain simplifying assumptions concerning the relative values of the different Coulomb integrals and the relative values of the different resonance integrals.

For unsubstituted aromatic hydrocarbons all the carbon atoms are assigned the same Coulomb integral (α) and all C—C bonds are assigned the same resonance integral (β).

In heteroaromatic molecules the approximate Coulomb integral for the heteroatom is expressed in terms of α and β, the standard integrals associated with the carbocyclic aromatic hydrocarbons. There has been considerable variation in the Coulomb integral used for the neutral nitrogen atom as typified by that in pyridine; the values used have ranged from $\alpha + 2.0\beta$ to $\alpha + 0.2\beta$, the lower values being the more recent. The Coulomb integral for nitrogen is considered to depend considerably on the chemical environment, and the approximate values are discussed under the compounds concerned. It has been suggested that a different Coulomb integral should be used for the nitrogen atom of pyrrole in simple Hückel-type MO calculations, giving a value of $\alpha + 1.9\beta$. Non-empirical calculations indicate that the π-electrons of the pyrrole anion are almost evenly distributed over all five atoms, so that carbon and nitrogen atoms should be assigned the same Coulomb integrals in the simple MO treatment.

The Coulomb integral (α_C) of the carbon atoms adjacent to the heteroatom (more electronegative than the carbon atoms in benzene because of the inductive effect of the heteroatom as relayed through the σ-bonds) is accommodated by making the appropriate Coulomb integrals more negative than α. This increases the agreement between the simple MO calculations and those based on elaborate, non-empirical treatments. It is convenient to express the value of α_C in terms of

α and β, and so the Coulomb integrals used for the heteroatom and for the adjacent carbon atoms may be defined by two parameters h and h' according to equations (1) and (2).

$$\text{Heteroatom} \qquad \alpha_X = \alpha + h\beta \tag{1}$$

$$\text{Adjacent carbon atoms} \qquad \alpha_C = \alpha + h'\beta \tag{2}$$

The resonance integral of the π-bond between the heteroatom and carbon is another possible parameter in the treatment of heteroatomic molecules. However, for nitrogen compounds more detailed calculations have suggested that this resonance integral is similar to that for a C—C bond and moreover the relative values of the reactivity indices at different positions are not very sensitive to change in this parameter.

Theoretical reactivity indices of heteroaromatic systems distinguish reactivity toward electrophilic, nucleophilic and homolytic reactions.

2.4.2.2 Electron Densities

The π-electron density refers to the electron density at a given carbon atom obtained by summing the contributions from all the filled molecular orbitals. Electrophilic attack occurs where this density is highest, and nucleophilic attack where it is lowest; π-electron densities are not dominant in determining the orientation of homolytic substitution.

Values for the π-electron densities in imidazole and two related ions are given in Figure 1. The π-electron densities in the conjugate acid of imidazole are greater at the 2-position than at the 4-position and thus bear no relation to the chemical reactivity, as nucleophiles attack at the 2-position and electrophiles at the 4-position. The results for the neutral molecule and the conjugate base are more satisfactory; however, the uncertainty in these values, estimated as 0.02 units, exceeds the difference between the π-electron density at the 2-position and that at the more reactive 4(5)-positions in all three reactive forms of imidazole.

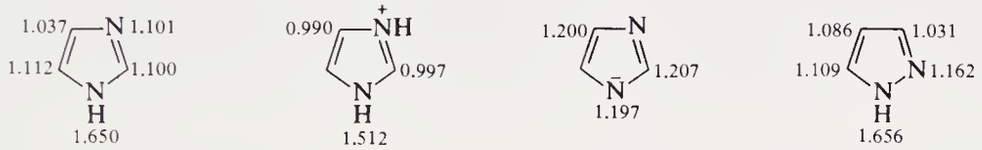


Figure 1 The π-electron densities in imidazole, its conjugate acid and base, and pyrazole

Results for the neutral pyrazole molecule show a considerable spread. The π-electron and total ($\pi + \sigma$) densities predict electrophilic substitution at the 4-position as found. Results for thiazole also agree with experimentally determined electrophilic and nucleophilic reactivity.

The π-electron distribution in benzimidazole favors substitution at the 4-position in the conjugate acid, at the 4- and 5-positions in the neutral molecule, and at the 2-position in the conjugate base. These results do not explain the apparently exclusive substitution at the 5-position in nitration. There is thus no general agreement between the π-electron distribution and the chemical reactivity.

Values for π-electron density on nitrogen atoms generally indicate the position of electrophilic attack, *e.g.* at the 3-position of 1,2,3-thiadiazoles.

The net σ-charge on ring hydrogen atoms can also be significant; for thiazole the order of decreasing acidity of the hydrogens is H-2 $\geqslant$ 5 > 4, consistent with experiment.

2.4.2.3 Frontier Electron Densities

An alternative approach is in terms of frontier electron densities. In electrophilic substitution, the frontier electron density is taken as the electron density in the highest filled MO. In nucleophilic substitution the frontier orbital is taken as the lowest vacant MO; the frontier electron density at a carbon atom is then the electron density that would be present in this MO if it were occupied by two electrons. Both electrophilic and nucleophilic substitution thus occur at the carbon atom with the greatest appropriate frontier electron density.

The significance of frontier electron densities is limited to the orientation of substitution for a given aromatic system, but this approach has been developed to give two more complex reactivity

indices termed superdelocalizabilities and Z values, which indicate the relative reactivities of different aromatic systems.

2.4.2.4 Localization Energies

Localization energies refer to the difference between the π-electron energy in the isolated molecule and that in the related system where the carbon atom at the point of substitution has been removed from the cyclic conjugation by bonding with the reagent. The Wheland structure, originally considered to be a suitable model of the transition state, generally corresponds to an intermediate. Nevertheless, the relative stabilities of the different transition states in the same molecule appear to be in the same order as the calculated localization energies, and this reactivity index is probably the best guide to the orientation of substitution in aromatic and heteroaromatic systems.

The localization energies for the neutral diazoles were originally calculated on the assumption that the Coulomb integrals for the two nitrogen atoms are equal; for the neutral diazoles these results may therefore require some modification. For the neutral molecule and conjugate acid of pyrazole the orientation of electrophilic attack is correctly assigned to the 4-position. For the neutral molecule and conjugate acid of imidazole the orientation of electrophilic attack is correctly assigned to the 4(5)-positions. If the Coulomb integral of the nitrogen atoms in the conjugate base of imidazole is set equal to that for the carbon atoms, then the localization energies for the 2- and 4,5-positions become equal. In reactions of the conjugate base of imidazole the orientation appears to depend on the reagent, but there is probably little difference between the reactivity of the 2- and 4-positions.

The localization energies for electrophilic substitution in benzimidazole predict that all three reactive forms should undergo substitution in the 4-position. This does not explain the formation of the 5-nitro compound or that of the 2-deutero compound. It is doubtful whether any electrophilic substitution occurs preferentially in the 4-position.

The calculation of localization energies in heteroaromatic systems derived from alternant hydrocarbons has been simplified by Dewar and Maitlis ⟨57JCS2521⟩. This approach has had considerable success; the results provide a somewhat empirical index of reactivity.

2.4.2.5 Semi-empirical Methods

The simple, or Hückel based, molecular orbital theory described above frequently provides useful qualitative insights but cannot be used reliably in a quantitative sense. For this purpose it is necessary to use a method which takes account of all the electrons as well as their mutual repulsions. This is usually done within the framework of a formalism developed independently by Roothaan ⟨51MI40100⟩ and Hall ⟨51MI40101⟩. Procedures of this kind are variously known as RH, non-empirical or, most frequently, *ab initio* molecular orbital calculations. Here, once the forms of the atomic orbitals, *i.e.* basis sets, are specified, no further approximations are made. While numerous alternative basis sets are possible, most practical applications of *ab initio* MO theory now utilize one of the carefully optimized expansions of Gaussian functions introduced by Pople and his co-workers ⟨74MI40100⟩. The simplest (and least accurate) is designated STO-3G, while the most complex in common use is designated 6-31G. Fortunately, even the simplest basis sets seem to give excellent descriptions of the electron distribution, especially when expressed in terms of integrated spatial populations ⟨80MI40101⟩. Palmer, in particular, has presented electron distribution data in many heterocyclic systems ⟨78JST(43)33⟩. Unfortunately, apart from those special cases in which species having the same numbers of each type of bond are compared, the quantitative estimation of relative energies in *ab initio* theory usually requires a basis set of at least 3-21G quality. Moreover, for reliable results the geometries of the species being compared must be calculated at the *ab initio* level. The expense inherent in the use of the more complex basis set, as well as that of geometry optimization, has tended to limit the most detailed studies to rather small heterocyclic ring systems ⟨77JA7806, 78JA3674, 83JA309⟩.

The major bottleneck in *ab initio* calculations occurs in the computation and storage of the enormous number of electron-repulsion integrals involved. Early efforts by Pople and co-workers to reduce this problem led to the CNDO, INDO and NDDO approximations ⟨70MI40100⟩. Although once popular, these methods in their original forms are now largely superseded. Dewar

has implemented modifications of the two latter approximations which have proved to be very successful. The most recent versions are designated MINDO/3 ⟨75JA1285⟩ and MNDO ⟨77JA4899⟩ respectively. Since their inception these methods have been somewhat controversial since they were parameterized to reproduce not the results of the *ab initio* methods from which they are derived (as was done in CNDO/2 and INDO), but experimental geometries and energies. These semiempirical MO procedures therefore appear to involve several theoretical inconsistencies which have yet to be fully resolved ⟨B-77MI40100⟩. Nevertheless, judged on purely empirical criteria, they seem to work well. Indeed they are frequently comparable in accuracy (relative to experiment) to *ab initio* calculations using moderately sized basis sets and much better than those using minimal basis sets ⟨79JA5558⟩. Semi-empirical procedures of this kind have been used to study the reactions of various five-membered heterocyclic systems ⟨77JCS(P2)724⟩.

2.4.2.6 Other Applications of Theory

Applications of MO methods to such diverse problems as aromaticity, tautomeric structure, dipole moments, and UV, NMR and PE spectroscopy are discussed in various monograph chapters.

2.4.3 STRUCTURAL METHODS

2.4.3.1 X-Ray Diffraction

Details of bond lengths and bond angles for all the X-ray structures of heterocyclic compounds through 1970 are listed in 'Physical Methods in Heterocyclic Chemistry', volume 5. This compilation contains many examples for five-membered rings containing two heteroatoms, particularly pyrazoles, imidazoles, isoxazoles, oxazoles, isothiazoles, thiazoles, 1,2-dithioles and 1,3-dithioles. Further examples of more recent measurements on these heterocyclic compounds can be found in the monograph chapters.

For compounds with three or four heteroatoms in the ring the number of measurements is much fewer, and these are summarized in Table 1.

2.4.3.2 Microwave Spectroscopy

Microwave spectra provide a rich source of minute details of molecular structures. They tell us about the molecular geometry because the spectra are primarily analyzed in terms of the accurate average values of the reciprocals of the three moments of inertia. This generally gives at once the general molecular conformation and some precise structural features may emerge. To obtain a complete structure it is necessary to measure the changes in moments of inertia which accompany the isotopic replacements of each atom in turn ⟨74PMH(6)53⟩.

From accurate measurements of the Stark effect when electrostatic fields are applied, information regarding the electron distribution is obtained. Further information on this point is obtained from nuclear quadrupole coupling effects and Zeeman effects ⟨74PMH(6)53⟩.

Microwave studies also provide important information regarding molecular force fields, particularly with reference to low frequency vibrational modes in cyclic structures ⟨74PMH(6)53⟩.

2.4.3.2.1 Molecular geometry

Structural parameters in aromatic five-membered rings are shown in Table 2. All the C—H distances are near 107.5 pm, close to the C—H link in ethylene. With heteroatoms at adjacent ring positions, the C—H groups are displaced from the bisector of the ring angles toward the adjacent heteroatom ⟨74PMH(6)53⟩

The N—H bond lengths in pyrazole and imidazole (99.8 pm) are a little shorter than those found in dimethylamine. Delocalization in pyrazole, imidazole, 1,2,3-triazole and 1,2,4-triazole is sufficient to bring the hydrogen attached to nitrogen into the plane of the other atoms. The N—H bond in pyrazole does not lie in the bisector of the ring angle (as is required by symmetry in pyrrole), but is displaced by around 5° toward the second nitrogen ⟨74PMH(6)53⟩.

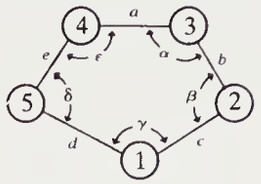
Table 1 X-Ray Structures of Compounds with Five-membered Rings and Two, Three or Four Heteroatoms[a]

Ring	*Ring position* 1	2	3	4	5	*Examples of compounds studied*
C_3N_2	N	N	—	—	—	Pyrazole;[b] substituted pyrazoles; Δ^1- and Δ^2-pyrazolines; pyrazolinones; pyrazolidines; pyrazolidinones
	N	—	N	—	—	Imidazole;[b] 4,5-di-*t*-butylimidazole; histamine dihydrochloride; 2-thiohydantoin
C_2N_3	N	N	N	—	—	1,3-Dimethyl-4-(1 2,3-triazolyl) sulfide; 3-methyl-2-phenyl-1,2,3-triazol-1-ine-4-thione
	N	N	—	N	—	1,2,4-Triazole[b]
CN_4	N	N	N	N	—	5-Amino-2-methyltetrazole;[b] 5-aminotetrazole monohydrate;[b] sodium tetrazolate monohydrate[b]
C_3NO	O	N	—	—	—	5,5′-Biisoxazole;[b] 3-hydroxy-5-phenylisoxazole;[b] 3,3′-bi-2-isoxazoline;[b] 3-hydroxy-5-phenylisoxazole;[b] 3-phenylisoxazolin-5-one[b]
C_3NS	S	N	—	—	—	Methyl 3-hydroxy-4-phenylisothiazole-5-sulfonate; dehydromethionine
C_3NO	O	—	N	—	—	2,2′-*p*-Phenylenebis(5-phenyloxazole); 2-(4-pyridyl)oxazole;[b] 2,4-dimethyl-5-(*p*-nitrophenyl)oxazole;[b] 2-oxazolidinone[b]
C_3NS	S	—	N	—	—	Thiamine hydrochloride monohydrate;[b] rhodanine;[b] 2-imino-5-phenyl-4-thiazolidinone[b]
C_2N_2O	O	N	N	—	—	*N*-(*p*-Bromophenyl)sydnone;[b] 4,4′-dichloro-3,3′-ethylenebis(sydnone)
	O	N	—	N	—	3-(2-Aminopyridyl)-5-methyl-1,2,4-oxadiazole
	O	N	—	—	N	3-(*p*-Bromophenyl)-4-methyl-1,2,5-oxadiazole 2-oxide;[b] 3-(*p*-bromophenyl)-4-methyl-1,2,5-oxadiazole 5-oxide;[b] 3,4-diphenyl-1,2,5-oxadiazole
	O	—	N	N	—	Monoaryl-1,3,4-oxadiazoles[c]
C_2N_2S	S	N	N	—	—	5-Acylamino-3-methyl-1,2,3-thiadiazole; 5-phenyl-1,2,3-thiadiazole 3-oxide
	S	N	—	N	—	5-Imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline[d]
	S	N	—	—	N	3,4-Diphenyl-1,2,5-thiadiazole; 1,2,5-thiadiazole-3,4-dicarboxamide
	S	—	N	N	—	1,3,4-Thiadiazole; 2,5-diphenyl-1,3,4-thiadiazole[b]
CN_3O	O	N	N	N	—	Mesoionic 3-phenyl-1,2,3,4-oxatriazole-5-phenylimine; mesoionic 3-phenyl-1,2,3,4-oxatriazol-5-one
CN_3S	S	N	N	N	—	5-Phenyl-1,2,3,4-thiatriazole; 5-amino-1,2,3,4-thiatriazole; 5-phenyl-1,2,3,4-thiatriazole 3-oxide
	S	N	N	—	N	2-Acetyl-5-chloro-2*H*-1,2,3,5-thiatriazolo[4,5-*a*]isoquinoline 5-oxide
C_3O_2	O	—	O	—	—	Bis(dioxolane); ethylene carbonate; *cis*-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one; 2-methyl-1,3-dioxolan-2-ylium perchlorate
C_3OS	O	S	—	—	—	3,3-Diphenyl-1,2-oxathiolane 2,2-dioxide; 5*H*-1,2-benzoxathiole 2,2-dioxide
	O	—	S	—	—	Cholestan-4-one-3-spiro(2,5-oxathiolane)
C_3S_2	S	S	—	—	—	1,2-Dithiolane-4-carboxylic acid;[b] 3-phenyl-1,2-dithiolylium iodide;[b] 4-methyl-1,2-dithiole-3-thione[b]
	S	—	S	—	—	Bis-1,3-dithiol-2-yl;[b] 4,5-dioxo-2-thioxo-1,3-dithiolane;[b] 1,3-dithiolane-2-thione 5-oxide;[b] tetrathiafulvalene[e]
C_2O_3	O	O	—	O	—	*trans*-5-Anisyl-3-methoxycarbonyl-1,2,4-trioxolane[f]
C_2S_3	S	S	—	S	—	1,2,4-Trithiolane-3,5-dione diphenylhydrazone[g]
C_2O_2S	O	S	O	—	—	1,3,2-Dioxathiolane 2,2-dioxide;[h] 1,3,2-dioxathiole 2,2-dioxide[h]
C_2NS_2	S	S	N	—	—	2,4,6-Tri-*t*-butyl-7,8,9-dithiazabicyclo[4.3.0]nona-1(9),2,4-triene[i]
C_2NS_2	S	S	—	N	—	5-Amino-1,2,4-dithiazolin-3-one ('Rhodan hydrate');[j] 5-amino-1,2,4-dithiazoline-3-thione ('Xanthane hydride');[k] 3,5-diamino-1,2,4-dithiazolium chloride ('Thiuret hydrochloride')[l]
C_2NOS	O	S	N	—	—	2,4-Dioxo-2-(4-methylphenyl)-1,2,3-oxathiazoline;[m] 1,2,3-oxathiazolo-[5,4-*d*][1,2,3]oxathiazole 2,2,5,5-tetraoxide[n]
	O	S	—	N	—	6,10b-Dihydro-3-(2,2,6,6-tetramethylcyclohexyliden)-1,2,4-oxathiazolo-[5,4-*a*]isoquinoline[o]
	O	N	S	—	—	4-Phenyl-1,3,2-oxathiazolin-5-one[p]
	O	—	S	N	—	2-Trichloromethyl-5-phenyl-Δ^4-1,3,4-oxathiazoline[q]

[a] Unless otherwise indicated data are taken from the appropriate chapter of 'Comprehensive Heterocyclic Chemistry'. [b] Data taken from ⟨72PMH(5)1⟩, which gives references to the original literature. [c] X-Ray powder data; *cf.* Chapter 4.23. [d] ⟨78CC652⟩. [e] ⟨71CC889⟩. [f] ⟨70ACS2137⟩. [g] ⟨71JCS(B)415⟩. [h] ⟨68JA2970⟩. [i] ⟨80AX(B)1466⟩. [j] ⟨66ACS754⟩. [k] ⟨63ACS2575, 63AX1157⟩. [l] ⟨66ACS1907⟩. [m] ⟨71TL4243⟩. [n] ⟨80MI40100⟩. [o] ⟨78AG(E)455⟩. [p] ⟨72G23⟩. [q] ⟨81JCS(P1)2991⟩.

The ring angles at C and N are usually 108 ± 5°, but drop nearer to 90° at sulfur and selenium. Minor variations in the bond lengths reflect variations in the double bond character and, for example, suggest larger delocalization in 1,3,4-thiadiazole than in 1,3,4-oxadiazole ⟨74PMH(6)53⟩. In thiazole the geometry of the SCN part of the ring resembles the corresponding part of 1,3,4-thiadiazole, while the remaining part of the ring resembles the corresponding thiophene.

Table 2 Structure Parameters in Five-membered Rings from Microwave Spectra



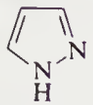
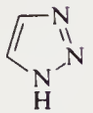
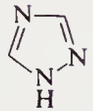
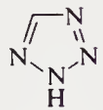
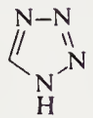
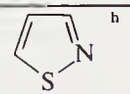
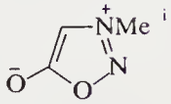
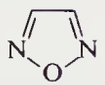
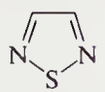
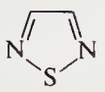
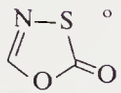
Compound	*Bond length* (pm)[a,b]					*Angle* (°)[b]					*Dipole moment* (10^{-30} C m)[a]
	a	*b*	*c*	*d*	*e*	α	β	γ	δ	ε	
 [c]	141.6	133.1	134.9	135.9	137.3	111.9	104.1	113.1	106.4	104.5	7.37
 [d]	(137.8)	(132.6)	(134.9)	(136.9)	(135.8)	(105.4)	(111.3)	(107.2)	(106.3)	(109.8)	12.8
 [d]	—	—	—	—	—	—	—	—	—	—	5.97
 [e]	135.9	132.3	135.9	133.1	132.4	114.6	102.1	110.2	110.1	103.0	9.07
 [e]	135.1	128.4	132.4	133.4	131.0	—	—	—	—	—	7.31
 [f]	(134.5)	(128.3)	(134.7)	(135.1)	(129.0)	(112.2)	(106.9)	(105.3)	—	—	17.05
 [g]	—	—	—	—	—	—	—	—	—	—	9.21

Table 2 (*continued*)

Compound	Bond length (pm)[a,b] a	b	c	d	e	Angle (°)[b] α	β	γ	δ	ε	Dipole moment (10^{-30} C m)[a]
 [h]	—	—	—	—	—	—	—	—	—	—	8.67
 [e]	139.5	129.3	135.7	137.0	135.3	103.9	115.0	103.9	108.1	109.1	5.00
 [e]	137.2	130.4	172.4	171.3	136.7	110.1	115.2	89.3	109.6	115.8	5.37
 [i]	(133.4)	(131.3)	(138.9)	—	—	(111.3)	(103.8)	(114.4)	—	—	21.12
 [j]	(138.0)	(130.3)	(141.8)	—	—	(106.1)	(103.2)	(114.2)	—	—	5.44
 [c]	142.1	130.0	138.0	138.0	130.0	109.0	105.8	110.4	105.8	109.0	11.28
 [e]	141.7	132.7	163.0	163.0	132.7	113.8	106.5	99.4	106.5	113.8	5.27
 [c]	139.9	129.7	134.8	134.8	129.7	105.6	113.4	102.0	113.4	105.6	10.14
 [k]	136.6	129.0	169.2	168.9	136.9	114.0	111.2	92.9	107.8	114.2	11.98
 [l]	136.6	131.7	164.9	170.7	131.3	120.1	107.1	92.8	112.3	107.7	1.5
 [c]	142.0	132.8	163.1	163.1	132.8	113.8	106.4	99.6	106.4	113.8	5.24

 [c]	137.1	130.2	172.1	172.1	130.2	112.2	114.6	86.4	114.6	112.2	10.94
 [e]	—	—	—	—	—	—	—	—	—	—	3.97
 [m]	156.3	142.8	—	142.8	156.3	105.1	—	—	105.1	101.7	—
 [n]	143.6	139.5	147.0	139.5	143.6	106.2	99.2	99.2	106.2	99.2	3.64
 [o]	169.0	176.6	140.2	135.6	128.6	93.8	106.3	110.8	121.1	107.9	—

[a] 1 Å = 100 pm; 1 D = 3.336×10^{-30} C m. [b] X-Ray diffraction data are enclosed in parentheses. [c] Data taken from ⟨74PMH(6)53⟩. which see for references to the original literature. [d] Dipole moment is concentration-dependent (*cf.* CHEC 4.06.3.2). [e] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'. [f] No bond lengths or angles given in ⟨74JSP(49)423⟩; calculated values taken from CHEC 4.13. [g] Bond lengths and angles for 5-bromotetrazole; dipole moment for tetrazole in dioxane. [h] Measured in benzene; *cf.* CHEC 4.16.1.4.1(i). [i] Bond lengths and angles from X-ray data for 4,4′-dichloro-3,3′-ethylenebis(sydnone) ⟨67JA5977⟩; calculated dipole moment for 3-methylsydnone ⟨71JST(9)321⟩. [j] Bond lengths and angles from X-ray data for 3-(2-aminopyridyl)-1,2,4-oxadiazole ⟨79AX(B)2256⟩; dipole moment for 3-methyl-5-phenyl-1,2,4-oxadiazole ⟨35G152⟩. [k] Dipole moment from ⟨76MI40100⟩. [l] ⟨74TH40100⟩. [m] Values calculated from experimentally derived rotational constants; *cf.* CHEC 4.30.1.3.2. [n] ⟨72JA6337⟩. [o] Values for 1,3,4-oxathiazolin-2-one determined from electron diffraction measurements and refined using rotational parameters from microwave spectra; *cf.* CHEC 4.34.2.3.2.

Microwave spectroscopy distinguishes readily between possible tautomeric forms of 1,2,3- and 1,2,4-triazole, which are both in the 1*H*-form. In tetrazole both the 1*H*- and 2*H*-forms are detected ⟨74PMH(6)53⟩.

Dipole moments can also be obtained from the microwave spectral data ⟨74PMH(6)53⟩ and available values are given in Table 2.

2.4.3.2.2 Partially and fully saturated ring systems

Relatively few such heterocyclic systems have been studied by microwave spectroscopy; some data are included in Table 2. In 1,3-dioxolane the bent form is more stable than the twisted, and pseudorotation occurs. In 1,2,4-trioxocyclopentane the equilibrium conformation is twisted, and there is a barrier of 6.3 kJ mol^{-1} opposing pseudorotation ⟨74PMH(6)53⟩.

2.4.3.3 ^{1}H NMR Spectroscopy

Proton chemical shifts and spin coupling constants for ring CH of fully aromatic neutral azoles are recorded in Tables 3–6. Vicinal CH—CH coupling constants are small; where they have been measured (in rather few cases) they are found to be 1–2 Hz.

For the NH azoles (Table 3), the two tautomeric forms are usually rapidly equilibrating on the NMR timescale (except for triazole in HMPT). The *N*-methyl azoles (Table 4) are 'fixed'; chemical shifts are shifted downfield by adjacent nitrogen atoms, but more by a 'pyridine-like' nitrogen than by a 'pyrrole-like' *N*-methyl group.

Table 3 ^{1}H NMR Spectral Data for Ring Hydrogens of Nitrogenous Azoles: (a) NH Derivatives

Compound	*^{1}H Chemical shifts* (δ, p.p.m.) *H-2*	*H-3*	*H-4*	*H-5*	*Coupling constants, J* (Hz)	*Solvent*	*Ref.*
Pyrazole	—	7.61	7.31	7.61	2.1	—	71PMH(4)121, B-73NMR
Imidazole	7.86	—	7.25	7.25	1.0	$CDCl_3$	71PMH(4)121, B-73NMR
1,2,3-Triazole	—	—	7.75	7.75	—	$CDCl_3$	[a]
1,2,4-Triazole	—	7.92	—	8.85	—	HMPT	71PMH(4)121, B-73NMR
Tetrazole	—	—	—	9.5	—	D_2O	

[a] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.

Table 4 ^{1}H NMR Spectral Data for Ring Hydrogens of Nitrogenous Azoles: (b) *N*(1)-Methyl Derivatives

Compound	*^{1}H Chemical shifts*[a] (δ, p.p.m.) *H-2*	*H-3*	*H-4*	*H-5*
Pyrazole[b,c]	—	7.49	6.22	7.35
Imidazole[b]	7.47	—	7.08	6.88
1,2,3-Triazole[b]	—	—	7.74	7.59
1,2,5-Triazole[b]	—	7.75	7.75	—
1,2,4-Triazole[b]	—	7.94	—	8.09
1,3,4-Triazole[b]	8.23	—	—	8.23
1,2,3,4-Tetrazole[d]	—	—	—	8.98
1,2,3,5-Tetrazole[d]	—	—	8.60	—

[a] Spectra measured in $CDCl_3$.
[b] Data taken from ⟨B-73NMR⟩ which contains references to the original literature.
[c] Coupling constants are $J_{3,4} = 2.0$ Hz; $J_{3,5} = 0.7$ Hz; $J_{4,5} = 2.3$ Hz.
[d] Value for *N*-methyl derivative; *cf.* CHEC 4.13.

Comparison of the relevant data shows that an adjacent oxygen (Table 5) and especially a sulfur atom (Table 6) induce lower field shifts than either type of nitrogen atom.

Table 5 ^{1}H NMR Spectral Data for Ring Hydrogens of Azoles Containing Oxygen

Compound	^{1}*H Chemical shifts* (δ, p.p.m.) *H-2*	*H-3*	*H-4*	*H-5*	*Solvent*
Isoxazole[a]	—	8.14	6.28	8.39	CS_2
Oxazole[b]	7.95	—	7.09	7.69	CCl_4
1,2,4-Oxadiazole[c]	—	8.2	—	8.7	C_6H_6
1,2,5-Oxadiazole[d]	—	8.19	8.19	—	$CHCl_3$
1,3,4-Oxadiazole[e]	8.73	—	—	8.73	$CDCl_3$

[a] Coupling constants: $J_{3,4} = 1.78$ Hz; $J_{3,5} = 0.27$ Hz; $J_{4,5} = 1.69$ Hz ⟨74CJC833⟩.
[b] Coupling constants: $J_{2,4} = 0$ Hz; $J_{2,5} = 0.8$ Hz; $J_{4,5} = 0.8$ Hz.
[c] ⟨76AHC(20)65, 64HCA942⟩.
[d] CHEC 4.22.1.3.1.
[e] CHEC 4.23.2.2.1.

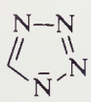
Table 6 ^{1}H NMR Spectral Data for Ring Hydrogens of Azoles Containing Sulfur

Compound	^{1}*H Chemical shifts* (δ, p.p.m.) *H-2*	*H-3*	*H-4*	*H-5*	*Solvent*
Isothiazole[a]	—	8.54	7.26	8.72	CCl_4
Thiazole[b,c]	8.88	—	7.98	7.41	$CDCl_3$
1,2,3-Thiadiazole[g]	—	—	(AB multiplet centered at 8.80)		CCl_4
1,2,4-Thiadiazole	—	8.66[d]	—	9.90[e]	
1,2,5-Thiadiazole[h]	—	8.70	8.70	—	CCl_4
1,3,4-Thiadiazole[f]	7.55	—	—	7.55	$CDCl_3$

[a] Coupling constants: $J_{3,4} = 11.66$ Hz; $J_{3,5} = 0.15$ Hz; $J_{4,5} = 4.66$ Hz.
[b] Coupling constants: $J_{2,4} = 0$ Hz; $J_{2,5} = 1.95$ Hz; $J_{4,5} = 3.15$ Hz.
[c] ⟨79HC(34-1)67, 79HC(34-1)73⟩.
[d] Value given for 5-phenyl derivative ⟨80JOC3750⟩.
[e] Value given for 3-phenyl derivative ⟨74JOC962⟩.
[f] ⟨78BAP291⟩. [g] ⟨78JOC2487⟩. [h] ⟨64DIS2690⟩.

The effects of anion and cation formation on ^{1}H chemical shifts can be assessed from data in Tables 7 and 8. Anion formation always results in shifts to higher field; however, the effect is relatively modest except for the 4-position of pyrazole because in all other cases the adjacent nitrogen lone pair partially cancels the shift. Conversely, in the cations (Table 8), the downfield shift is especially large for the CH groups next to nitrogen. The coupling constants appear to be significantly greater in the cations.

Table 7 ^{1}H NMR Spectral Data for Ring Hydrogens of Azole Anions

Compound	^{1}*H Chemical shifts* (δ, p.p.m.) *H-2*	*H-3*	*H-4*	*H-5*	*Solvent*	*Ref.*
	—	7.35	6.05	7.35	KOD/D_2O	68JA4232
	7.80	—	7.21	7.21	—	71PMH(4)121
	—	—	7.86	7.86	$NaOD/D_2O$	[a]
	—	8.19	—	8.19	$NaOD/D_2O$	71PMH(4)121
	—	—	—	8.73	—	71PMH(4)121

[a] Data taken from CHEC 4.11.

Table 8 ^{1}H NMR Spectral Data for Ring Hydrogens of Azole and Related Cations: Two Heteroatoms

Compound	*^{1}H Chemical shifts* (δ, p.p.m.)					*Coupling constants, J* (Hz)				
	H-2	*H-3*	*H-4*	*H-5*	*Solvent*	2,4	2,5	3,4	3,5	4,5
Pyrazolium[a,b]	—	8.57	6.87	8.57	DMSO-d_6	—	—	2.9	—	2.9
Imidazolium[c]	8.6	—	7.5	7.5	H_2SO_4	1.4	1.4	—	—	2.4
Isoxazolium[i]	—	9.18	7.26	9.01	D_2SO_4	—	—	2.8	—	1.9
Isothiazolium[a]	—	9.1	7.9	9.6	H_2SO_4	—	—	2.7	0.6	5.6
Thiazolium[d]	9.55	—	8.23	7.93	—	0.70	1.55	—	—	3.10
1,2-Oxathiolylium[e]	—	—	7.64	—	—	—	—	—	—	—
1,2-Dithiolylium[c]	—	6.71	1.44	−0.26	—	—	—	4.9	—	4.9
1,3-Dioxolylium[f]	10.4	—	—	—	—	—	—	—	—	—
1,3-Oxathiolylium[g]	—	—	8.12	—	—	—	—	—	—	—
1,3-Dithiolylium[h]	11.65	—	9.67	9.67	—	2.0	2.0	—	—	—

[a] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.
[b] Values given for 1,2-dimethylpyrazolium.
[c] Data taken from ⟨71PMH(4)121⟩ and ⟨B-73NMR1⟩ which see for references to the original literature.
[d] ⟨66BSF3524⟩.
[e] Value given for 5-methyl-3-(2-oxo-1-propyl)-1,2-oxathiolylium perchlorate.
[f] Value given for 1,3-benzodioxolylium fluorosulfonate.
[g] Value given for 2,5-diphenyl-1,3-oxathiolylium perchlorate.
[h] ⟨74JOC3608⟩. [i] ⟨83PC40100⟩.

Relatively few data are available on the ^{1}H NMR spectra of azolinones and related thiones and imines (Table 9).

Table 9 ^{1}H NMR Spectral Data for Ring C—H of Azolinones

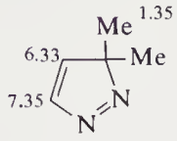
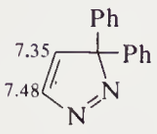
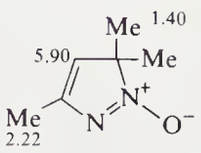
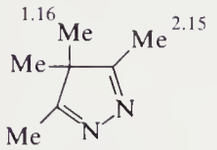
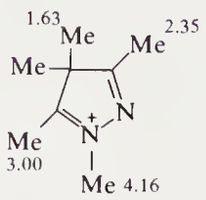
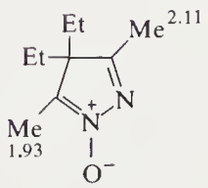
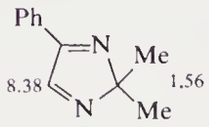
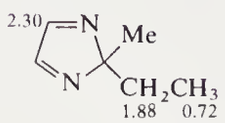
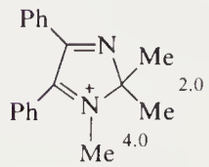
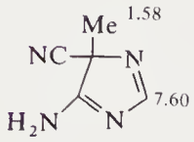
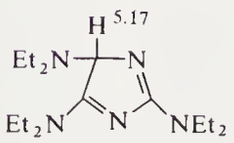
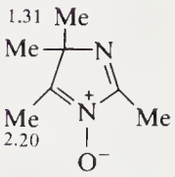
Compound	*^{1}H Chemical shifts* (δ, p.p.m.)				
	H-2	*H-3*	*H-4*	*H-5*	*Solvent*
Pyrazolin-3-one[b]	[a]	—	5.45	7.22	$CDCl_3$
Imidazolin-2-one[c]	—	—	6.50	6.50	—
Pyrazoline-3-thione[b]	—	—	6.23	[d]	—
1,2,4-Triazoline-3-thione	—	—	—	8.20	DMSO
Pyrazolin-3-imine[f]	—	—	5.46	[e]	$CDCl_3$
1,2,4-Triazolin-5-imine	—	2.05	—	—	$CDCl_3$
Δ^2-1,3,4-Oxadiazoline-5-thione[g]	8.88	—	—	—	DMSO-d_6
Isothiazolin-3-one[h,i]	—	—	6.05	7.98	—
1,3-Thiazolin-2-one[j,k]	—	−1.14	3.21	3.7	DMSO-d_6
Isothiazoline-3-thione[l,m]	—	—	6.90	8.25	—
1,3-Thiazoline-2-thione[k,n]	—	6.68	2.7	3.05	C_3D_6O
1,3-Thiazolin-2-imine[o,p]	—	—	3.03	3.37	$CDCl_3$

[a] Values given for 1,2-dimethylpyrazolin-3-one; $J_{4,5} = 3.5$ Hz. [b] ⟨76AHC(S1)1⟩. [c] Data taken from ⟨B-73NMR⟩ which contains references to the original literature. [d] Values given for 1,5-dimethyl-2-phenylpyrazoline-3-thione. [e] Values given for 1,5-dimethyl-2-phenylpyrazolin-3-imine. [f] ⟨72BSF2807⟩. [g] CHEC 4.23.2.2.1. [h] Values given for 2-methylisothiazolin-3-one; $J_{4,5} = 6.0$ Hz. [i] ⟨71JHC571⟩. [j] Coupling constants: $J_{3,4} = 2.5$ Hz; $J_{3,5} = 1.1$ Hz; $J_{4,5} = 5.3$ Hz. [k] ⟨79HC(34-2)385⟩. [l] Values given for 2-methylisothiazoline-3-thione; $J_{4,5} = 6.0$ Hz. [m] ⟨80CPB487⟩. [n] $J_{4,5} = 4.6$ Hz. [o] Values given for 2-ethoxycarbonylimino-3-ethyl-Δ^4-1,3-thiazoline. [p] ⟨79HC(34-2)26⟩.

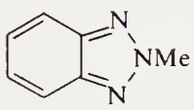
Some available data on ^{1}H NMR spectra of non-aromatic azoles containing two ring-double bonds are given in Table 10. Here there is no ring current effect and the chemical shifts are consequently more upfield.

Tables 11 and 12 give some available chemical shifts for azolines and azolidines, respectively. Unfortunately data for many of the parent compounds are lacking, often because the compounds themselves are unknown.

Table 10 ^{1}H NMR Spectral Data (δ, p.p.m.) for Ring Hydrogens of Non-aromatic Azoles with Two Ring Double Bonds ⟨83UP40100⟩

3*H*-Pyrazoles			
4*H*-Pyrazoles			
2*H*-Imidazoles			
4*H*-Imidazoles			

Proton–proton coupling constants of benzo rings of benzazoles can illuminate the bonding in such compounds. Thus, comparison of the *J* values for naphthalene with those for benzotriazoles of different types (Table 13) shows evidence of bond fixation, particularly in the 2-methyl derivative (**98**) ⟨71PMH(4)121⟩.



(**98**)

2.4.3.4 ^{13}C NMR Spectroscopy

Chemical shifts for aromatic azoles are recorded in Tables 14–17. As for the proton spectra, fast tautomerism renders two of the chemical shifts equivalent for the NH derivatives (Table 14). However, data for the *N*-methyl derivatives (Table 15) clearly indicate that the carbon adjacent to a 'pyridine-like' nitrogen shows a chemical shift at lower field than that adjacent to a 'pyrrole-like' *N*-methyl group (in contrast to the H chemical shift behavior). In azoles containing oxygen (Table 16) and sulfur (Table 17), the chemical shifts are generally at lower field than those for the wholly nitrogenous analogues, but the precise positions vary.

Azolinone derivatives and the corresponding thiones and imines are listed in Table 18; only substituted derivatives have been measured frequently. The ^{13}C chemical shifts of non-aromatic azole derivatives are given in Tables 19–21; relatively few data are available and these are generally for substituted derivatives rather than for the parent compounds.

2.4.3.5 Nitrogen NMR Spectroscopy

Available data are recorded in Table 22. In azoles the chemical shift of a 'pyridine-like' nitrogen atom is around −125 p.p.m. in *N*-methylimidazole or oxazole. Additional nitrogen atoms in the

Table 11 ^{1}H NMR Spectral Data for Ring Hydrogens of Azolines (Non-aromatic Azoles with One Ring Double Bond)

Compound	*Substituents*	^{1}*H Chemical shifts* (δ, p.p.m.) *H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*Solvent*	*Coupling constants, J* (Hz)
Pyrazole								
2,3-Dihydro- [a]	1,2,3-trimethyl-	2.55	2.60	1.71	4.60	3.65	$CDCl_3$	3,5 = 1.8; 4,5 = 1.8
4,5-Dihydro-3*H*- [a]	—	—	—	4.27	1.46	4.27	Neat	—
4,5-Dihydro- [a]	—	5.33	—	6.88	2.65	3.31	$CDCl_3$	3,4 = 1.4; 4,5 = 9.8
1,2,3-Triazole								
4,5-Dihydro- [b,d]	—	—	—	—	5.35	4.77	—	4,5 = 2.0
[c,d]	—	—	—	—	5.73	4.60	—	4,5 = 7.5
1,2,4-Oxadiazole								
2,5-Dihydro- [e]	2,5-dimethyl-3-phenyl-	—	—	—	—	6.0	—	—
4,5-Dihydro- [f]	5-ethyl-3-phenyl-	—	—	—	5.38	5.64	—	4,5 = 4.5
1,3,4-Oxadiazole								
2,3-Dihydro- [a]	3-benzoyl-5-phenyl-	—	5.9	—	—	—	—	—
Thiazole								
2,5-Dihydro- [i]	—	—	4.79[g]	3.03[g]	6.12[g]	—	—	—
4,5-Dihydro- [j]	—	—	2.26	—	5.83	6.84	—	2,4 = 2.2; 4,5 = 8.6
1,3,4-Thiadiazole								
2,3-Dihydro- [k]	2,3,5-triphenyl-	—	—	—	—	6.38	—	—
1,2,4-Dioxazole								
2,3-Dihydro- [a]	3-carboxymethyl-5-phenyl-	—	—	6.39	—	—[l]	$CDCl_3$	—
1,3,4-Dioxazole								
2,3-Dihydro- [a]	2-benzyl-5-phenyl-	—	6.20	—	—	—[l]	$CDCl_3$	—
1,3,4-Oxathiazole								
2,3-Dihydro- [a]	5-methyl-2-trichloromethyl-	—	6.30	—	—	—[l]	$CDCl_3$	—
1,2,4-Dithiazole								
2,3-Dihydro- [a]	5-phenyl-	—	—	5.70	—	—[l]	CCl_4	—

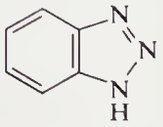
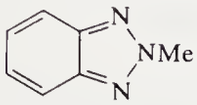
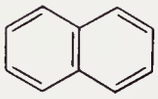
[a] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'. [b] Values given for *trans*-5-propyloxy-4-methyl-1-(4-nitrophenyl) derivative. [c] Values given for *cis* isomer of compound named in footnote b. [d] ⟨65CB1153⟩. [e] ⟨73BSF2996⟩. [f] ⟨77JOC1555⟩. [g] Value taken from 5,5-dimethyl-Δ^3-thiazoline. [h] Value taken from 2,2,4-trimethyl-Δ^3-thiazoline. [i] ⟨66BSF3524⟩. [j] ⟨64MI40100⟩. [k] ⟨81JCS(P1)360⟩. [l] Substituent in this position.

Table 12 ^{1}H NMR Spectral Data for Ring Hydrogens of Azolidines (Non-aromatic Azoles without Ring Double Bonds)

Compound	*Substituents*	^{1}*H Chemical shifts* (δ, p.p.m.) *H-2*	*H-3*	*H-4*	*H-5*	*Solvent*
Tetrahydro						
-pyrazole[a]	1,2-dimethyl-3-phenyl-	—	6.51	7.85	6.76	$CDCl_3$
-thiazole[b,c]	—	5.9	8.2	6.8	7.2	—
-1,2,4-oxadiazole[d]	2-*t*-butyl-3,4-diphenyl-5-thioxo-	—	5.93	—	—	—
-1,3,4-oxadiazole[e]	3,4-dimethyl-	4.27	—	4.27	—	—
-1,2,4-dioxazole[e]	3,5-di-*n*-propyl-	—	4.63	—	4.63	—
-1,3,2-dioxazole[e]	*N*-alkyl-	—[f]	—	3.97	3.97	—
-1,3,4-dioxazole[e]	2,5-di-*t*-butyl-4-phenyl-	4.96	—	—[f]	4.58	—
-1,2,4-dithiazole[e]	3,4-dialkyl-3-phenyl-	—	—[f]	—[f]	4.72	—
-1,3,2-dithiazole[e]	2-methyl-	—[f]	—	3.58	3.58	—

[a] ⟨71T133⟩. [b] $J_{4,5}$ values are $J_{A,B'} = J_{A',B} = 7.61$ Hz; $J_{A,B} = J_{A',B'} = 4.71$ Hz; $J_{5,5} = -13.7$ Hz; $J_{4,4} = -7.2$ Hz. [c] ⟨74JA1465⟩. [d] ⟨74JOC957⟩. [e] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'. [f] Substituent in this position.

Table 13 Proton–Proton Coupling Constants (Hz) in Benzotriazoles[a]

Compound	$J_{4,5}$	$J_{5,6}$	$J_{4,6}$
Benzotriazole[b]	8.3	6.7	1.4
2-Methylbenzotriazole	9.4	3.6	0.5
Naphthalene	8.6	6.0	1.4

[a] Data taken from ⟨71PMH(4)141⟩ which contains references to the original literature.
[b] Rapid tautomerism between 1- and 3-positions occurs.

Table 14 ^{13}C NMR Chemical Shifts for Nitrogenous Azoles: (a) NH Derivatives

Compound	^{13}*C Chemical shifts* (p.p.m.)[a] *C-2*	*C-3*	*C-4*	*C-5*	*Solvent*
Pyrazole[b]	—	134.6	105.8	134.6	CH_2Cl_2
Imidazole[c]	135.9	—	122.0	122.0	—
1,2,3-Triazole[b]	—	—	130.4	130.4	Me_2CO
1,2,4-Triazole[c]	—	147.8	—	147.8	—
Tetrazole[c]	—	—	—	144.2	—

[a] All chemical shifts expressed in p.p.m. from TMS (original values converted where necessary).
[b] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.
[c] Data taken from ⟨71PMH(4)121⟩, which contains references to the original literature.

Table 15 ^{13}C NMR Chemical Shifts for Nitrogenous Azoles: (b) *N*(1)-Methyl Derivatives

Compound	^{13}*C Chemical shifts* (p.p.m.)[a] *C-2*	*C-3*	*C-4*	*C-5*	*Solvent*	*Ref.*
Pyrazole	—	138.7	105.1	129.3	$CDCl_3$	[b]
Imidazole	138.3	—	129.6	120.3	—	74JOC357
1,2,3-Triazole	—	—	134.3	125.5	DMSO-d_6	[b]
1,2,3,4-Tetrazole	—	—	—	142.1	DMSO-d_6	74JOC357
1,2,3,5-Tetrazole	—	—	151.9	—	DMSO-d_6	74JOC357

[a] All chemical shifts expressed in p.p.m. from TMS (original values converted where necessary).
[b] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.

Table 16 ^{13}C NMR Chemical Shifts for Azoles Containing Oxygen[a]

Compound	^{13}*C Chemical shifts* (p.p.m.)[b] *C-2*	*C-3*	*C-4*	*C-5*	*Solvent*
Oxazole	150.6	—	125.4	138.1	$CDCl_3$
1,3,4-Oxadiazole[c]	159.5	—	—	166.3	—
1,2,5-Oxadiazoles[d]	—	139–160	—	—	—

[a] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.
[b] All chemical shifts expressed in p.p.m. from TMS (original values converted where necessary).
[c] Values given for 5-methoxy-2-methyl derivative.
[d] 3-Substituted 4-phenyl derivatives.

Table 17 ^{13}C NMR Chemical Shifts for Azoles Containing Sulfur

Compound	^{13}*C Chemical shifts* (p.p.m.)[a] *C-2*	*C-3*	*C-4*	*C-5*	*Solvent*	*Ref.*
Isothiazole	—	157.0	123.4	147.8	$CDCl_3$	[b]
Thiazole	153.4	—	143.7	119.7	—	79HC(34-1)76
1,2,3-Thiadiazole	—	—	147.3	135.8	$CDCl_3$	[b]
1,2,4-Thiadiazole	—	170.0	—	187.1	—	81JPR279
1,3,4-Thiadiazole 3-amino-5-methylthio-	152.7	—	—	152.7	$CDCl_3$	78BAP291
1,2,3,4-Thiatriazole 5-phenyl-	—	—	—	178.5	$CDCl_3$	[b]

[a] All chemical shifts expressed in p.p.m. from TMS (original values converted where necessary).
[b] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.

Table 18 ^{13}C NMR Chemical Shifts for Azolinones

Compound	^{13}*C Chemical shifts* (p.p.m.)[a] *C-2*	*C-3*	*C-4*	*C-5*	*Solvent*	*Ref.*
2-Pyrazolin-5-one 3-methyl-1-phenyl-	—	156.2	43.0	170.6	—	[b]
3-Pyrazolin-5-one 2,3-dimethyl-1-phenyl-	—	156.0	98.1	165.7	—	[b]
Imidazolin-2-one	183.8	—	44.4	44.4	DMSO-d_6	80CS(15)193
Imidazoline-2-thione	164.8	—	40.3	40.3	DMSO-d_6	80CS(15)193
Tetrazolin-5-one 1-phenyl-	—	—	—	148.7	—	[b]
Tetrazoline-5-thione	—	—	—	162.9	—	[b]
Δ^4-Thiazoline-2-thione	—	118.4	128.9	114.0	$CHCl_3$	79HC(34-1)388
1,2,3-Oxadiazolin-5-imine 3-methyl-	—	—	97.3	170.4	—	80RCR28
Δ^2-1,3,4-Oxadiazolin-5-one	145.7	—	—	155.7	—	82OMR(18)159
Δ^2-1,3,4-Thiadiazoline-5-thione	157.2	—	—	186.4	—	77JOC3725
1,3,4-Oxathiazolin-2-one 5-methyl-	174.2	—	—	158.7	—	[b]
1,2,4-Dithiazoline-3-thione 5-anilino-	—	209.3	—	179.1	—	[b]

[a] All chemical shifts expressed in p.p.m. from TMS (original values converted where necessary).
[b] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.

Table 19 ^{13}C NMR Chemical Shifts for Non-aromatic Azoles with Two Ring Double Bonds ⟨83UP40100⟩

Compound	^{13}*C Chemical shifts* (p.p.m.) *C-2*	*C-3*	*C-4*	*C-5*
4*H*-Pyrazoles	—	178–182	63–68	178–182
3*H*-Pyrazoles	—	93–110	125–150	130–170
2*H*-Imidazoles	101–119	—	158–165	158–165
4*H*-Imidazoles	163–181	—	66–115	180–190

Table 20 ^{13}C NMR Chemical Shifts for Azolines (Non-aromatic Azoles with One Ring Double Bond)

Compound	^{13}*C Chemical shifts* (p.p.m.)[a] *C-2*	*C-3*	*C-4*	*C-5*	*Ref.*
Δ^2-Pyrazoline	—	142.9	33.2	45.4	80TH40100
Δ^2-Imidazoline					
1-methyl-2-methylthio-	165.3	—	[b]	54.3	76TL3313
Δ^4-Imidazoline-2-thione					
1-methyl-	161.3	—	[b]	119.8	76TL3313
Δ^2-Thiazoline	229.4	—	321.7	354.7	70CR(C)(270)1688
1,3,4-Thiadiazoline					
2-benzylamino-5-phenyl-5-tosyl-	151.5	—	—	149.5	[c]
Δ^2-1,3,4-Oxathiazoline					
2-phenyl-5-trichloromethyl-	95.9	—	—	157.6	[c]
1,2,4-Dithiazoline	—	146.36[d]	—	156.19[e]	[c]

[a] All chemical shifts expressed in p.p.m. from TMS (original values converted where necessary).
[b] No C-4 shift reported.
[c] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.
[d] $^1J_{C,F} = 275.7$ Hz.
[e] $^3J_{C,F} = 15.9$ Hz.

Table 21 ^{13}C NMR Chemical Shifts for Azolidines (Non-aromatic Azoles without Ring Double Bonds)

Compound	^{13}*C Chemical shifts* (p.p.m.)[a] *C-2*	*C-3*	*C-4*	*C-5*	*Ref.*
Imidazoline-2-thione, 1-methyl-	183.2	—	[b]	50.4	76TL3313
Oxazolidine, *cis*-4-methyl-5-phenyl-	85.4	—	60.3	80.3	79MI40100
Thiazole, tetrahydro-	248.4	—	245.9	226.9	74CR(C)(279)717
1,3,4-Thiadiazolidine, 2,2-dimethyl-4-phenyl-					
5-phenylimino-	79.2	—	—	176.3	80JCS(P1)574
1,3,2-Dioxazole, tetrahydro-*N*-alkyl-	—	—	67.6	67.6	[c]
1,2,3-Oxathiazole, dihydro-*N*-phenyl, *S*-oxide	—	—	45.9	70.9	[c]

[a] All chemical shifts expressed in p.p.m. from TMS (original values converted where necessary).
[b] C-4 shift not reported.
[c] Data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.

ring cause small upfield shifts if they are non-adjacent, but sizable downfield shifts for adjacent nitrogen atoms. Adjacent ring oxygen gives a large downfield shift, but the effect of ring sulfur is less if adjacent.

A 'pyrrole-like' nitrogen in a ring *N*-methyl group gives a peak around −220 p.p.m. if adjacent to two carbon atoms; one or two neighboring nitrogens shift the peak downfield by about 40 and 90 p.p.m., respectively.

2.4.3.6 UV Spectroscopy

2.4.3.6.1 Parent compounds

In general, aza substitution (replacement of cyclic CH by N) has little effect on UV spectra (Table 23). Typically, aza analogues of pyrrole show λ_{max} at 217 nm or lower with log ε *ca.* 3.5, whereas aza analogues of thiophene show λ_{max} at 230–260 nm with log ε *ca.* 3.7 (Table 23); insufficient data are available for aza analogues of furan to generalize but these compounds appear to have maxima below 220 nm.

Relatively few data are available for protonated cationic species, but from what there are it appears that protonation has little effect on the position and intensity of the absorption.

2.4.3.6.2 Benzo derivatives

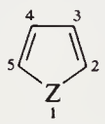
Benzo derivatives show at least two, and up to seven, maxima in the range 200–320 nm (Table 24). The longest wavelength maximum occurs at 275–315 nm and generally at rather longer wavelengths for the sulfur derivatives than for their N or O analogues, and also for the benzo[*c*] compared with the benzo[*b*] derivatives.

Table 22 ^{15}N NMR Chemical Shifts for Nitrogenous Azoles[a,b]

Nitrogen position(s)	*Positions of ring nitrogen*	*^{15}N Chemical shifts with heteroatom in 1-position* (p.p.m.) *NH*	*NMe*	*O*	*S*
2-Aza	1	−135	−181	—	—
	2	−135	−76	+3	−82
3-Aza	1	−173	−221	—	—
	3	−173	−125	−124	−57
2,3-Diaza	1	−128	−144	—	—
	2	−60	−15	−35[c]	—
	3	−60	−28	−106[d]	—
2,4-Diaza	1	−174	−173	—	−106
	2	—	−84	−20	−186[e]
	4	−132	−130	−140	−70
2,5-Diaza	1	−128	−132	—	—
	2,5	−60	−53	+33	−35
3,4-Diaza	1	—	−222	—	—
	3,4	—	−82	−82	−10
2,3,4-Triaza	1	−106	−159	—	—
	2	−15	−14	—	—
	3	−25	+9	—	—
	4	−106	−54	—	—
2,3,5-Triaza	1	—	−99	—	—
	2	—	−4	—	—
	3	—	−43	—	—
	5	—	−69	—	—

[a] Chemical shifts expressed in p.p.m. referred to internal $MeNO_2$.
[b] Data taken from ⟨B-73MI40100⟩ or ⟨81MI40100⟩, which contain references to the original literature.
[c] Value for 3-methylsydnone ⟨80OMR(13)274⟩.
[d] Value for 5-acetyl-3-methylsydnonimine ⟨80OMR(13)274⟩.
[e] Value for 2-amino-5-methyl-1,3,4-thiadiazole ⟨78H(11)121⟩.

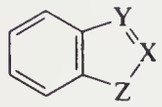
Table 23 UV Absorption Maxima for Azoles[a]



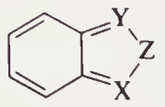
Additional nitrogen atoms	*Z = NH* λ_{max} (nm) (log ε)	*Z = O* λ_{max} (nm) (log ε)	*Z = S* λ_{max} (nm) (log ε)
2	210 (3.53)	211 (3.60)	244 (3.72)
3	207–208 (3.07) end absorption	240	207.5 (3.41), 233 (3.57)[b]
2,3-di	210 (3.64)	—	211 (3.64), 249 (3.16), 294 (2.29)[c]
2,4-di	216.5 (3.66)	—	229 (3.73)
2,5-di	—	220	250 (3.86), 253 (3.87), 257 (2.83), 260 (3.68)[d]
3,4-di	—	200[e]	220
2,3,4-tri	205	—	280 (4.03)[f]

[a] Unless otherwise indicated data taken from ⟨71PMH(3)67⟩ which contains references to the original literature.
[b] Measured in ethanol.
[c] Measured in cyclohexane.
[d] Measured in isooctane; *cf.* CHEC 4.26.2.4.
[e] 2-Methyl-1,3,4-oxadiazole exhibits a maximum at 206 nm (log ε 2.62) in MeOH; *cf.* CHEC 4.23.2.2.2.
[f] 5-Phenyl-1,2,3,4-thiatriazole.

Table 24 UV Absorption Maxima for Benzazoles[a]



X	Y	Z = NH λ_{max} (nm) (log ε)	Z = O λ_{max} (nm) (log ε)	Z = S λ_{max} (nm) (log ε)
N	CH	250 (3.65), 284 (3.63), 296 (3.52)	235 (4.00), 243 (3.91), 280 (3.46)	205 (4.20), 222 (4.37), 252 (3.56), 261 (3.39), 297 (3.58), 302 (3.57), 3.08 (3.56)[b]
CH	N	242 (3.72), 265 (3.58), 271 (3.70), 277 (3.69)	231 (3.90), 263 (3.38), 270 (3.53), 276 (3.51)	217 (4.27), 251 (3.74), 285 (3.23), 295 (3.13)
N	N	259 (3.75), 275 (3.71)	[c]	213.5 (4.20), 266 (3.72), 312.5 (3.40)
S^+	N	—	—	238 (3.91), 350 (4.35), 425 (3.29)[d]



X	Y	Z = NMe λ_{max} (nm) (log ε)	Z = O λ_{max} (nm) (log ε)	Z = S λ_{max} (nm) (log ε)
N	CH	275 (3.80), 292 (3.79), 295 (3.78)	—	203 (4.16), 221 (4.21), 288s (3.88), 298 (3.46), 315s (3.60)[e]
N	N	274 (3.96), 280 (3.98), 285 (3.97)	310 (3.5), 275 (3.6)	221–222 (4.16), 304 (4.14), 310 (4.14), 330s (3.39)

[a] Unless otherwise indicated data taken from ⟨71PMH(3)67⟩ which contains references to the original literature.
[b] ⟨73JHC267⟩.
[c] Unknown; see Scheme 2 in CHEC 4.21.1.
[d] In concentrated H_2SO_4 ⟨69ZOR153⟩.
[e] Data taken from CHEC 4.17.3.6.

2.4.3.6.3 Effect of substituents

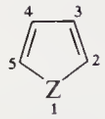
Although UV spectra have been measured for a large number of substituted azoles, there has been no systematic attempt to explain substituent effects on such spectral maxima. Readily available data are summarized in Table 25, and some major trends are apparent. However, detailed interpretation is hindered by the fact that different solvents have been used and that in aqueous media it is not always clear whether a neutral, cationic or anionic species is being measured. Furthermore, values below 220 nm are of doubtful quantitative significance.

2.4.3.7 IR Spectroscopy ⟨71PMH(4)265, 63PMH(2)161⟩

2.4.3.7.1 Aromatic rings without carbonyl groups

For many of the parent compounds, complete assignments have been made ⟨71PMH(4)265⟩. For substituted derivatives, group frequencies have been derived. In the ring systems under discussion, IR bands may be placed in the following categories. (a) CH stretching modes near 3000 cm^{-1} which are of little diagnostic utility. (b) Ring stretching modes at 1650–1300 cm^{-1} (Table 26), four or five bands generally being found which lie in well-defined regions. The intensities of these bands vary according to the nature and orientation of substituents. (c) CH and ring deformation modes at 1300–1000 cm^{-1} (Table 27) and at 1000–800 cm^{-1} (Table 28). The former are largely in-plane CH and the latter out-of-plane CH and in-plane ring deformation modes. (d) Substituent vibrations: these are discussed later.

Table 25 Effects of Substituents on UV Absorption Maxima (nm)[a,b]



		Z = NH Substituent position				*Z = O* Substituent position				*Z = S* Substituent position			
Substituent	*Aza positions*	*2*	*3*	*4*	*5*	*2*	*3*	*4*	*5*	*2*	*3*	*4*	*5*
Me	2	—	213	220	(≡3)	—	217	221	213	—	246.5	251[c]	243[c]
	3	210	—	215	(≡4)		—			235	—	241	239
	2,3	—	—	216	(≡4)	—	—			—	—	213	217
	2,4	—	<220	—	(≡3)	—		—		—		—	
	2,5	—	—	—	—	—		(≡3)	—	—	257[m]	(≡3)	—
	3,4	—	—	—	—	206	—	—	(≡2)	<230	—	—	(≡2)
Ph	2	—	248	250.5	(≡3)	—	239		260	—	270, 291	266[d]	266[d]
	3	271	—	260	(≡4)	263	—	243	267	287	—	252	275
	2,3	—	—	245	(≡4)	—	310[e]			—	—		
	2,4	—	241.5	—	(≡3)	—	238[e]	—	250[e]	—		—	
	2,5					—		(≡3)	—	—	280[m]	(≡3)	
	3,4					247.5	—	—	(≡2)	268	—	—	(≡2)
	2,3,4	—	—	—	241	—	—	—		—	—	—	

Br (Cl)	2	—		221	(≡3)	—				—	(244)[f]	256[c]	241[c]
	3	220*	—	217	(≡4)		—			245	—	246	247
OMe (OH)	2	—			(≡3)	—	220			—	255[g]		
	3		—		(≡4)		—			239	—		
	2,3	—	—	234*	(≡4)	—	—			—	—		
	2,5					—		(≡3)	—	—	273	(≡3)	—
	2,3,4	—	—	—	213*	—	—	—		—	—	—	
NH_2 (NMe_2)	2	—	228		(≡3)	—	228.5		245.5	—	278[h]	286[c]	(258)
	3		—	230*	(≡4)		—			254.4*	—		
	2,3	—	—	228	(≡4)	—	—			—	—		
	2,4	—	<220	—	(≡3)	—		—		—		—	247[i]
	3,4						—	—	(≡2)	251	—	—	(≡2)
	2,3,4	—	—	—	218	—	—	—		—	—	—	
CO_2Me (CO_2H, CHO)	2	—	217		(≡3)	—		216[j]	244	—	256	(250)[f]	263[c]
	3	285	—	256.5	(≡4)		—				—	230	
	2,5	—		—	(≡3)	—		(≡3)	—	—	263[m]	(≡3)	—
	3,4					243[k]	—	—	(≡2)		—	—	(≡2)
NO_2	2	—	261	275	(≡3)	—		239		—		272	
	3	325	—	298	(≡4)		—				—		
	2,4	—	215, 245[l]	—	(≡3)	—		—		—		—	
	2,5					—		(≡3)	—	—		(≡3)	—

[a]Unless otherwise indicated, data taken from ⟨71PMH(3)67⟩, which contains references to the original literature. A dash indicates that a substituent cannot be in that position; a blank means that the value has not been reported. [b]Asterisk (*) indicates, exceptionally, acidified or basified solvent; for details, see references quoted in ⟨71PMH(3)67⟩. [c]⟨64JCS446⟩. [d]In cyclohexane ⟨66T2119⟩. [e]⟨64HCA942⟩. [f]Value based on 'average increment' observed for a large number of compounds; *cf.* CHEC 4.17. [g]⟨70T2497⟩. [h]Perchlorate salt in MeOH ⟨71JHC657⟩. [i]⟨54CB57⟩. [j]2-Benzyl-5-methyl derivative. [k]2-Benzyl-5-methyl derivative. [l]In water. [m]*cf.* CHEC 4.26.2.4.

Table 26 Azoles: IR Ring Stretching Modes in the 1650–1300 cm^{-1} Region[a]

Compound	*Stretching modes* (cm^{-1})				
Isoxazoles	1650–1610	1580–1520	1510–1470	1460–1430	1430–1370
Isothiazoles	—	—	1488	1392	1342
Pyrazoles	—	1600–1570	1540–1510	1490–1470	1380–1370
Oxazoles	1650–1610	1580–1550	1510–1470	1485	1380–1290
Thiazoles	1625–1550	—	1550–1470	1440–1380	1340–1290
Imidazoles	1605	1550–1520	1500–1480	1470–1450	1380–1320
1,2,4-Oxadiazoles	—	1590–1560	—	1470–1430	1390–1360
1,2,5-Oxadiazoles	—	1630–1560	1530–1515	1475–1410	1395–1370
1,3,4-Oxadiazoles	1680–1650	1630–1610	1600–1580	1430–1410	—
1,2,4-Thiadiazoles	—	1590–1560	1540–1490	—	—
1,2,3-Thiadiazoles	1650–1590	—	1560–1420	1350–1325	1260–1180
1,2,5-Thiadiazoles[b]	—	—	—	1461	1350
1,2,3,4-Thiatriazoles	1720–1690	1610–1530	—	—	1300–1260
1,2,3-Triazoles	1650–1615w	—	1530–1485	1440w	1420–1400w
1,2,4-Triazoles	—	—	1545–1535	1470–1460	1365–1335
Tetrazoles	1640–1615	—	1450–1410	1400–1335	1300–1260

[a] Data taken from ⟨71PMH(4)265⟩, which contains references to the original literature; w = weak.
[b] Data taken from CHEC 4.26.2.5.

Table 27 Azoles: Characteristic IR Bands in the 1300–1000 cm^{-1} Region[a]

Compound	*β(CH) modes* (cm^{-1})			*Ring breathing* (cm^{-1})
Isoxazoles	1218m	1155–1130	1088s	1028–1000
Isothiazoles	—	1070m	1060m	980s
Pyrazoles	1310–1130	1160–1090	1090–990	1040–975
Thiazoles	1240–1230	1160–1075	1105–1055	1040
Imidazoles	1285–1260	1140	1100	1060
1,2,4-Oxadiazoles	—	—	1070–1050	—
1,2,5-Oxadiazoles	1360–1175	1190–1150	1160–1150	1035–1000
1,2,4-Thiadiazoles	1270–1215	1185–1170	1160–1080	1050
1,2,3-Thiadiazoles	—	—	1150–950	—
1,2,5-Thiadiazoles[b]	1251–1227	—	1041	—
1,3,4-Thiadiazoles	1230–1165	1190–1120	1075–1045	1040
1,2,3,4-Thiatriazoles	1235–1210	1120–1090	1060–1030	—
1,2,3-Triazoles	1300–1275	1150–1070	1095–1045	1005–970
Tetrazoles	1210–1110	1170–1035	1060	995–900

[a] Data taken from ⟨71PMH(4)265⟩, which contains references to the original literature; s = strong, m = medium, w = weak.
[b] Data taken from CHEC 4.26.2.5.

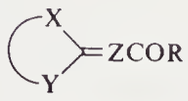
Table 28 Azoles: Characteristic IR Bands below 1000 cm^{-1} [a]

Compound	*CH modes* (?) (cm^{-1})		*β-Ring* (?) (cm^{-1})	*CH modes* (?) (cm^{-1})
Isoxazoles	970–920	899	945–845	774
Isothiazoles	915w	—	810s	740vs
Pyrazoles	960–930	860–855	805–790	765–750
Thiazoles	980–880	890–785	800–700	745–715
Imidazoles	970–930	895	840	760
1,2,4-Oxadiazoles	—	—	915–885	750–710
1,2,5-Oxadiazoles	980–900	—	890–825	715–700
1,2,3-Thiadiazoles	—	—	910–890	—
1,2,4-Thiadiazoles	1030–935	890	860–795	750–740
1,2,5-Thiadiazoles	—	—	860–800	780[b]
1,3,4-Thiadiazoles	975–905	905–875	850	775–750
1,2,3,4-Thiatriazoles	960–930	—	910–890	—
1,2,3-Triazoles	—	855–825	970–700	—
1,2,4-Triazoles	—	—	865–855(?)	—
Tetrazoles	960	—	—	810–775

[a] Data taken from ⟨71PMH(4)265⟩ which contains references to the original literature; vs = very strong, s = strong, w = weak.
[b] Data taken from CHEC 4.26.2.5.

2.4.3.7.2 Azole rings containing carbonyl groups

The carbonyl group is found in a wide variety of situations in five-membered rings accommodating diverse heteroatoms. Carbonyl frequencies to be discussed range from about 1800 to below 1600 cm^{-1}; some such frequencies are so low that they often fail to be recognized as carbonyl absorptions at all, *e.g.* carbonyl joined to a heterocyclic ring *via* an exocyclic double bond as in structure (**99**). Low frequency υ(C=O) bands are widespread because five-membered heterocyclic rings are inherently π-electron donors. The transfer of electrons into the exocyclic double bond [υ(C=Z) of **99**] is likely to be extensive when both X and Y are electron donor atoms.



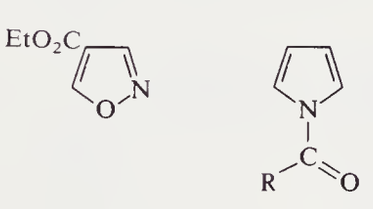
(**99**)

In Table 29 the υ(C=O) and other characteristic bands are given for some saturated five-membered heterocycles, and compared with the corresponding absorption frequencies for cyclopentanone. Adjacent NH groups and sulfur atoms have the expected bathochromic effect on υ(C=O), whereas an adjacent oxygen atom acts in the reverse direction. The CH_2 vibrations of cyclopentanone are repeated to a considerable extent in the heterocyclic analogues.

Table 30 reports υ(C=O) for a variety of azolinones containing ring double bonds. The hypsochromic effect of an oxygen atom or CR_2 group *versus* the bathochromic effect of NR, S or C=C can readily be traced.

2.4.3.7.3 Substituent vibrations

In general, substituent frequencies in azoles are consistent with those characteristic of the same substituents in other classes of compounds. Some characteristic trends are found, and these have been used to measure electronic effects. Thus, for example, the frequencies of υ(C=O) in 3-, 4- and 5-alkoxycarbonylisoxazoles (*cf.***100**) are respectively 9–12, 2–8 and 17–18 cm^{-1} higher than those of the corresponding alkyl benzoates, indicating the following order of electron donor power: phenyl > 4- > 3- > 5-position of isoxazole. Similar work has been reported for other ring systems and substituents ⟨63PMH(2)161⟩.



(**100**) (**101**) (**102**) (**103**)

Otting ⟨56CB1940, 57MI40100⟩ has shown that the υ(C=O) for acetylazoles (*cf.***101**) increases with the number of cyclic nitrogen atoms (Table 31). Additional nitrogen atoms in the ring act as powerful electron-withdrawing substituents and decrease the importance of forms such as (**102**). Staab *et al.* ⟨57MI40100⟩ give data for benzo analogues (Table 31) and show that υ(C=O) values for substituted benzoyl-imidazoles (**103**) and -triazoles follow the Hammett equation. For data on *N*-acylpyrazoles, see reference ⟨59MI40100⟩.

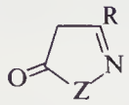
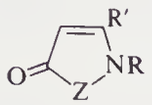
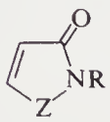
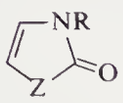
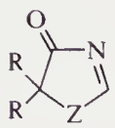
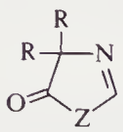
Substituent vibrations in IR spectra have been extensively used to determine tautomeric structure, particularly C=O, NH, OH and SH stretching modes. For example, 3-hydroxyisoxazoles show broad υ(OH) at 2700 cm^{-1} (dimers). Boulton and Katritzky developed a technique for determining the structure of potentially tautomeric amino compounds by partial deuterium exchange. If the compound under investigation contains an amino group, the change from NH_2 to NHD produces a new single υ(NH) at a frequency between those of the original doublet for asymmetrical and symmetrical $\upsilon(NH_2)$. If the compound does not contain an amino group and the two bands are derived from two separate NH groups, there should be no new band between the original two in the partially deuterated derivative. The method was applied to aminoisoxazoles ⟨61T(12)51⟩.

Table 29 IR Absorption Assignments for 2,5-Dihetero Derivatives of Cyclopentanone[a]

C=X:	*C=O*	*C=O*	*C=S*	*C=O*	*C=O*	*C=S*	*C=S*	*C=O*	*C=S*	*C=O*	*C=S*
2-Position:	*CH_2*	*CH_2*	*CH_2*	*O*	*S*	*S*	*O*	*O*	*S*	*NH*	*NH*
5-Position:	*O*	*N*	*N*	*O*	*S*	*S*	*NH*	*NH*	*NH*	*NH*	*NH*
Vibration type	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})
ν(C=X)	1770	1695	1109	1795	1638	1058	1171	1724	1047	1661	1208
CH_2 scissors	1490	1494	1478	1483	1434	1416	1464	1485	1458	1488	1459
	1466	1440	1458	1422	1422	1370	1402	1412	1432	1449	1368
	1426	1426	1420	1394					1380		
	1379	1378									
CH_2 wag	1284	1270	1309	1226	1275	1275	1319	1333	1250	1200	—
	1242	1230	1215		1254	1243	1230	1230	1203		
CH_2 twist	1192	1169	1168	1175	1158	1148	1203	—	1160	—	—
CH_2 rock	990	995	970	1005	983	983	969	967	998	988	980
ν ring	1166	1285	1290	1140	888	882	1290	1250	1294	1270	1273
	1037	1068	1059	1071	826	831	1035	1077	1080	1103	1042
	890	915	915	971	677	670	942	1021	650	1037	1003
	929	887	880	894	939	946	914	918	927	933	919
γ ring	800	805	493	773	—	457	—	770	—	768	—

[a] Data taken from ⟨63PMH(2)161⟩, which contains references to the original literature.

Table 30 ν(C=O) Frequencies for Some Azolinones[a]

Ring system substituent(s) R = H or Me	*Z = NH* (cm^{-1})	*Z = O* (cm^{-1})	*Z = S* (cm^{-1})
	1705–1695[b]	—	—
	1680–1630	—	—
	—	—	1660[c]
	1684–1677[d]	1780–1750	1640[e]
	—	1770–1740	1780–1700
	—	*ca.* 1820	1725[f]

[a] Unless otherwise indicated, data taken from appropriate chapter, 'Comprehensive Heterocyclic Chemistry'.
[b] Z = NR', R' = alkyl, aryl.
[c] R = Me ⟨64TL1477⟩.
[d] Data taken from ⟨63PMH(2)161⟩ which contains references to the original literature.
[e] ⟨79HC(34-2)421⟩.
[f] ⟨79HC(34-2)430⟩.

Table 31 Carbonyl Frequencies for *N*-Acetylazoles[a]

N-Acetylazole	ν(C=O) (cm^{-1})	*N-Acetylazole*	ν(C=O) (cm^{-1})
Pyrrole	1732	Indole	1711
Imidazole	1747	Benzimidazole	1729
1,2,4-Triazole	1765	Benzotriazole	1735
Tetrazole	1779		

[a] Data taken from ⟨56CB1940⟩ and ⟨57MI40100⟩ which contain references to the original literature.

2.4.3.8 Mass Spectrometry ⟨66AHC(7)301, B-71MS⟩

Among the most important fragmentation pathways of the molecular ions of azoles are the following.

(a) Loss of RCN or HCN; this occurs particularly readily for systems containing (**104**), *i.e.* imidazoles and thiazoles. It does not occur so readily for oxazoles, but is found again in the 1,2,4-oxadiazoles (**105**) and also for pyrazoles (**106**).

(b) Loss of RCO^+; this is important for systems (**107**) in oxazoles and in 1,3,4-oxadiazoles. It is also found in isoxazoles, where it probably occurs after skeletal rearrangement of the isoxazole *via* (**108**) into an isomeric oxazole.

(c) Loss of NO^+ and/or NO· occurs for furazans (**109**) and sydnones (**110**).

Table 32 Melting and Boiling Points[a,b,c]

Ring system	*H*	*Me*	*Et*	*COMe*	*CO_2H*	*CO_2Et*	*$CONH_2$*	*CN*	*NH_2*	*OH*	*OMe*	*SH*	*SMe*	*Cl*	*Br*
Benzene	80	111	136	212	**122**	211	**130**	190	184	**43**	154	168	187	131	155
Pyrrole-1	130	114	129	180	**95d**	180	**166**	—	—	—	—	—	—	—	—
Pyrrole-2	130	148	181	**90**	**205d**	39	**174**	—	—	**83**[g]	—	—	—	—	—
Pyrrole-3	130	158	179	**115**	**148**	**78d**	**152**	—	—	—	—	—	208–14	—	—
Furan-2	31	64	92	**31**	**133**	**34**	**142**	147	**68**	**80**	110	—	—	78	103
Furan-3	31	65	—	**54**	**122**	179	**168**	—	—	**58**	—	—	—	80	103
Thiophene-2	84	113	133	214	**129**	218	**180**	196	214	217	156	166	—	128	150
Thiophene-3	84	115	135	**57**	**138**	208	**178**	179	—	—	—	171	—	136	157
Pyrazole-1	**70**	127	137	234	103	213	141	37	—	—	—	—	—	—	—
Pyrazole-3	**70**	205	209	**101**	**214d**	**160**	**148**	**150**	**40**	**166**	—	—	>370[d]	**40**	**70**
Pyrazole-4	**70**	207	244	**114**	**278**	**79**	—	**92**	**81**	**118**	**62**	—	—	**77**	**97**
Isoxazole-3	95	118	139	**16**	**149d**	—	**134**	168	—	—	—	—	—	—	—
Isoxazole-4	95	127	—	—	—	—	—	—	—	—	—	—	—	—	130
Isoxazole-5	95	121	—	**52**	**149**	—	**174**	—	—	—	—	—	—	—	—
Imidazole-1	**90**	199	226	**102**	—	218	—	—	—	—	—	—	—	—	—
Imidazole-2	**90**	**141**	**80**	**80**	**164d**	—	—	—	—	**250d**	—	**227**	**139**	**165**	**207**
Imidazole-4	**90**	**56**	—	—	**275d**	**157**	**215**	—	—	—	—	—	—	—	130
Oxazole-2	69	87	—	—	—	—	—	—	97	—	—	—	—	—	—
Oxazole-4	69	—	—	—	**142**	**48**	—	—	—	—	—	—	—	—	—
Thiazole-2	118	128	158	226	**102d**	**48**	118	**31**	**92**	—	164	**79**	230	145	147
Thiazole-4	118	133	—	**56**	**196**	**52**	**150**	**60**	—	—	—	—	—	165	190
Thiazole-5	118	141	**142**	—	**218**	217	**186**	**53**	**83**	—	176	—	222	140	192
1,2,3-Triazole-1	206	228	238	—	—	—	—	—	**51**	—	—	—	—	—	—
1,2,4-Triazole-1	**121**	**20**	199	**40–2**	—	230	**138**	—	—	—	—	—	—	**81–2d**	**136–8d**
1,2,4-Triazole-3	**121**	**95**	65–6	—	**137**	**178**	**312**	**187**	**159**	**234**	oil	**216**	**105**	**167**	**189**

1,2,4-Triazole-4	**121**	**90**	oil	—	—	—	—	—	**76–7**	—	—	—	—	—	—
Tetrazole-5	**156**	**148**	—	—	—	**86**	**234**	**99**	**203**	**260**	**154**	**205**	**151**	**73**	**148**
Tetrazole-1	**156**	**39**	265	—	—	—	—	—	>370	—	—	—	—	—	—
Tetrazole-2	**156**	147	163	—	—	—	—	—	>370	—	—	—	—	—	—
Isothiazole-3	113	134	—	**32**	**135**	290	**154**	**60**	**33**	**74**	147	—	—	160	—
Isothiazole-4	113	146	—	—	**161**	**174**	**192**	**94**	**45**	—	—	—	—	143	**34**
Isothiazole-5	113	142	—	250	**201d**	—	**172**	**47**	**112**	—	—	—	—	149	150
1,2,3-Oxadiazole (sydnone)	—	36	340	—	—	—	—	—	—	—	—	—	—	—	—
1,2,4-Oxadiazole-3	87	105	—	—	—	—	—	—	—	—	—	—	—	—	—
1,2,4-Oxadiazole-5	87	104	—	—	—	—	—	—	—	—	—	—	—	—	—
1,3,4-Oxadiazole-2	150	164	174.5	—	—	255	—	—	**156**	**120**	—	**89–91**	—	—	—
1,2,3-Thiadiazole-4	160	**87–9**	—	**140**	**227–8**	**86**	**220–2**	**62–3**	**44–6**	—	—	—	—	170	—
1,2,3-Thiadiazole-5	160	—	—	—	**104–6**	222	—	—	145–7	—	—	—	—	—	—
1,2,4-Thiadiazole-3	121	132	—	—	—	—	—	—	—	—	—	—	**32**	—	—
1,2,4-Thiadiazole-5	121	—	—	—	—	—	—	—	**119**	**120**	—	**93**	220	122	—
1,2,3,4-Thiatriazole-5	—	—	—	—	—	—	—	—	**128–30**	—	**44–5d**[e]	**50–65d**	**34**	expl.[f]	—
1,3,4-Thiadiazole	**43**	201d	—	—	—	—	**221**	—	**193**	—	—	**143**	—	**33**	**73**
1,3-Dioxole-4	51	76	—	—	—	—	—	—	—	—	—	—	—	—	—
1,2-Dithiol-3-one-4	>370	>370	>370	—	—	—	—	—	**79.5–80.5**	—	—	—	—	**62–3**	—
1,2-Dithiol-3-one-5	>370	—	—	—	**214–6**	>370	**223**	—	—	—	—	—	—	—	—
1,2,4-Trioxolane-3,3-di	116	88	—	—	—	—	—	—	—	—	—	—	—	—	—
1,2,4-Trioxolane-3,5-di	116	90	140	—	—	**42**	—	—	—	—	—	—	—	—	—
1,2,4-Trithiolane-3,5-di	78	>200	>230	—	—	—	—	—	—	—	—	—	—	—	—

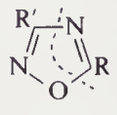
[a] Melting points above 30 °C are given in bold; melting points below 30 °C are not included.
[b] Boiling points are given at atmospheric pressure to facilitate comparison; those reported at other than atmospheric pressure were converted using a nomogram ⟨57MI40101⟩.
[c] A dash indicates that the compound is unstable, unknown, or the data are not readily available.
[d] Value given for EtS derivative.
[e] Value given for EtO derivative.
[f] Explodes.
[g] Value given for the monohydrate.

(d) Loss of N_2 from triazoles and tetrazoles (but *not* pyrazoles).

(e) Whenever the structural element (**111**) occurs, a McLafferty rearrangement can take place (**111**→**112**).

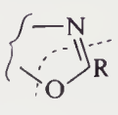
(f) Isothiazoles are rather stable and show intense molecular ions with some HCN loss, probably *via* rearrangements analogous to (**108**) to give thiazoles.

(**104**) X = S or NR′

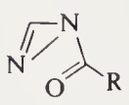


(**105**)

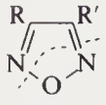
(**106**)



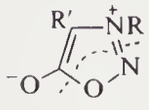
(**107**)



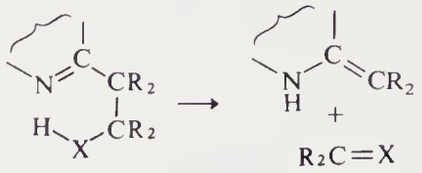
(**108**)



(**109**)



(**110**)



(**111**) (**112**)

There are correlations between mass spectral fragmentations and thermal and photochemical fragmentations and rearrangements; see Sections 3.4.1.2.1 and 3.4.1.2.2.

2.4.3.9 Photoelectron Spectroscopy ⟨74PMH(6)1⟩

In this method, photons of an energy well in excess of the ionization potential are directed onto a molecule. The photoelectron spectrum which results allows assessment of the energies of filled orbitals in the molecule, and thus provides a characterization of a molecule. Comparisons between photoelectron spectra of related compounds give structural information, for example, on the tautomeric structure of a compound by comparison of its spectrum with those of models of each of the fixed forms.

Photoelectron spectra have been discussed and assigned in the following series: pyrazole (CHEC 4.04.1.4.9), 1,2,3-triazole (CHEC 4.11.3.2.9), isothiazole (CHEC 4.17.2.2), 1,3,4-oxadiazole (CHEC 4.23.2.2.5), 1,2,5-thiadiazole (CHEC 4.26.2.2), 1,3,4-thiadiazole (CHEC 4.27.2.3.10), 1,3-dioxolane (CHEC 4.30.1.4.5), 1,2-dithiole (CHEC 4.31.1.4), and 1,2,4-trioxolane and 1,2,4-trithiolane (CHEC 4.33.2.2.5).

2.4.4 THERMODYNAMIC ASPECTS

2.4.1.1 Intermolecular Forces

2.4.4.1.1 Melting and boiling points

In the parent unsubstituted ring systems (*cf.* first column of Table 32) replacement of a —CH=CH— group with a sulfur atom has little effect, and replacement of a —CH=CH— group with an oxygen atom lowers the boiling point by *ca.* 40 °C.

Introduction of nitrogen atoms into the ring is accompanied by less regular changes. Substitution of either a —CH=CH— group by an NH group or of a =CH— group by a nitrogen atom increases the boiling point. When both of these changes are made simultaneously the boiling point is increased by an especially large amount due to the possibilities of association by hydrogen bonding.

The effect of substituents on melting and boiling points can be summarized as follows.

(a) Methyl and ethyl groups attached to ring carbon atoms usually increase the boiling point by *ca.* 20–30 and *ca.* 40–60 °C, respectively. However, conversion of an NH group into an NR group results in large decreases in the boiling point (*e.g.* pyrazole to 1-methylpyrazole) because of decreased association.

(b) The acids and amides are all solids. Many of the amides melt in the range 130–180 °C; the melting points of the acids vary widely.

(c) Compounds containing a hydroxy, mercapto or amino group are usually relatively high-melting solids. For many hydroxy and mercapto compounds this can be attributed to their tautomerism with hydrogen-bonded 'one' and 'thione' forms. However, hydrogen bonding can evidently also occur in amino compounds.

(d) Methoxy, methylthio and dimethylamino derivatives are often liquids.

(e) Chloro compounds are usually liquids which have boiling points similar to those of the corresponding ethyl compounds. Bromo compounds boil approximately 25 °C higher than their chloro analogues.

2.4.4.1.2 Solubility of heterocyclic compounds ⟨63PMH(1)177⟩

In general, the solubility of heterocyclic compounds in water (Table 33) is enhanced by the possibility of hydrogen bonding. 'Pyridine-like' nitrogen atoms facilitate this (compare benzene and pyridine). In the same way, oxazole is miscible with water, and isoxazole is very soluble, more so than furan.

Table 33 Solubilities of Some Five-membered Heterocycles in Water at 20 °C[a]

Compound	*Parts soluble in 1 part of water*	*Compound*	*Parts soluble in 1 part of water*
Furan	0.03	Pyrrole	0.06
Isoxazole	0.02	Pyrazole	0.40
Oxazole	Misc.[b]	2-amino-4-hydroxy-	0.009
Benzoxazole	0.008	Imidazole	1.8
Sydnone	—	2,5-dihydroxy-	0.02
3-methyl-[c]	Misc.	1-methyl-	Misc.
1,2,4-Oxadiazole[d]	Misc.	1,2,4-Triazole	1
Thiophene	0.001	3-amino-	0.3
Isothiazole	0.03	3-hydroxy-	0.05
Thiazole	—	Tetrazole	1
2-methyl-	Misc.	Benzimidazole	0.002
2-amino-	0.05	Indazole	0.0008
1,2,3-Thiadiazole	0.03	3-hydroxy-	0.002
1,3,4-Thiadiazole	Misc.	Purine	0.5

[a] Unless otherwise indicated, data taken from ⟨63PMH(1)177⟩ or from appropriate chapter, 'Comprehensive Heterocyclic Chemistry', which contain references to the original literature.
[b] Misc. = miscible.
[c] At 40 °C ⟨80JCS(P2)553⟩.
[d] ⟨65MI40100⟩.

The effect of amino, hydroxy or mercapto substituents is to increase hydrogen bonding properties. However, if stable hydrogen bonds are formed in the crystal, then this can decrease their solubility in water ⟨63PMH(1)177⟩, *e.g.* indazole and benzimidazole are less soluble than benzoxazole.

Other solvents can be divided into several classes. In hydrogen bond-breaking solvents (dipolar aprotics), the simple amino, hydroxy and mercapto heterocycles all dissolve. In the hydrophobic solvents, hydrogen bonding substituents greatly decrease the solubility. Ethanol and other alcohols take up a position intermediate between water and the hydrophobic solvents ⟨63PMH(1)177⟩.

2.4.4.1.3 Gas–liquid chromatography ⟨71PMH(3)297⟩

Gas–liquid chromatography has been widely used for the identification of reaction mixtures and for the separation of heterocycles. Some typical conditions are shown in Table 34.

2.4.4.2 Stability and Stabilization

2.4.4.2.1 Thermochemistry and conformation of saturated heterocycles ⟨74PMH(6)199⟩

Calculation of group increments for oxygen, sulfur and nitrogen compounds has allowed the estimation of conventional ring-strain energies (CRSE) for saturated heterocycles from enthalpies

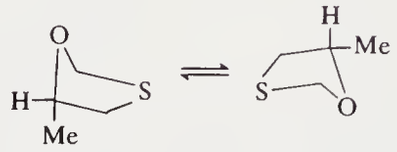
Table 34 Operating Conditions for GLC Separation of Five-membered Heterocycles with More Than One Heteroatom[a]

Compound	*Conditions*
Pyrazolines	10% Cyanethylated mannite on Celite 545.
Imidazoles	5% OV-17 on Chromosorb W, AW-DMCS (H.P.).[b]
Thiazoles	Carbowax 4000, dioleate on firebrick, 190 °C.
Oxadiazoles	Silicone grease on Chromosorb P.
1-Phenylpyrazoles	Apiezon L on firebrick C-22, 220 °C.
Purines	15% Hallcomid M-18 on firebrick.
Dioxolanes	Carbowax 20M on Gas-Chrom P.
Oxazolines	Ethyleneglycol succinate on Diatoport-S.

[a] Data taken from ⟨71PMH(3)297⟩, which contains references to the original literature.
[b] Simple alkyl- and aryl-imidazoles. *N*-Unsubstituted compounds are *N*-acylated prior to injection.

of formation. For 1,3-dioxolane, CRSE is about 20 kJ mol^{-1}. In 2,4-dialkyl-1,3-dioxolanes the *cis* form is always thermodynamically the more stable by approximately 1 kJ mol^{-1}.

For 1,3-dithiolanes the ring is flexible and only small energy differences are observed between the diastereoisomeric 2,4-dialkyl derivatives.The 1,3-oxathiolane ring is less mobile and pseudoaxial 2- or 5-alkyl groups possess conformational energy differences (*cf.* **113**⇌**114**); see also the discussion of conformational behavior in Section 2.4.4.3.



(**113**) 13% (*a*) (**114**) 87% (*e*)

2.4.4.2.2 Aromaticity

This subject has been dealt with in ⟨74AHC(17)255⟩, which should be consulted for further details and references to the original literature.

(i) Imidazole, pyrazole, thiazole, isothiazole and oxazole

ERE (empirical resonance energy) and 'conjugation energy' data (Table 35) suggest that pyrazole is more aromatic than both imidazole and pyrrole. LCAO–SCF calculations on various azoles, however, lead to the conclusion that the stability of azoles decreases on increasing substitution of nitrogen atoms for carbon atoms, with the stabilities of pyrazole and imidazole being comparable.

Table 35 Empirical Resonance Energy Data (kJ mol^{-1}) for Azoles[a,b]

Compound	*Method A*[c]	*Method B*[d]	*Method C*[e]
Pyrazole	173.6	112.1	136.8
Imidazole	134.3	53.1	74.1
1,2,4-Triazole	205.8	83.7	151.5
Tetrazole	—	231.0	264.0
Indazole	309.2	246.9	248.9
Benzimidazole	287.9	203.8	204.2
Benzotriazole	—	346.9	312.5

[a] Adapted from ⟨74AHC(17)255⟩ which contains further details and references to the original literature.
[b] 1×10^{-7} J = 2.3901×10^{-8} cal.
[c] Results obtained using Pauling's bond energy terms.
[d] Using the bond energy terms reported by Cottrell.
[e] Using Coates and Sutton's bond energy terms.

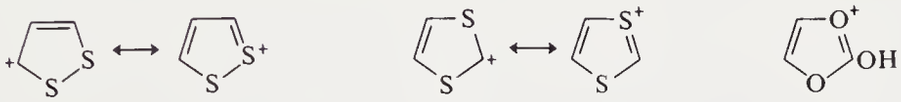
Data relevant to the aromaticity of these compounds have been obtained by a variety of other techniques, many of which are discussed elsewhere in this chapter. Aromaticity implies planarity; X-ray and microwave data support planarity. The NMR method has been extensively applied; thus ^{1}H NMR shifts for imidazoles, pyrazoles and pyrroles are comparable; ^{13}C NMR spectral data for imidazole show appreciable ring current anisotropy. The ring protons of thiazoles and the methyl protons in methylthiazoles are deshielded relative to signals from the corresponding imidazoles. Elvidge has interpreted these NMR data as evidence that the thiazole ring has the same degree of aromatic character as benzene ⟨65PC40100⟩.

The precise geometrical data obtained by microwave spectroscopy allow conclusions regarding bond delocalization and hence aromaticity. For example, the microwave spectrum of thiazole has shown that the structure is very close to the average of the structures of thiophene and 1,3,4-thiadiazole, which indicates a similar trend in aromaticity. However, different methods have frequently given inconsistent results.

^{1}H NMR data for 4-methyloxazole have been compared with those of 4-methylthiazole; the data clearly show that the ring protons in each are shielded. In a comprehensive study of a range of oxazoles, Brown and Ghosh also reported NMR data but based a discussion of resonance stabilization on pK and UV spectral data ⟨69JCS(B)270⟩. The weak basicity of oxazole (pK_a 0.8) relative to 1-methylimidazole (pK_a 7.44) and thiazole (pK_a 2.44) demonstrates that delocalization of the oxygen lone pair, which would have a base-strengthening effect on the nitrogen atom, is not extensive. It must be concluded that not only the experimental measurement but also the very definition of aromaticity in the azole series is as yet poorly quantified. Nevertheless, its importance in the interpretation of reactivity is enormous.

(ii) Diheterolylium ions and related compounds

The 1,2-dithiolylium and 1,3-dithiolylium ions (**115**) and (**116**) are iso-π-electronic with the tropylium ion, from which they may be formally derived by replacing double bonds by sulfur atoms. Various calculations and structural data demonstrate that the rings are stabilized by π-electron delocalization.



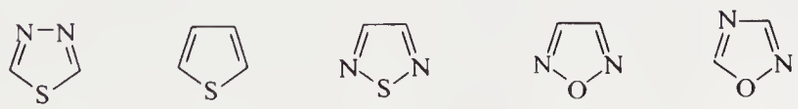
(**115a**) (**115b**) (**116a**) (**116b**) (**117**)

The NMR spectrum of the 2-hydroxy-1,3-dioxolylium cation (**117**) ⟨68JA1884⟩ shows a significant ring current. The aromaticity of vinylene carbonate was pointed out by Balaban ⟨59MI40100⟩.

(iii) Compounds containing three heteroatoms

The aromatic character is critically dependent upon the position of the heteroatoms in the ring, and oxygenated compounds have marked diene character. Various ERE determinations of 1,2,4-triazole have given values ranging between 83.7 and 205.8 kJ mol^{-1} (Table 35). LCAO–SCF calculations, however, suggest that the ring is substantially less stable than the diazoles but more stable than tetrazole.

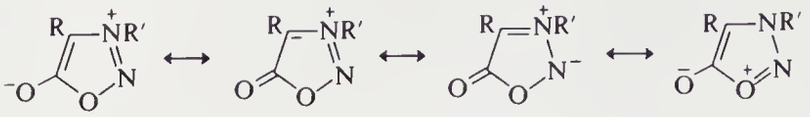
Microwave spectra of 1,3,4-thiadiazole (**118**), thiophene (**119**), 1,2,5-thiadiazole (**120**) and 1,2,5-oxadiazole (**121**) yield the following order of decreasing aromaticity based on bond lengths: (**120**), (**119**), (**118**), (**121**), (**122**). 1,2,5-Oxadiazole is planar with a C=N bond length of 130.0 pm. intermediate between that of formaldoxine (127.0 pm) and pyridine (134.0 pm), suggestive of a high degree of 'diene' character. Comparison with cyclopentadiene indicates that 1,2,5-oxadiazole has some small degree of aromatic character.



(**118**) (**119**) (**120**) (**121**) (**122**)

The sydnones may be represented by structures (**123a–d**), of which the zwitterionic structure (**123a**) most clearly implies an aromatic sextet. The diamagnetic susceptibility exaltation for *N*-phenylsydnone of 11.0×10^{-6} cm^3 mol^{-1} is comparable with the corresponding value for pyrrole

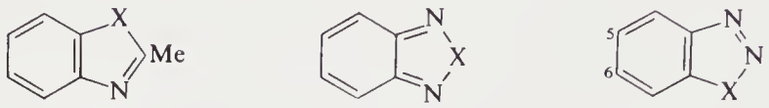
(10.2×10^{-6}). 3-*p*-Bromophenylsydnone (**123**; R = H, R′ = *p*-bromophenyl) is essentially planar; however, the O—N bond and O(1)—C(5) bond lengths are not very different from normal single bond distances.



(**123a**) (**123b**) (**123c**) (**123d**)

(*iv*) *Benzo derivatives*

In the series 1,3-benzoselenazole (**124**; X = Se), -benzothiazole (**124**; X = S) and -benzoxazole (**124**; X = O) the deshielding effect on the methyl protons on changing the heteroatom X is in the opposite sense to the electronegativity of the atom. This has been explained in terms of decreasing aromaticity in the order (**124**; X = Se), (**124**; X = S), (**124**; X = O).

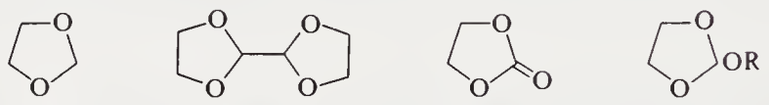


(**124**) (**125**) (**126**)

In 2,1,3-benzoselenadiazole (**125**; X = Se), 2,1,3-benzothiadiazole (**125**; X = S) and 2,1,3-benzoxadiazole (**125**; X = O) the effect of the heteroatom X on the ring is similar to that in the previous system; thus a decreasing scale of aromatic character (**125**; X = Se), (**125**; X = S), (**125**; X = O) is again suggested. The *ortho* proton–proton coupling constants (5,6), and hence bond fixation and aromatic character, decrease in the order (**126**; X = S), (**126**; X = NMe), (**125**; X = NMe), (**125**; X = S), (**125**; X = O). The ratios of $J_{5,6}$:$J_{4,5}$ for these compounds are 0.859, 0.824, 0.781, 0.748 and 0.706, respectively.

2.4.4.3 Conformation

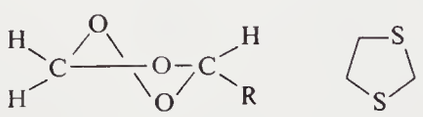
Saturated five-membered heterocyclic compounds are non-planar, existing in half-chair or envelope conformations. The far-IR spectra of THF and 1,3-dioxolane (**127**) show both to have barriers of *ca.* 0.42 kJ mol^{-1}.



(**127**) (**128**) (**129**) (**130**)

1,3-Dioxolane also pseudorotates essentially freely in the vapor phase. 2,2′-Bi-1,3-dioxolane (**128**) has been shown by X-ray crystallography to have a conformation midway between the half-chair and envelope forms. The related compound 2-oxo-1,3-dioxolane (**129**) shows a half-chair conformation. This result is confirmed by microwave spectroscopy and by ^{13}C NMR data. Analysis of the AA′BB′ NMR spectra of the ring hydrogen atoms in some 1,3-dioxolane derivatives is in agreement with a puckered ring. Some 2-alkoxy-1,3-dioxolanes (**130**) display *anti* and *gauche* forms about the exocyclic C(2)—O bond.

The 1,2,4-trioxolane ring prefers a half-chair conformation (**131**); the C—O—C portion of the ring forms the reference plane, and alkyl substituents prefer the equatorial positions.



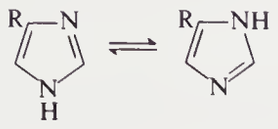
(**131**) (**132**)

1,3-Dithiolane (**132**) derivatives also possess non-planar skeletons; the most important conformation is probably of symmetry C_2 (half-chair). The dithiolane ring may be quite flexible and a minimum energy conformation is only well defined if there is a bulky substituent at the 2-position.

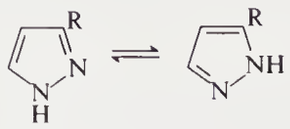
2.4.5 TAUTOMERISM ⟨76AHC(S1)1⟩

2.4.5.1 Annular Tautomerism

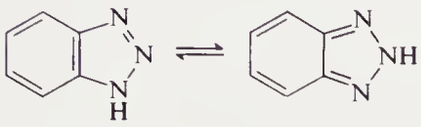
Annular tautomerism (*e.g.* **133**⇌**134**) involves the movement of a proton between two annular nitrogen atoms. For unsubstituted imidazole (**133**; R = H) and pyrazole (**135**; R = H) the two tautomers are identical, but this does not apply to substituted derivatives. For triazoles and tetrazoles, even the unsubstituted parent compounds show two distinct tautomers. However, interconversion occurs readily and such tautomers cannot be separated. Sometimes one tautomeric form predominates. Thus the mesomerism of the benzene ring is greater in (**136**) than in (**137**), and UV spectral comparisons show that benzotriazole exists predominantly as (**136**).



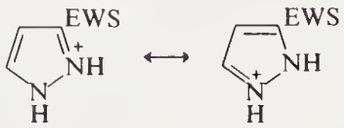
(**133**) (**134**)



(**135**)



(**136**) (**137**)



(**138**)

Table 36 summarizes the known annular tautomerism data for azoles. The tautomeric preferences of substituted pyrazoles and imidazoles can be rationalized in terms of the differential substituent effect on the acidity of the two NH groups in the conjugate acid, *e.g.* in (**138**; EWS = electron-withdrawing substituent) the 2-NH is more acidic than 1-NH and hence for the neutral form the 3-substituted pyrazole is the more stable.

Table 36 Annular Tautomerism of Azoles[a]

Azole	*Parent*	*Substituted compounds*
Pyrazole	Equivalent	Electron-withdrawing group prefers 3-position
Imidazole	Equivalent	Electron-withdrawing group prefers 4-position
v-Triazole	1,2,5 > 1,2,3	—
s-Triazole	1,2,4 > 1,3,4	—
Tetrazole	1,2,3,4 > 1,2,3,5	—

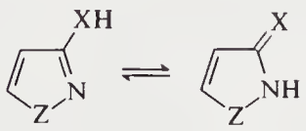
[a] Data taken from ⟨76AHC(S1)296⟩ which contains references to the original literature.

The situation is more complex for triazoles and tetrazoles where other effects such as lone-pair repulsions intervene; see discussion in ⟨76AHC(S1)296⟩.

2.4.5.2 Substituent Tautomerism

2.4.5.2.1 Azoles with heteroatoms in the 1,2-positions

3-Substituted isoxazoles, pyrazoles and isothiazoles can exist in two tautomeric forms (**139**, **140**; Z = O, N or S; Table 37). Amino compounds exist as such as expected, and so do the hydroxy compounds under most conditions. The stability of the OH forms of these 3-hydroxy-1,2-azoles is explained by the weakened basicity of the ring nitrogen atom in the 2-position due to the adjacent heteroatom at the 1-position and the oxygen substituent at the 3-position. This concentration of electron-withdrawing groups near the basic nitrogen atom causes these compounds to exist mainly in the OH form.



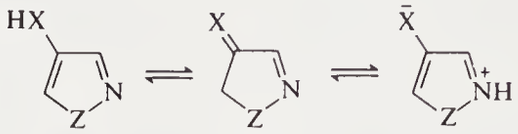
(**139**) (**140**)

Table 37 Tautomerism of 3-Substituted Azoles with Heteroatoms-1,2[a]

Substituent	*Ring*	*Phase(s)*	*Conclusions*
OH	1-Substituted pyrazole	C_6H_{12}, $CHCl_3$, H_2O, xtal.	OH except in H_2O where OH/NH coexist
	Isoxazole	C_6H_{12}, $CHCl_3$, H_2O, xtal.	Mainly OH in all media
	Isothiazole	MeOH, xtal.	OH
NH_2	1-Substituted pyrazole	MeOH, KBr	NH_2
	Isoxazole	$CHCl_3$, H_2O	NH_2
	Isothiazole	CCl_4	NH_2
SH	Isothiazole	CCl_4	SH

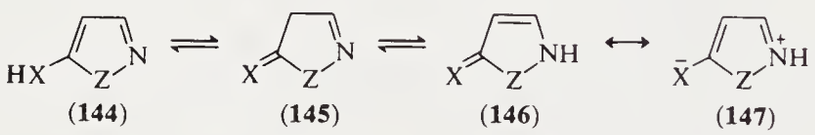
[a] For further details and original references see ⟨70C134⟩ and ⟨76AHC(S1)1⟩.

The 4-substituted analogues can exist in two uncharged tautomeric forms (**141**) and (**142**) and, in addition, in the zwitterionic form (**143**), but all the evidence shows that the compounds all exist predominantly in the NH_2 or OH form (**141**).



(**141**) (**142**) (**143**)

For 5-substituted isoxazoles, pyrazoles and isothiazoles, three uncharged tautomeric forms are possible: (**144**), (**145**) and (**146**). Some conclusions are recorded in Table 38. Again, the amino derivatives exist as such. In the case of the hydroxy compounds, the hydroxy form is of little importance (except in special cases where a suitable substituent in the 4-position can form a hydrogen bond with the 5-hydroxy group). The relative occurrence of the 4*H*-oxo form (**145**) and 2*H*-oxo tautomer (**146**) depends on the substitution pattern and on the solvent. Tautomer (**146**) is considerably more polar than (**145**), with a large contribution from the charge-separated canonical structure (**147**). Hence, it is not unexpected that the 2*H*-oxo tautomer (**146**) is strongly favored by polar media. A substituent at the 4-position also tends to favor form (**146**) over (**145**) because of conjugation or hyperconjugation of the 4-substituent with the 3,4-double bond.



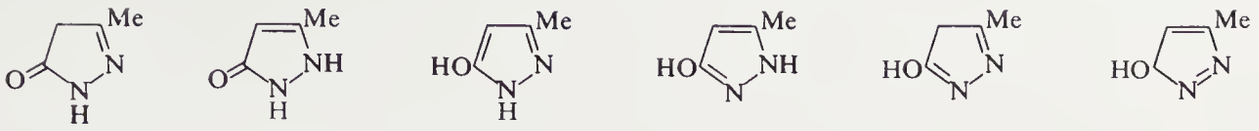
(**144**) (**145**) (**146**) (**147**)

Table 38 Tautomerism of 5-Substituted Azoles with Heteroatoms-1,2[a]

Substituent	*Ring*	*Phase(s)*	*Conclusions*
OH	1-Substituted pyrazole	C_6H_{12}, $CHCl_3$, EtOH, H_2O, xtal.	CH in non-polar;
	Isoxazole	C_6H_{12}, $CHCl_3$, EtOH, H_2O, xtal.	Increasing NH in polar; NH favored by 4-substituent
NH_2	1-Substituted pyrazole	CCl_4	NH_2
	Isoxazole	$CHCl_3$, H_2O	NH_2
	Isothiazole	CCl_4	NH_2
SH	Isoxazole	C_6H_{12}, CCl_4, MeOH, xtal.	SH

[a] For further details and original references see ⟨70C134⟩ and ⟨76AHC(S1)1⟩.

Complex tautomerism for azoles with heteroatoms in the 1,2-positions occurs for pyrazoles which are not substituted on nitrogen. Scheme 10 shows the four important tautomeric structures (**148**)–(**151**) for 3-methylpyrazolin-5-one, and (**152**) and (**153**) as examples of other possible structures. A detailed investigation of this system disclosed that in aqueous solution (polar medium) the importance of the tautomers is (**149**) > (**151**) ≫ (**150**) or (**148**), whereas in cyclohexane solution (non-polar medium) (**151**) > (**148**) ≫ (**149**) or (**150**).



(148) (149) (150) (151) (152) (153)

Scheme 10

2.4.5.2.2 Azoles with heteroatoms in the 1,3-positions

The tautomerism of 2-substituted 1,3-azoles (**154**⇌**155**) is summarized in Table 39. Whereas amino compounds occur invariably as such, all the potential hydroxy derivatives exist in the oxo form, and in this series the sulfur compounds resemble their oxygen analogues. There is a close analogy between the tautomerism for all these derivatives with the corresponding 2-substituted pyridines.

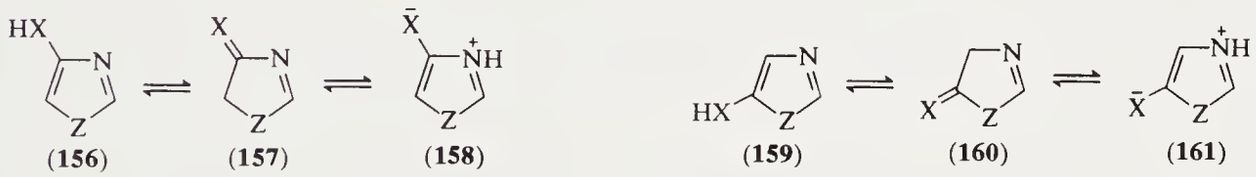
(154) (155)

Table 39 Tautomerism of 2-Substituted Azoles with Heteroatoms-1,3[a]

Substituent	*Ring*	*Phase(s)*	*Conclusions*
OH	1-Substituted imidazole	KBr disc	NH, C=O
	Oxazole	MeOH, CCl_4	NH, C=O
	Thiazole	Alcohol, CS_2	NH, C=O
NH_2	1-Substituted imidazole	0.1N aq. KCl, EtOH/aq. KCl	NH_2
	Oxazole	MeOH	NH_2
	Thiazole	EtOH, $CDCl_3$	NH_2
SH	1-Substituted imidazole	Liquid film, MeOH, EtOH	NH, C=S
	Oxazole	CCl_4, MeOH	NH, C=S
	Thiazole	CCl_4, EtOH	NH, C=S

[a] For further details and original references see ⟨70C134⟩ and ⟨76AHC(S1)1⟩.

4-Substituted 1,3-azoles exist in two non-charged tautomeric forms (**156**) and (**157**) together with the zwitterionic form (**158**). 5-Substituted 1,3-azoles also exist in forms (**159**) and (**160**) together with the zwitterionic forms (**161**). Some results are summarized in Table 40; for the potential hydroxy forms, the non-aromatic tautomers of types (**157**) and (**160**) clearly can be of importance.



(156) (157) (158) (159) (160) (161)

Table 40 Tautomerism of 4- and 5-Substituted Azoles with Heteroatoms-1,3[a]

Substituent	*Ring*	*Phase(s)*	*Conclusions*
4-OH	Oxazole	EtOH, xtal., Me_2SO	CH
	Thiazole	Me_2SO, Me_2CO	OH and CH
5-OH	Oxazole	Xtal.	CH
5-NH_2	Oxazole	$CHCl_3$, xtal.	NH_2

[a] For further details and original references, see ⟨70C134⟩ and ⟨76AHC(S1)1⟩.

2.5

Structure of Small and Large Rings*

The division of compounds of these classes into aromatic and non-aromatic (also antiaromatic) types is much less clear-cut than for the five- and six-membered rings.

Heterocyclic aromaticity requires a planar or nearly planar, conjugated system containing $4n + 2$ π-electrons. The subject has been reviewed ⟨74AHC(17)339⟩. Planarity often cannot be achieved because of increased strain in going from puckered to planar geometries. The Hückel condition often can be met, utilizing the system's π-bonds and n electron pairs, and sometimes by forming cations or anions to adjust the number of participating electrons. Aromatic heterocyclic systems are known with 7 to 21 ring members. Still, a great many heterocycles having the right number of electrons are polyenic rather than aromatic, due to the excessive energy required to achieve near planarity. The aromatic systems are diatropic as seen in their ^{1}H NMR spectra, and show double bond delocalization in their electronic spectra and bond length equalization in their X-ray or electron diffraction structures. Cases intermediate between polyenic and aromatic are found as well (CHEC 5.20.2.2.1). Aromatic systems known include 1,3-dithiepin anions (CHEC 5.18.4.2, 1,4-dihydro-1,4-diazocines (CHEC 5.19.4.4), azonine (CHEC 5.20.2.2.2), 2,7-methanoaza[10]annulene (CHEC 5.20.2.3) ⟨78AG(E)853⟩ and *trans,trans,trans*-aza[13]annulene (CHEC 5.20.2.4).

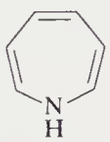
2.5.1 SURVEY OF POSSIBLE STRUCTURES

2.5.1.1 Small Rings

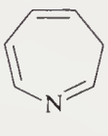
Tables 1 and 2 list the three- and four-membered rings, respectively, which have been made or for which there is strong evidence (such as from isotope or stereochemical studies). A recent addition to the list is a triaziridine, a long sought for molecule, which turns out to be relatively stable.

2.5.1.2 Large Rings

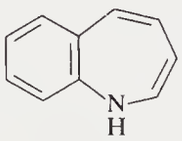
The number of possible heterocyclic rings of seven or more members is enormous. Many are known. Some of the most important ring systems are listed in Scheme 1, with reference to the CHEC chapter where they are discussed.



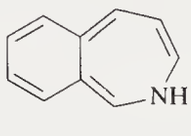
1*H*-Azepine
(5.16)



3*H*-Azepine
(5.16)



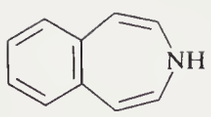
1*H*-1-Benzazepine
(5.16)



2*H*-2-Benzazepine
(5.16)

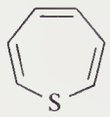
Scheme 1 Examples of seven-membered and larger rings with references to the relevant CHEC chapter in parentheses

*Based on Chapter 5.01 of 'Comprehensive Heterocyclic Chemistry', by W. Lwowski, New Mexico State University.

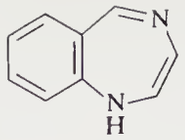


3*H*-3-Benzazepine
(5.16)

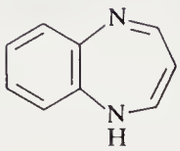
Oxepin
(5.17)



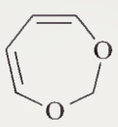
Thiepin
(5.17)



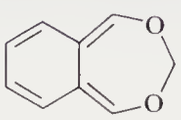
1*H*-1,4-Benzodiazepine
(5.18)



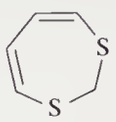
1*H*-1,5-Benzodiazepine
(5.18)



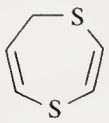
1,3-Dioxepin
(5.18)



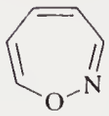
2,4-Benzodioxepin
(5.18)



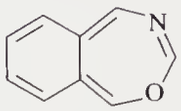
1,3-Dithiepin
(5.18)



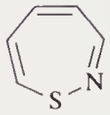
5*H*-1,4-Dithiepin
(5.18)



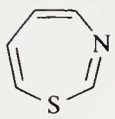
1,2-Oxazepine
(5.18)



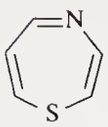
2,4-Benzoxazepine
(5.18)



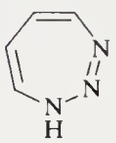
1,2-Thiazepine
(5.18)



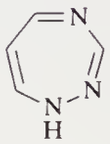
1,3-Thiazepine
(5.18)



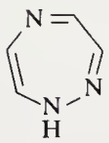
1,4-Thiazepine
(5.18)



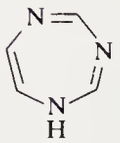
1*H*-1,2,3-Triazepine
(5.18)



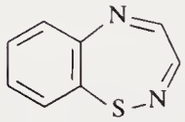
1*H*-1,2,4-Triazepine
(5.18)



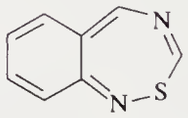
1*H*-1,2,5-Triazepine
(5.18)



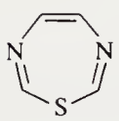
1*H*-1,3,5-Triazepine
(5.18)



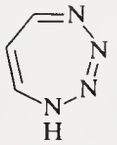
1,2,5-Benzothiadiazepine
(5.18)



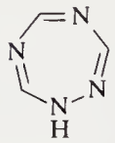
2,1,4-Benzothiadiazepine
(5.18)



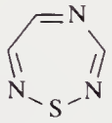
1,3,6-Thiadiazepine
(5.18)



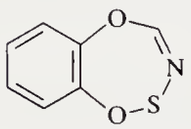
1*H*-1,2,3,4-Tetrazepine
(5.18)



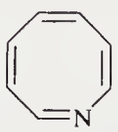
1*H*-1,2,4,6-Tetrazepine
(5.18)



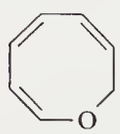
1,2,4,7-Thiatriazepine
(5.18)



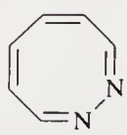
1,5,2,3-Benzodioxathiazepine
(5.18)



Azocine
(5.19)

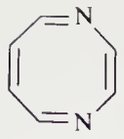


2*H*-Oxocin
(5.19)

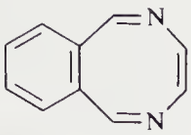


1,2-Diazocine
(5.19)

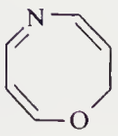
Scheme 1 Examples of seven-membered and larger rings with references to the relevant CHEC chapter in parentheses (*continued*)



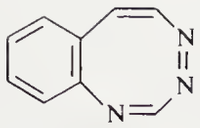
1,4-Diazocine
(5.19)



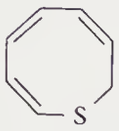
2,5-Benzodiazocine
(5.19)



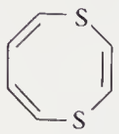
2*H*-1,5-Oxazocine
(5.19)



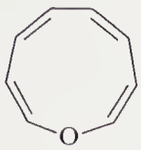
1,3,4-Benzotriazocine
(5.19)



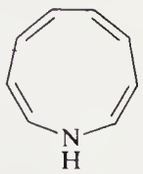
2*H*-Thiocin
(5.19)



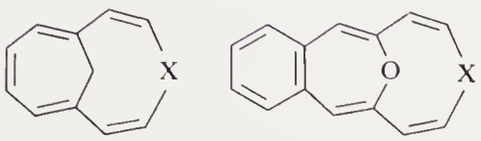
1,4-Dithiocin
(5.19)



Oxonin
(5.20)

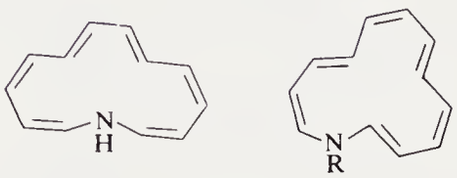


1*H*-Azonine
(5.20)

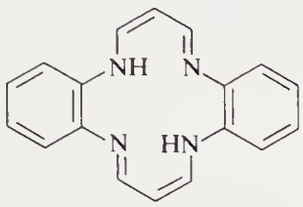


X = O, S

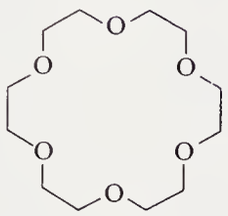
Hetero[11]annulenes
(5.20)

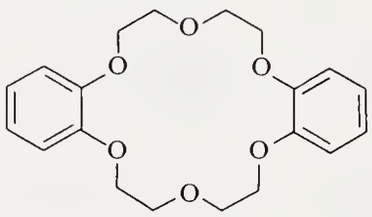


Hetero[13]annulenes
(5.20)

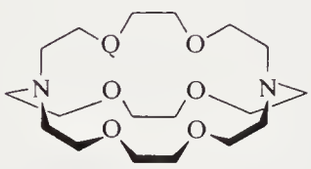


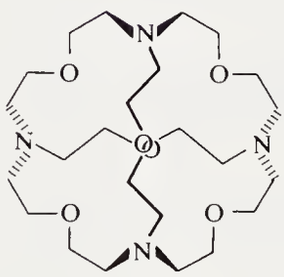
Hetero[14]annulene
(5.20)



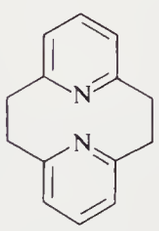


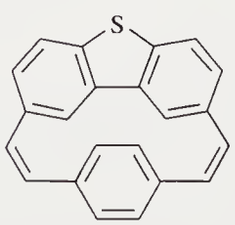
Crown ethers
(5.21)





Cryptands
(5.22)





Heterophanes
(5.22)

Scheme 1 Examples of seven-membered and larger rings with references to the relevant CHEC chapter in parentheses (*continued*)

Table 1 Structures of Known Three-membered Heterocyclic Compounds

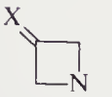
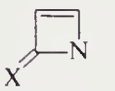
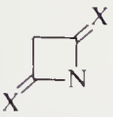
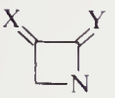
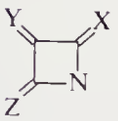
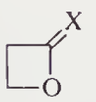
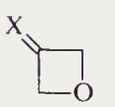
Skeleton	*Name*	*CHEC chapter or section number*	*Skeleton*	*Name*	*CHEC chapter or section number*
	Aziridine	5.04		Diaziridine	5.08
	1-Azirine	5.04		1-Diazirine	5.08
	Aziridinone Alkylideneaziridine Aziridineimine	5.04 5.04 5.04		Diaziridinone Diaziridinimine	5.08 5.08
	Aziridinedione	5.04		Oxaziridine	5.08
	Azirinimine	5.04		Dioxirane	5.08
	2-Azirine	5.04.2.1		Dioxiranone	—
	Oxirane	5.05		Thiaziridine 1,1-dioxide	5.08.1
	Oxiranone Alkylideneoxirane Oxiranimine	5.05 5.05 5.05		Oxathiirane	5.08.1
	Oxirene	5.05.6		Thiaziridineimine	5.08.1
	Thiirane	5.06		Triaziridine	5.08
	Thiiranone Thiiranimine Alkylidenethiirane	5.06 5.06 5.06		Triazirine	—
	Thiiranediimine	5.06		Oxadiaziridine	—
	Thiirene	5.06		Thiadiaziridine 1,1-dioxide	—

2.5.2 THEORETICAL METHODS

Elaborate *ab initio* calculations employing large basis set correlated wave functions have been largely restricted to studies of three-membered rings. Notable in this connection, for example, are recent investigations on the antiaromatic analogues of the cyclopropenium ion ⟨82JOC1869, 83CJC2596, 83JA5541, 83JA396⟩.

Studies on larger systems have tended to be limited to semi-empirical or small basis set *ab initio* methods with most emphasis on five- and six-membered rings. However, their possible role in commercially useful conducting polymers has stimulated significant interest in the calculated properties of large rings incorporating sulfur and nitrogen heteroatoms ⟨84JA312, 82JA2691, 80JA6687⟩.

Table 2 Structures of Known Four-membered Heterocyclic Compounds

Skeleton	*Name*	*CHEC chapter or section number*
	Azetidine	5.09
	1-Azetine	5.09.4.1
	2-Azetine	5.09.4.3.3
	Azetidin-2-one	5.09
	Azetidin-3-one	5.09
	Azete (benz[*b*]-) Azete [tris(dimethylamino)-]	5.09.5
	2-Azetin-4-one	5.09.4.3.5
	Azetidine-2,4-dione 4-Thioxoazetidin-2-one	5.09
	X = N, Y = O X = CR_2, Y = O	5.09 5.09
	X = CR_2, Y = Z = O X = CR_2, Y = O, Z = N	5.09 5.09
	Oxetane	5.13
	Oxete	5.13
	Oxetan-2-one Oxetan-2-imine	5.13 5.13
	Oxetan-3-one Oxetan-3-imine 3-Alkylidenoxetane	5.13 5.13 5.13
	Thietane	5.14
	Thiete	5.14
	Thiacyclobutadiene	5.14.2.6

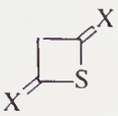
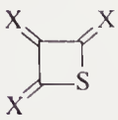
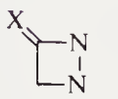
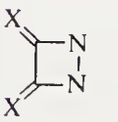
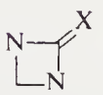
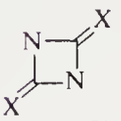
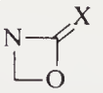
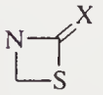
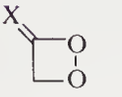
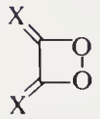
Skeleton	*Name*	*CHEC chapter or section number*
	Thietan-2-one (benzo[*b*]-)	5.14.2.5
	Thietane-2,4-diimine	5.14
	Thietane-2,3,4-triimine	5.14
	1,2-Diazetidine	5.15.1.2.1
	3*H*,4*H*-Diazetine	5.15
	1*H*,2*H*-Diazetine	5.15
	1,2-Diazetidin-3-one	5.15
	1,2-Diazetidine-3,4-dione	5.15
	1,2-Oxazetidine	5.15.1.2.2
	4*H*-1,2-Oxazetine	5.15.1.2.2
	1,2-Thiazetine (1,1-dioxide, benzo[*b*]-)	5.15.1.2.3
	1,3-Diazetidin-2-one 1,3-Diazetidin-2-imine	5.15.1.2.4 5.15.1.2.4
	1,3-Diazetidine-2,4-dione	5.15.1.2.4
	1,3-Oxazetidin-2-one	5.15.1.2.5
	1,3-Thiazetidin-2-imine	5.15.1.2.6
	1,2-Dioxetane	5.15.1.2.2
	1,2-Dioxetanone	5.15.1.2.2

Table 2 (*continued*)

Skeleton	Name	CHEC chapter or section number	Skeleton	Name	CHEC chapter or section number
	1,2-Dioxetanedione	5.15.1.2.2		4-Alkylidene-1,2-thietane 1,1-dioxide	5.15.1.2.8
	1,2-Oxathietane	5.15.1.2.8		1,2-Dithietane	5.15.1.2.9
	1,2-Oxathiete (benz[*b*]-)	5.15.1.2.8		1,3-Dithietane	5.15.1.2.10

For calculated resonance energies of seven-membered heterocycles see Table 3. Calculations of inversion barriers have met with mixed success. The MNDO SCF method gives results which compare well with experimental values, including the high barriers of *N*-halo- and *N*-amino-aziridines, and the low ones for *N*-trimethylsilyl- and *N*-phosphino-aziridines ⟨80JCS(P2)1512⟩.

2.5.3 STRUCTURAL METHODS

2.5.3.1 X-Ray Diffraction

The geometry of three- and four-membered rings has been determined mainly by X-ray diffraction on crystalline materials ⟨72PMH(5)1, p. 12⟩. Three-membered heterocycles generally have shorter C—C bonds than does cyclopropane, thiirane dioxides being an exception. The C—X bonds are longer than in CH_3—X—CH_3. The CXC angles in oxirane and aziridine are close to 60°, and the peripheral HCH bond angles are near 118°. Table 4 gives representative data.

The geometry of four-membered rings is far more complex; the rings are usually not planar (see Table 5).

Heterocyclics with seven and more ring members display an enormous variety of shapes. Bond lengths are often close to those of open chain counterparts, but bond angles can be greatly different.

The bond lengths of fully saturated seven-membered rings are the same as those in corresponding open chain compounds, while the bond angles tend to be larger.

2.5.3.2 Microwave Spectroscopy

Microwave spectra have been used to determine molecular dimensions for, *inter alia,* aziridines and 1-azirines (CHEC 2.04.2.2), diazirine and substituted derivatives (CHEC 5.08.2.2), oxetanes (CHEC 5.13.2.2), thietanes and thietes (CHEC 5.14.2.1).

2.5.3.3 ^{1}H NMR Spectroscopy

The NMR spectra of three- and four-membered heterocyclics display regularities of great value to structure determination. For protons on adjacent carbons the coupling constants J_{cis} seem to be always greater than J_{trans}. In three-membered rings J_{gem} is almost always smaller than J_{cis} and J_{trans}. Extensive tables are found in ⟨B-73NMR138⟩. The average values for 64 aziridines are $J_{gem} = 1.4$, $J_{trans} = 3.3$ and $J_{cis} = 6.4$ Hz ⟨71PMH(4)121, p. 126⟩. The size of J_{gem} and of the vicinal C—H coupling constants seems to depend more on the number of non-bonding electron pairs at the heteroatom than on its electronegativity. Each electron pair contributes + 5.5 Hz to J_{gem}, −2.5 Hz to J_{cis}, and −2.7Hz to J_{trans} ⟨80OMR(13)45⟩. Table 6 gives some examples, the data being

Table 3 Structure and ^{1}H NMR Data of Seven-membered Heterocyclic Compounds

X	*Y*	*Bond lengths* (Å) a	b	c	d	*Resonance* (kJ mol^{-1})	$\delta(^1H)$ (p.p.m.) H-2	H-3	H-4	H-5	H-6	H-7	*Longest wavelength UV absorption* (nm)	log ε
C	C	1.45	1.37	1.48	1.35	—	—	—	—	—	—	—	—	—
O	C	1.39	1.35	1.46	1.35	+0.5	5.7	5.7	6.3	—	—	—	305	2.95
HN	C	1.42	1.35	1.46	1.35	−0.75	—	—	—	—	—	—	—	—
EtOCON	C	—	—	—	—	—	5.95	5.51	6.15	—	—	—	318	2.83
EtOCON	N	—	—	—	—	—	—	6.23	5.75	6.55	6.25	7.40	355	2.38
S	C	1.79	1.35	1.46	1.35	−6.1	—	—	—	—	—	—	—	—

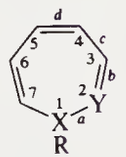
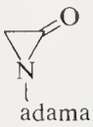
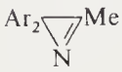
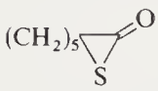
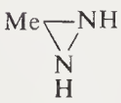
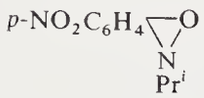
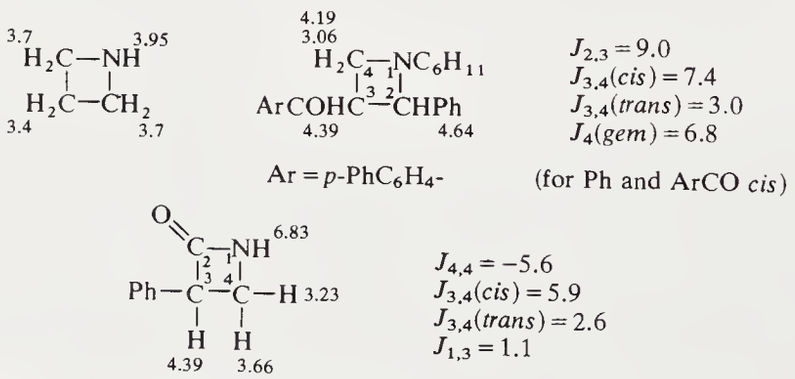
Ring number is 

Table 4 Bond Lengths and Bond Angles of Three-membered Heterocyclic Compounds

Structure	*Bond lengths* (Å) a	b	c	*Bond angles* (°) ca	ab	bc	*CRSE* (kJ mol^{-1})	*CHEC section number/ref.*
	1.482	1.491	1.482	—	—	—	113	5.04.2.2
	1.49	1.49	1.50	59.9	60.4	59.8	—	74PMH(6)1, p. 8
	1.33	1.45	1.51	60.9	—	53.4	—	5.04.2.2
	1.256	1.463	1.598	60.3	—	48.2	—	5.04.2.2
	1.44	1.47	1.44	61.24	59.18	59.18	114	5.05.2.2
	1.815	1.484	1.815	48.3	—	—	—	5.06.2.1
	1.726	1.460	1.916	49.6	73.4	59.7	—	5.06.2.1
	1.79–1.98	1.25–1.29	—	—	—	—	—	5.06.2.1
	1.468	1.479	1.479	59.5	59.5	61	—	5.08.2.2
	1.228	1.428	1.428	64.5	64.5	50.9	—	5.08.2.2
	1.50	1.405	1.434	57.2	59.0	63.8	—	5.08.2.2

taken from the monograph chapters of CHEC and from ⟨B-73NMR, 71PMH(4)121, 80OMR(13)45⟩. Data on some three-membered heterocycles with an *exo* methylene group are found in Table 7 ⟨78RTC214⟩.

In azetidine derivatives the proton–proton coupling constants J_{gem} on the carbons adjacent to N are 5–7.5 Hz, and J_{cis} is larger than J_{trans}. Long range coupling between ring protons is common. Scheme 2 gives some examples ⟨B-73NMR142, 71PMH(4)121, p. 144⟩.



Scheme 2 ^{1}H NMR shifts and coupling constants of azetidine derivatives

The NMR spectra of heterocyclic compounds with seven or more ring members are as diverse as the shape, size and degree of unsaturation of the compounds. Proton–proton coupling constants provide a wealth of data on the shape of the molecules, while chemical shift data, heteroatom–proton coupling constants and heteronuclear spectra give information of the electronic structure. Some data on seven-membered rings are included in Table 3.

2.5.3.4 Heteronuclear NMR Spectroscopy

Aside from $^{13}C-H$ coupling constants (often obtained from ^{13}C satellites in ^{1}H NMR spectra) not very much information is available on the ^{13}C NMR spectra of small heterocycles ⟨B-79MI50101⟩.

Nitrogen-15 NMR spectra of aziridines and azetidines have been measured by Lichter *et al.* ⟨80JOC1277⟩. Relative to anhydrous ammonia the aziridine nitrogen absorbs at −8.5 p.p.m., and *N*-alkylation moves this shift downfield. For N—Me the signal is at 0.7 p.p.m., for N—$CHMe_2$ at 30.2 p.p.m., and for N—CMe_3 at 33.5 p.p.m. Substitution on the *β*-carbon shifts the ^{15}N resonance downfield relative to unsubstituted aziridine. This effect decreases with increasing bulk of the substituent, so that 2-methylaziridine has the nitrogen signal at 10.5 p.p.m., and 2-*t*-butylaziridine has it at 3.4 p.p.m. Further substitution on one or both *β*-carbons causes more downfield shift, the effect being only poorly reproduced by assuming group contributions to be additive.

Aziridine ^{15}N shifts parallel the ^{13}C shifts—in a plot of ^{13}C *vs.* ^{15}N shifts of 13 aziridines, the correlation coefficient was 0.953 and the slope 2.1 p.p.m. N/p.p.m. C⟨80JOC1277⟩.

Azetidine ^{15}N shifts are similar to those of the aziridines. Unsubstituted azetidine has its ^{15}N resonance (relative to anhydrous ammonia) at 25.3 p.p.m., and *N*-*t*-butylazetidine shows the signal at 52 p.p.m. ⟨80JOC1277⟩.

2.5.3.5 UV Spectroscopy

2.5.3.5.1 Electronic spectra of small-ring heterocyclic compounds

Saturated three- and four-membered heterocyclics absorb little in the readily accessible regions of the UV spectrum. Sulfur-containing rings are an exception, as can be seen in Table 8. Despite the lack of absorption of most parent compounds, there is a wealth of photochemistry of small heterocyclics. Light absorption by substituents, and energy transfer from photoexcited molecules present in the photoreactive system make photoconversion of the heterocycles practical. On the other hand, the lack of substantial absorption of their own can be exploited in the preparation of small heterocycles, by designing the system to be unsuitable for destructive energy transfer.

The introduction of a second heteroatom (other than sulfur) does not drastically change the absorption characteristics of small heterocycles. Oxaziridine and diaziridine are still 'transparent' to light of wavelengths above 220 nm (CHEC 5.08.2.3.2).

2.5.3.5.2 Electronic spectra of large-ring heterocyclic compounds

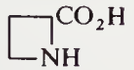
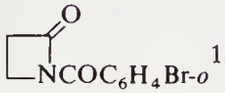
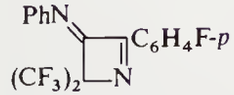
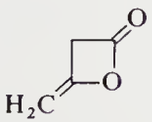
Electronic spectra, so very important in the characterization of five- and six-membered heterocycles, have played a much lesser role in the study of large heterocyclic rings, and far fewer data are available for comparison. Aromaticity in large heterocycles can be detected by their electronic absorption.

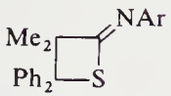
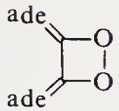
Table 3 gives some data on bond lengths, calculated resonance energies and the longest wavelength electronic absorption of seven-membered heterocycles ⟨70T4269, 70JA1453, 81H(15)1569⟩.

2.5.3.6 IR Spectroscopy

IR spectroscopy can give a great deal of information on small ring heterocyclics, because of the effects of ring strain on the frequencies of vibration of substituents attached to the ring, and because the ring vibrations fall into a readily accessible region of the IR spectrum. A wealth of data has been gathered and can be found in the monograph chapters of CHEC and in the following reviews ⟨71PMH(4)265, 63PMH(2)161, B-75MI50100, B-75MI50101⟩. This section concentrates on vibrations

Table 5 Bond Lengths and Bond Angles of Four-membered Heterocyclic Compounds

Structure	*Bond lengths* (Å) a	b	c	d	da	*Bond angles* (°) ab	bc	cd	*Pucker angle* (°)	*Ring inversion barrier* (kJ mol^{-1})	*CHEC section number/ref.*
	1.477	1.560	1.560	1.477	88	—	—	—	33	5.3	5.09.2.1, 80CRV231
	1.51	1.54	1.53	1.52	88	90	88	90	—	—	5.09.2.1
	1.51	1.53	1.51	1.51	84	96	84	97	—	—	B-79MI50100
	1.38	1.51	1.57	1.50	94.0	93.4	86.3	86.3	—	—	5.09.3.1
	1.307	1.467	1.575	1.504	92.4	97.9	83.6	86.1	Flat	—	5.09.4.1
	1.449	1.549	1.549	1.449	91.98 CRSE = 106 kJ mol^{-1}	91.73	88.55	91.98	Flat	0.18	80CRV231, 74MI50100
	1.39	1.51	1.54	1.47	95.8	83	91.3	90	Flat	—	80CRV231, 72PMH(5)1, p. 12

	1.847	1.549	1.549	1.847	76.8	90.6	95.6	90.6	26	3.3	5.14.2.1, 80CRV231, 74MI50100
	1.826	1.528	1.528	1.826	—	—	100.5	—	Flat	—	5.14.2.1
	1.777	1.524	1.591	1.868	77	95.8	—	90.1	20	—	5.14.2.1
	1.79	1.43	1.39	1.77	80.5	—	—	104.5	Flat	—	5.14.2.1
	1.427	1.481	1.537	1.471	—	—	—	—	24.3	—	5.15.1.2.1
	1.48	1.549	1.475	1.549	—	—	—	—	21.3	—	5.15.1.2.2

ade = adamantylidene

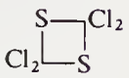
	2.146	1.835	1.564	1.835	99.1	—	80.9	—	—	—	5.15.1.2.3
	1.801	—	1.77	—	83.9	—	96.1	—	Flat	—	5.15.1.2.6

Table 6 Ranges of NMR Data of Three-membered Heterocyclic Systems

Skeleton	$\delta(C-H)$	J_{gem}	J_{cis}	J_{trans}	$J(^{13}C-H)$	$\delta(^{13}C)$
Cyclopropane	0.22	−3 to −1	6–12	−4 to 8	164	−2.2
Aziridine	1.48	0.9–4	5–9	2–7	168	18–22
Oxirane	2.54	5–7	2–5	1–3	176	39.7
Thiirane	2.27	−14 to 1	6–7	5–6	170	18
1-Azirine C-2	10	—	—	—	—	160–170
C-3	0.2–2.5					19–45
Diaziridine	1.2	—	—	—	—	56
1-Diazirine	0.4	—	—	—	—	—
Oxaziridine	4.5–5	—	—	—	—	56

Table 7 Ranges of NMR Data for Three-membered Heterocyclic Systems with Exocyclic Unsaturation

Skeleton	$\delta(C_2)$	$\delta(C_3)$	$\delta(C_{ex})$	$J(C_3-H)$	$J(C_{ex}-H)$
Cyclopropane	−2.6	−2.6	—	160.5	—
Methylenecyclopropane	131.0	3.0	103.5	161.5	160.8
N-*t*-Butyl-2-methyleneaziridine	134.0	23.8	80.6	170.7	165
2-Methylene-3-*t*-butyloxirane	144.3	68	70.5	—	—
2-Methylenethiirane	130.1	18.5	99.5	174	166

Table 8 Electronic Absorption Spectra of Small Heterocyclic Systems

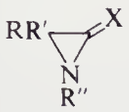
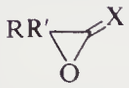
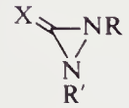
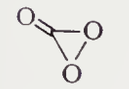
Skeleton	λ_{max} (nm)	*Absorption coefficient*	*CHEC section number/ref.*
	179 145 118	4200 6100 6300	69JCP(51)52, 72BCJ3026
	171.3 158 143	5600	5.05.2.5, 76JCP(64)2062
	260 205	40 4000	5.06.2.4
	191.7		76JCP(64)2062
	187 174 161 153	2000 2750	76JCP(64)2062
	275 218	30 600	5.14.2.4
	340 238	80 7440	5.15.1.2.9

of general diagnostic value. A treatment emphasizing the theoretical foundations is available ⟨63PMH(2)161, 71PMH(4)265⟩.

Small rings show high C—H absorption frequencies for the ring C—H bonds (between 3080 and 3000 cm^{-1}). The asymmetric C—H stretching frequency decreases with increasing ring size, from 3047 cm^{-1} for aziridine to 2966 cm^{-1} for azetidine and 2950 cm^{-1} for pyrrolidine. Analogous

changes are found in saturated oxygen heterocycles (3052, 2978, 2958 cm^{-1}) and their sulfur analogues (3047, 2968, 2959 cm^{-1}) ⟨71PMH(4)265, p. 278⟩. The stretching frequencies for exocyclic C=X bonds follow a similar sequence, with the smallest rings having the highest frequencies, as seen in Table 9. Four-membered rings have somewhat lower C=X frequencies; the carbonyl frequency of azetidin-2-one is 1786 cm^{-1} and that of oxetan-2-one is 1832 cm^{-1}.

Table 9 Stretching Frequencies for Exocyclic Double Bonds on Small Rings[a]

Skeleton	*Stretching frequencies* (cm^{-1}) X = C	X = N	X = O
	1770 (R = R′ = H, R″ = Et, X = C)	1805 (R = H, R′ = Bu^t, R″ = Me, X = NMe)	1837 (R = R′ = Me, R″ = Bu^t, X = O)
	1780 (R = R′ = Bu^t, X = $CHBu^t$)	—	1890 (R = R′ = Bu^t) 1990, 1945[b] (R = R′ = CF_3)
	1738 (R = R′ = Me, X = CMe_2)	1700, 1630[c] (R = R′ = Ph, X = NTs)	1785 (R, R′ = CH_2=)
	1690–1650[d] (R = Ar, R′ = SO_2Me, X = CMe_2)	1790 (R = R′ = *trans*-Bu^t, X = NBu^t)	1882[e] (R = R′ = Me)
	—	—	2045

[a] Taken from ⟨80AG(E)276⟩ unless otherwise stated. [b] ⟨82CC362⟩. [c] ⟨78AG(E)195⟩. [d] ⟨77AG(E)475⟩. [e] ⟨75AG(E)428⟩.

Table 10 Ring Breathing and C—H IR Absorptions of Small Heterocycles[a]

Structure	*Symmetry*	*Ring breathing*	*C—H stretch*	*CH_2 scissoring*	*CH_2 wagging*	*Ref.*
	C_s	1268, 1210	3078, 3012	1475, 1455	1128, 1131, 1088, 998	63PMH(2)161, 71PMH(4)265, p. 277
	C_{2v}	1266	3079, 3063, 3016, 3005	1490, 1470	1153, 1120	63PMH(2)161, 71PMH(4)265, p. 277
	C_{2v}	1112	3080, 3000	1446, 1427	1051, 1025	63PMH(2)161, 71PMH(4)265, p. 277
	—	980–970, 900	—	—	—	63PMH(2)161, 71PMH(4)265, p. 277
	—	738	2980, 2942	1438	1187	79MI50102

[a] cm^{-1}.

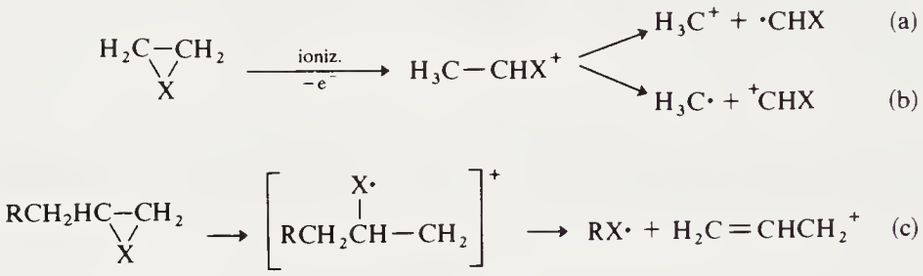
Ring breathing frequencies are shown in Table 10, together with some C—H IR absorptions. As expected, the ring breathing frequencies are lower for four- than for three-membered rings ⟨63PMH(2)161, 71PMH(4)265⟩.

IR spectra are less useful for the structure determination of large heterocyclic rings than for small ones. The ring breathing vibrations fall into a range well below that commonly used in the laboratory, and the absorptions are often broad and ill defined. Owing to the almost infinite variety of special effects, bond angle deformation and the consequent effect on the absorption frequencies of ring C—H, C=O and C=X bands are not easily used in the diagnosis of an unknown structure.

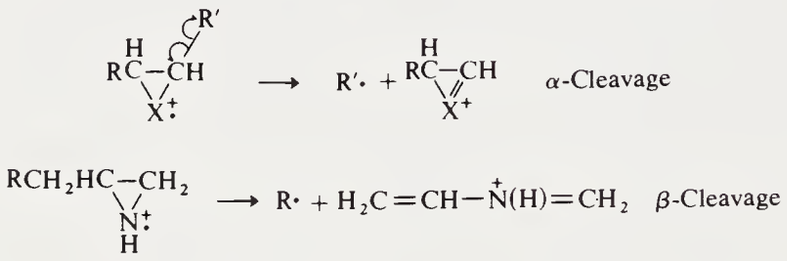
The IR spectra of, for example, oxepanes (C—O—C, C—H stretching, and CH_2 deformation) are similar to analogous non-cyclic compounds.

2.5.3.7 Mass Spectrometry

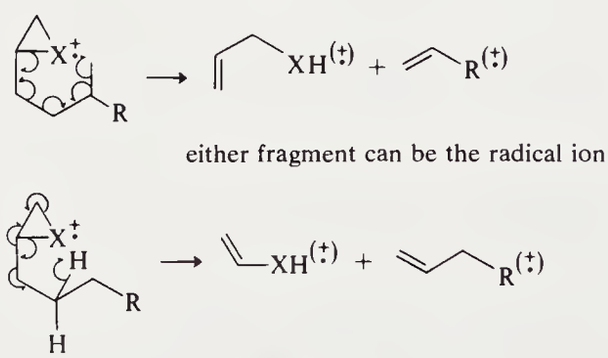
The mass spectral fragmentation patterns of three- and four-membered heterocycles consist of cleavages typical for substituents, of those due to the formation of particularly stable and accessible fragments (such as N_2), and of more characteristic patterns attributable to fragmentations promoted by ring strain and by stereochemical factors. Thus, small rings usually open after ionization. In aziridines this can be accomplished by loss of the substituent on the nitrogen, *i.e.* of H·, R·, *etc.*, to give ions of the type $R_2C{=}\overset{+}{N}{=}CR_2$ ⟨B-71MS296⟩. More generally, three-membered heterocyclics cleave into a radical and a cation, either of which can contain one or two of the original ring atoms (Scheme 3) (CHEC 5.04.2.8, 5.05.2.4 and 5.06.2.3). Especially in thiiranes, this may involve rearrangements, such as path (c) in Scheme 3. α-Cleavage, particularly important in oxiranes and thiiranes, may give a substituent radical and a cyclic ion (Scheme 4). β-Cleavage, more important in aziridines, gives a radical and an ion (Scheme 4). Longer side chains permit rearrangements, such as that in Scheme 5 ⟨B-71MS11⟩.



Scheme 3

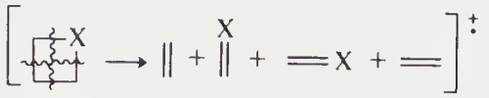


Scheme 4



Scheme 5

Four-membered heterocycles prefer to cleave, upon ionization, into two fragments, each containing two of the ring atoms. Further cleavages commence from these initial fragments (Scheme 6). Specific details can be found as follows: azetidines ⟨B-71MS296⟩, oxetanes ⟨B-71MS34⟩, thietanes (CHEC 5.14.2.3) ⟨B-71MS229⟩. The cleavage to two sets of two ring-atom fragments is illustrated by the formation of fragments with the masses of ethylene, methyleneimine and HC≡CNH from azetidine, and that of those with the masses of RNCO, ketenes and imines from azetidin-2-ones ⟨B-71MS300⟩.



Scheme 6

2.5.3.8 Photoelectron Spectroscopy

The photoelectron spectra of the following ring systems are mentioned in the section of CHEC quoted: thiiranes (5.06.2.3), diaziridines (5.08.2.3.2), diazirines (5.08.2.3.3), azetidines (5.09.2.1), oxetanes (5.13.2.3.4), thietanes (5.14.2.4), 1,2-diazetidines (5.15.1.2.1), dibenzazepines (5.16.2.6).

2.5.4 THERMODYNAMIC ASPECTS

2.5.4.1 Stability and Stabilization

2.5.4.1.1 Ring strain

The strain in three- and four-membered rings is mostly due to bond angle deformation. Some conventional ring strain energies (CRSEs) ⟨74PMH(6)199, p. 228⟩ are given in Tables 4 and 5. The ring strain in three- and four-membered rings is of the same magnitude, depending more on the nature of the heteroatom(s) than on the ring size. For comparison, the CRSE is 115 kJ mol^{-1} for cyclopropane and 111 kJ mol^{-1} for cyclobutane. As long as non-bonding interactions are avoided, alkyl substituents stabilize small rings by a few kJ mol^{-1}. For example, 2-methyloxirane is more stable than oxirane by 4 kJ mol^{-1} ⟨74PMH(6)199, p. 229⟩.

Exocyclic unsaturation can stabilize small ring heterocycles. In three-membered rings it is difficult to separate the contributions from increased angle strain and from electronic interactions between the unsaturation and the heteroatom. In four-membered rings such separation has been done ⟨74PMH(6)199, p. 235⟩. The CRSEs change from oxetane (106 kJ mol^{-1}) by −11 kJ mol^{-1} to oxetan-2-one (95 kJ mol^{-1}) (corrected for electronic effects) and 4-methyleneoxetan-2-one (95 kJ mol^{-1}). In contrast, an increase of 10 kJ mol^{-1} over the value for cyclobutane (111 kJ mol^{-1}) is observed on going to both methylenecyclobutane and 1,3-bismethylenecyclobutane.

2.5.4.1.2 Aromaticity and antiaromaticity

For the antiaromatic three-membered heterocycles, experimental data are available only for thiirenes (and there is some doubt about the true antiaromaticity of thiirenes). Bond lengths have been calculated, however, for these antiaromatic 4π-systems ⟨80PAC1623⟩. In comparison with the corresponding saturated heterocycles, the C—X bond lengths are increased by 0.05 to 0.17 Å and the C—C bond length is decreased by 0.2 Å.

For large rings, aromaticity is possible where the conditions of planarity and Hückel's rule are met, but the majority of fully unsaturated large heterocycles are not aromatic.

2.5.4.2 Conformation

2.5.4.2.1 Rings

Three-membered rings are necessarily planar.

Four-membered heterocycles are often puckered rather than planar (Table 5). As expected *exo*- and *endo*-unsaturation tend to make these systems planar.

Substituted rings have ring inversion conformers of different energies. Moreover, inversion of substituents on heteroatoms may multiply the number of conformers of different energies. The ring inversion barriers of saturated four-membered systems are often very low. From IR and microwave data the barriers are 5.27 kJ mol^{-1} for azetidine, nearly zero for oxetane, and 3.14 kJ mol^{-1} for thietane ⟨74MI150100, p. 273⟩. Table 5 gives bond lengths and angles for some four-membered heterocycles.

Fully unsaturated seven-membered heterocyclics have alternating bond lengths and are normally in boat conformations. Ring inversion barriers are 42.7 kJ mol^{-1} for 3-methyl-3*H*-azepine and 35.6 kJ mol^{-1} for 3*H*-azepin-2-one (CHEC 5.16.2.3). The barriers for oxepin and thiepin are somewhat lower (27 kJ mol^{-1} for 3-methyl-6-isopropylthiepin 1,1-dioxide; CHEC 5.17.1.4).

Annelation can introduce large conformational barriers, to the extent of making possible the resolution into enantiomers of a tribenzoxepin ⟨71CB2923⟩.

Fully saturated seven-membered heterocycles with one or two heteroatoms are normally in mobile twist-chair conformations (CHEC 5.17.1.1, CHEC 5.18) ⟨B-77SH(2)123⟩. Annelation and the introduction of exocyclic double bonds can have profound effects; oxepan-2-one, for example, is in a near chair conformation ⟨67JA5646⟩.

2.5.4.2.2 Inversions at ring nitrogen

Variable temperature studies on aziridines and diaziridines show a remarkable range of nitrogen inversion rates. Electron-delocalizing substituents on small-ring nitrogen lower the inversion barrier by lowering the energy of the transitional, 'flat' geometry in which three substituents of the nitrogen are all in the same plane ⟨67JA352⟩. Substituents bearing unshared electron pairs raise the inversion barrier to levels at which enantiomers can be isolated ⟨68JA508⟩. Pure invertomers have been obtained of *N*-haloaziridines ⟨B-73NMR137⟩ and *N*-alkoxyaziridines ⟨70JA1079, 73TL619⟩.

Some absolute configurations on nitrogen of aziridines are known, such as that of diethyl 1-methoxyaziridine-2,2-dicarboxylate ⟨79DOK(246)1150⟩.

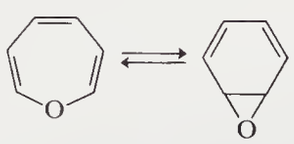
For oxaziridines the N-inversion barrier is considerably higher than that for similar aziridines. *N*-Alkyl-3,3-dialkyloxaziridines are resolvable and absolute configurations have been determined (CHEC 5.08.2.3.1).

Diaziridines also show slow nitrogen inversion, and carbon-substituted compounds can be resolved into enantiomers, which typically racemize slowly at room temperature (when *N*-substituted with alkyl and/or hydrogen). For example, 1-methyl-3-benzyl-3-methyldiaziridine in tetrachloroethylene showed a half-life at 70 °C of 431 min ⟨69AG(E)212⟩. Preparative resolution has been done both by classical methods, using chiral partners in salts ⟨77DOK(232)1081⟩, and by chromatography on triacetyl cellulose (CHEC 5.08.2.3.1).

N-Inversion in azetidine and azetidin-2-one is rapid, even at −77 and −40 °C, respectively ⟨B-73NMR144⟩. Again, halo substituents on nitrogen drastically slow the inversion rate, so that *N*-chloro-2-methylazetidine can be separated into two diastereomers ⟨B-77SH(1)54⟩. Substituent effects on N-inversion are much the same as in the aziridines: *N*-aryl and *N*-acyl compounds undergo N-inversion faster, whereas *N*-halo, *N*-amino and *N*-nitroso compounds are slower ⟨B-77SH(1)56⟩. By and large, the N-inversion barrier of azetidines is 38 kJ mol^{-1} lower than that of similarly substituted aziridines ⟨B-77SH(1)55⟩. In 1,2-diazetidines one finds the N-inversion rate lowered, and coalescence temperatures and free energies of activation have been reported for a number of 1,2-diaryldiazetidin-3-ones ⟨B-77SH(1)61⟩.

2.5.5 TAUTOMERISM

The most important type of tautomerism found for small and large rings is of the ring–chain type, rather than prototropy. A familiar example is the heterepine–heteranorcaradiene equilibrium shown in Scheme 7. The equilibrium position is strongly affected by substitution (see CHEC 5.17.1.2).



Scheme 7

Part 3
Reactivity of Heterocycles

3.1 Overview

3.1.1 REACTION TYPES

All reactions can be broken down into a succession of individual steps in each of which bonds are broken and/or formed. A chemical bond can be formed (or broken) in three ways.

(i) In a generalized ionic reaction step one of the atoms contributes both electrons to the bond either from a lone pair (**1**) or from another bond, often a multiple bond (**2**). The atom, molecule or ion which contributes the electron pair is a nucleophile and that which accepts it an electrophile.

(ii) In a free radical step each atom contributes one electron to the bond (**3**; the single-headed arrows represent the movement of single electrons). At least one of the reactants or products must contain an unpaired electron.

(iii) In a cyclic transition state the bond is formed or broken by the electrons moving in a ring.

(1) (2) (3)

3.1.2 HETEROAROMATIC REACTIVITY

The basic principles governing the degree and type of reactivity shown by heteroaromatic compounds are familiar from aliphatic and benzenoid chemistry. Three are very important:

(i) Oxygen, nitrogen or sulfur multiply-bonded to carbon can accept the whole of a shared pair of π-electrons (**4**) and thus allow a nucleophilic reagent to attack the carbon atom, as in many common reactions of carbonyl compounds. The attack by a nucleophilic reagent is easier when the heteroatom carries a positive charge (**5**).

(4) (5) (6) (7)

(ii) A shared pair of electrons on oxygen, nitrogen or sulfur adjacent to an unsaturated system can be made available for reaction through that system (**6**). This can also happen when the heteroatom carries a negative charge (**7**); the alkylation of the acetoacetate anion on carbon is an analogous reaction in aliphatic chemistry.

(iii) Aromatic compounds tend to 'revert to type', *i.e.* to return to their initial system of unsaturation, if disturbed.

These basic principles give much insight into the reactions of aromatic heterocyclic compounds.

3.1.3 ARRANGEMENT OF THE REACTIVITY SECTIONS

With each of the main groups of ring systems, the reactivity chapters are arranged in the same way, as is described in Section 1.3.4.2.

3.2
Reactivity of Six-membered Rings

3.2.1 REACTIVITY OF AROMATIC RINGS

3.2.1.1 General Survey of Reactivity

3.2.1.1.1 Pyridines

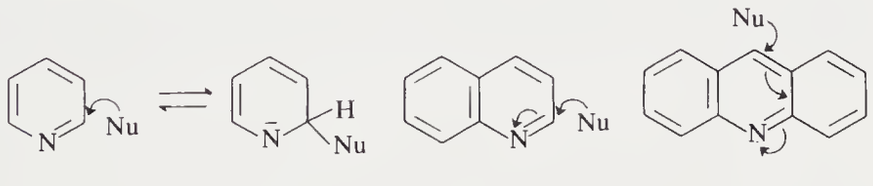
(i) Most pyridines are thermally and photochemically stable, but, just as in benzenes, polysubstitution can lead to susceptibility to such reaction modes.

(ii) As a first approximation, the reactions of pyridines with electrophiles may be compared with those of trimethylamine and benzene. Thus pyridine reacts easily at the nitrogen atom with reagents such as proton acids, Lewis acids, metal ions and reactive halides to form salts, coordination compounds, complexes and quaternary salts, respectively. Under much more vigorous conditions it reacts at ring carbons to form substitution products in nitration, sulfonation and halogenation reactions.

Pyridine is a weaker base (pK_a 5.2) than trimethylamine (pK_a 9.8): the sp^2-hybridized lone pair of the pyridine nitrogen atom is less available than the sp^3 lone pair. The conditions required for nitration or sulfonation of pyridine are far harsher than those needed for benzene. Substitution of a nitrogen atom for a CH group in benzene is equivalent to introducing an electron-withdrawing group (nitrogen is more electronegative than carbon); thus, pyridine itself should be substituted in the 3-position (about as readily as nitrobenzene). However, electrophilic reagents react at the pyridine nitrogen atom very readily, and in the strongly acid media used for nitration and sulfonation conversion to cation is essentially complete. Thus the CH in benzene is replaced by NH^+ and the positively charged nitrogen reduces the reactivity toward electrophilic substitution very much. It is for this reason that most pyridines are nitrated and sulfonated only with difficulty, and at high temperatures. Halogenation of pyridines is easier: *N*-halogenation is incomplete and *C*-halogenation can occur on the free base. Dihalogenation occurs since a halogen atom causes little additional deactivation of the ring.

(iii) The electron pull toward the nitrogen atom allows nucleophilic reagents to attack pyridines. Such attack may occur at α- or γ-ring carbon atoms or at the hydrogen of ring CH groups.

Nucleophilic attack at ring carbon occurs in benzenes only when electron-withdrawing substituents are present. Even with pyridine, only the strongest nucleophiles react. This is because formation of the initial adduct (**2**) involves de-aromatization of the pyridine ring and, once formed, many such adducts tend to re-aromatize by dissociation (**1** ⇌ **2**). Benzo fusion decreases the loss in aromaticity for the formation of the adduct and thus quinoline (**3**) and especially acridine (**4**) react more readily with nucleophiles.



(**1**) (**2**) (**3**) (**4**)

Reaction with nucleophiles by deprotonation at a CH bond occurs in pyridine much more readily than in benzene. The reactivity order is γ > ß > α rather than γ,α > ß because of lone pair – lone pair repulsion in the α-deprotonated species (*cf.* discussion in Section 3.2.1.7).

(iv) Pyridines undergo a variety of reactions with free radical reagents, and at surfaces: many of these parallel the corresponding reactions of benzenes. Electron uptake from a metal to form a radical anion occurs readily.

(v) Propensity toward cyclic transition state reactions again shows a parallel with benzenes: generally it is small for pyridines, but increases with suitable polysubstitution.

3.2.1.1.2 Azines

Extrapolation from benzene through pyridine to the diazines and then to the triazines and tetrazines delineates the main trends of azine chemistry.

(i) Reactions with electrophilic reagents become successively more difficult than those with pyridine, both at nitrogen (weakened basicity) and on ring carbon atoms (no reaction at all without activation, even in diazines).

(ii) Conversely, nucleophilic attack is increasingly easier than in pyridine. Nucleophiles which react only with quaternized pyridines will sometimes react with the parent diazines. Triazines and tetrazines are even attacked by weak nucleophiles.

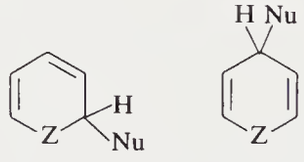
(iii) Successive introduction of nitrogen atoms into benzene causes a gradual reduction in aromatic stabilization. The diazines still show typical aromatic behavior in that in most of their reactions they revert to type. However, with the triazines and tetrazines decreasing aromaticity increases the ease both of thermal and photochemical fragmentations and rearrangements, and of cyclic transition state reactions with other reagents.

3.2.1.1.3 Cationic rings

(i) In the pyridinium, pyrylium and thiinium cations, there is no available nitrogen lone pair, and electrophilic attack at ring carbon is severely discouraged by the positive charge, although it can occur if sufficiently activating substituents are present.

Diazinium, oxazinium and thiazinium cations possess a 'pyridine-like' nitrogen atom, but it is of very weak basicity and nucleophilicity. However, pyridazines do form diquaternary salts with very strong alkylating agents such as oxonium compounds. Electrophilic attack at ring carbon in these compounds is practically unknown. These trends are emphasized in cationic rings with an increased number of nitrogen atoms.

(ii) A positive charge facilitates attack by nucleophilic reagents at positions α or γ to the heteroatom. Amines, hydroxide, alkoxide, sulfide, cyanide and borohydride ions, certain carbanions, and in some cases chloride ions react with pyridinium, pyrylium and thiinium cations under mild conditions to give initial adducts of types (**5**) and (**6**). These adducts undergo a wide variety of further transformations. Such reactions are further encouraged by the additional nitrogen atoms in diazinium, triazinium, *etc.*, cations.



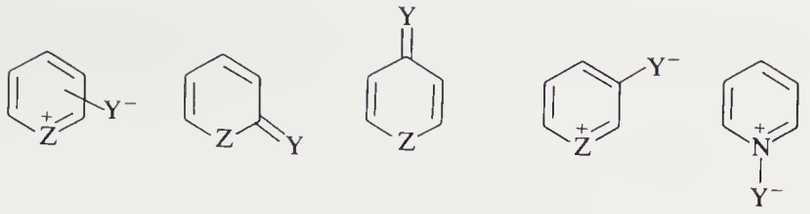
(**5**) (**6**)

(iii) A positive charge perturbs the electron distribution and thus reduces the aromaticity of a six-membered cationic ring. As expected, reaction with free radicals and reactions *via* cyclic transition states (both intra- and inter-molecular) are facilitated. The uptake of an electron to form a neutral radical is especially easy.

3.2.1.1.4 Pyridones, N-oxides and related compounds: betainoid rings

Three types of compound can be considered (see Section 2.2.1.2) to be derived from a cationic ring carrying a negatively charged substituent (**7**):

(i) If Y is α or γ to Z, then alternative uncharged canonicals (**8**) and (**9**) exist as in pyridones, pyridinethiones, *etc.* (see Section 3.2.3.7.2 for an overall survey of the reactivity of this type of compound).

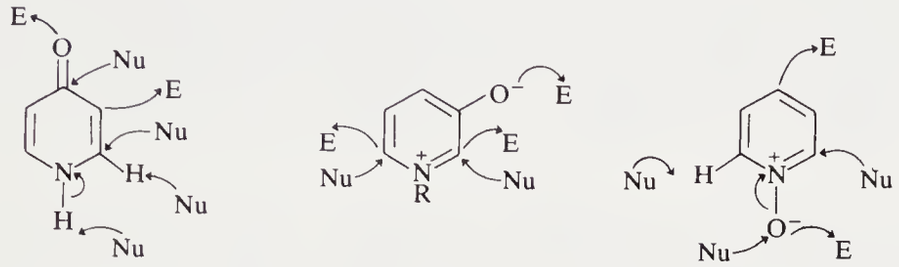


(7) (8) (9) (10) (11)

(ii) If Y is in the β-position, the compounds are true zwitterions (**10**) as in 3-oxidopyridinium, *etc.*

(iii) If Z is nitrogen, then the substituent Y can be directly attached to it, to give pyridine *N*-oxides, *N*-imides, *etc.* (**11**) (see Section 3.2.3.12.5 for an overall survey of their reactivity).

These compounds all contain both an electron source (Y^-) and an electron sink (Z^+). Furthermore, their aromaticity is significantly reduced by the non-uniform electron distribution. Hence they are highly reactive. The orientations of the reactions of these compounds with electrophilic and nucleophilic reagents are deducible from their canonical forms (see structures **12**–**14**).



(12) (13) (14)

(i) Electrophiles readily attack at the Y (not at the Z) atom and at C atoms *ortho* and *para* to Y. As a generalization, electrophilic attack at Y is relatively easy and relatively easily reversible, while that at C is more difficult, but less easily reversible.

(ii) Nucleophiles readily attack at C atoms α and γ to Z and at hydrogens attached to C atoms α to Z. If Z is NH, then nucleophiles can remove the NH proton to give a pyridone (*etc.*) anion.

(iii) Compounds of this type undergo a wide variety of thermal and photochemical rearrangements, and cycloaddition reactions *via* cyclic transition states.

(iv) Additional ring nitrogen atoms, as occur in, *e.g.* diazinones and thiazinones, alter but little the reactivity patterns of these compounds.

3.2.1.1.5 Anionic rings

Stable anions can be formed by the loss of a proton from *N*-unsubstituted pyridones or hydroxypyridines. They are the pyridine analogues of phenolate anions and react very readily with electrophilic agents at N, O or ring carbon (see Section 3.2.1.7.4).

3.2.1.1.6 Aromaticity and reversion to type

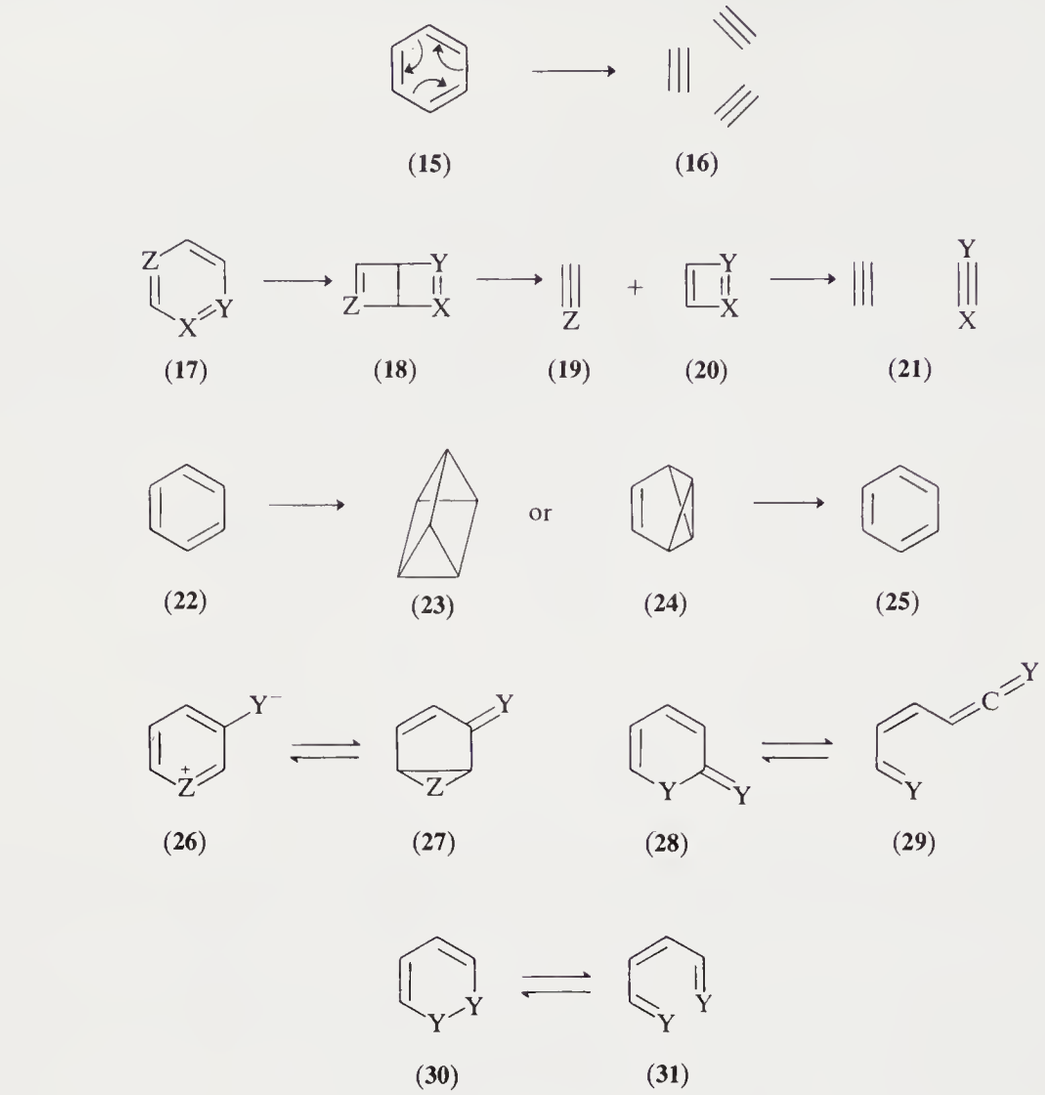
The aromaticity of six-membered rings is discussed in Section 2.2.4.2.

In general most of these compounds tend to react typically by substitution rather than addition, *i.e.* they tend to revert to type. However, ring oxygen atoms, an increasing number of ring heteroatoms, benzannelation and ring carbonyl groups all reduce the aromaticity. Thus phenoxazonium and phenothiazonium salts, oxazones and thiazones show increasing tendency to addition reactions.

3.2.1.2 Intramolecular Thermal and Photochemical Reactions

The fundamental types of thermally and photochemically induced intramolecular transformations are summarized in Scheme 1. All reactions of this class involve intermediates in which

aromaticity is lost; hence they are most common in the classes of less aromaticity, *i.e.* polyhetero rings, cationic rings, rings containing carbonyl groups. However, polysubstitution, especially by bulky groups, can also induce reactions by strain relief in transition states. Most of the reactions known are photochemical.



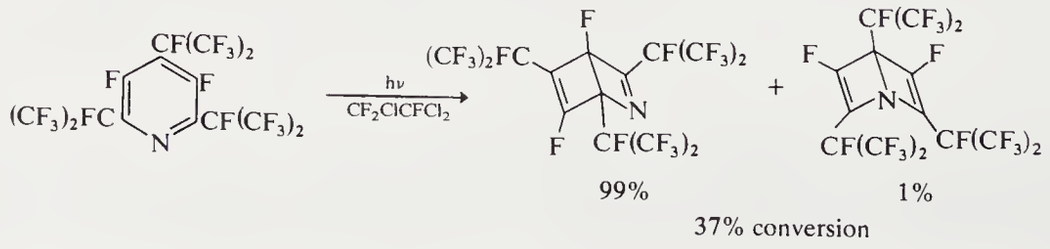
Scheme 1

3.2.1.2.1 Fragmentation (15→16)

Direct fragmentation (as opposed to those *via* rearrangement; see next section) only occurs in polyhetero rings. It is implicit in Scheme 1 that the presence of contiguous nitrogen atoms tends to labilize the rings, as well as provide extra stability to the fragmentation products (by increasing the possibilities for generating N_2 molecules). Thus, 1,2,4,5-tetrazines are thermolyzed to nitrogen and nitriles. (Photolysis affords the same products, but this may involve an intermediate of type (**18**).)

3.2.1.2.2 Rearrangement to or elimination via *Dewar heterobenzenes* (17)→(18)→(19), (20)→(21)

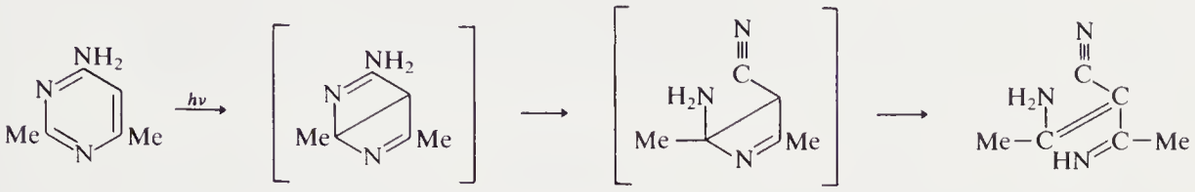
Certain polysubstituted pyridines yield isolable Dewar pyridines, as illustrated in equation (1) (see CHEC 2.05).



(1)

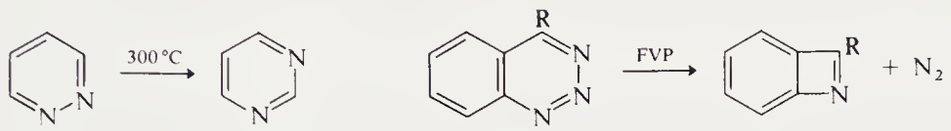
Irradiation of pyridine itself gives Dewar pyridine, observable spectroscopically, which in water is hydrolytically ring-opened to form $H_2N(CH{=}CH)_2CHO$, but in a matrix fragments to cyclobutadiene and HCN.

The photoisomerization of perfluoropyridazines to pyrazines is considered to involve Dewar diazine intermediates. Irradiation of 4-amino-2,6-dimethylpyrimidine gives the acyclic amino imine *via* the Dewar pyrimidine as shown in Scheme 2 ⟨82AHC(31)202⟩.



Scheme 2

Thermal reactions of this type are known, thus pyridazine (**32**) is isomerized to pyridimine (**33**) at 300 °C. Flash vacuum pyrolysis of 1,2,3-benzotriazines (**34**) gives benzazetes (**35**). It has been claimed that tris(dimethylamino)-1,2,3-triazine forms the monocyclic azete; trimethyl- and triphenyl-1,2,3-triazine, however, give nitrogen, a nitrile and the appropriate acetylene (*cf.* **20**→**21**).

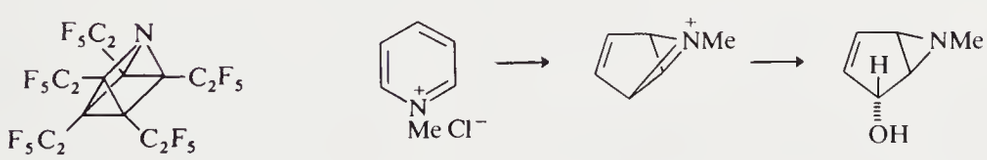


(**32**) (**33**) (**34**) (**35**)

This type of isomerization is much more common in carbonyl-containing rings. Thus 1-methyl-2-pyridone (**17**; XY = NMeCO, Z = CH) gives (**18**; XY = NMeCO, Z = CH), and irradiation of 2-pyranone similarly affords the bicyclic lactone (**18**; XY = OCO), which on further irradiation collapses to CO_2 and (**20**). Analogous compounds with additional ring nitrogen react similarly, *e.g.* 1,3-oxazin-6-ones (**17**; XY = OCO, Z = N) form the corresponding bicycle, which can eliminate CO_2, and 1,2,3-benzotriazin-4-ones similarly give the corresponding benzazetones.

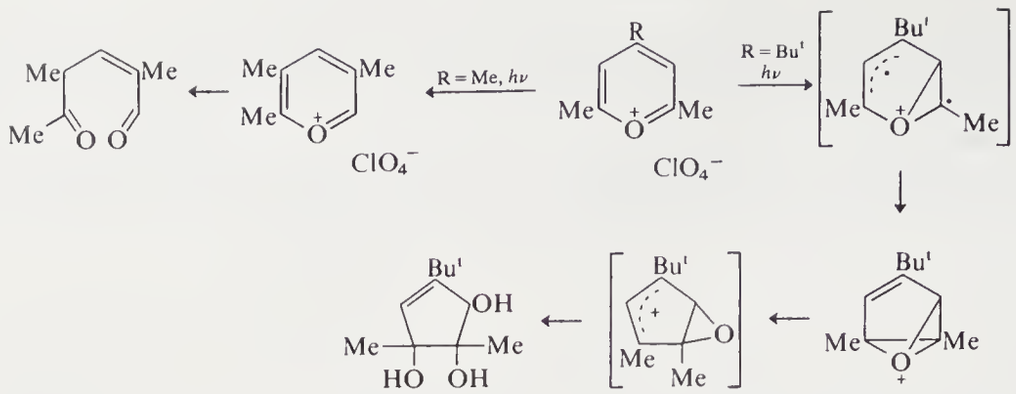
3.2.1.2.3 Rearrangement to or via *hetero-prismanes and -benzvalenes* (23), (24)

Pentakis(pentafluoroethyl)-1-azaprismane (**36**) can be isolated in 91% yield by irradiation of the corresponding pyridine. The photolytic isomerization of alkylpyridines (*e.g.* 2-picoline to 3- and 4-picolines) is believed to involve azaprismane intermediates.

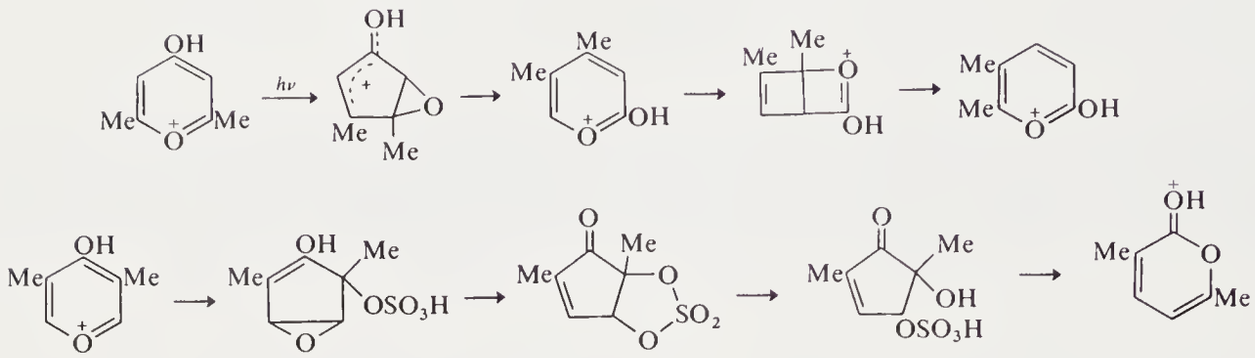


(**36**) (**37**) (**38**) (**39**)

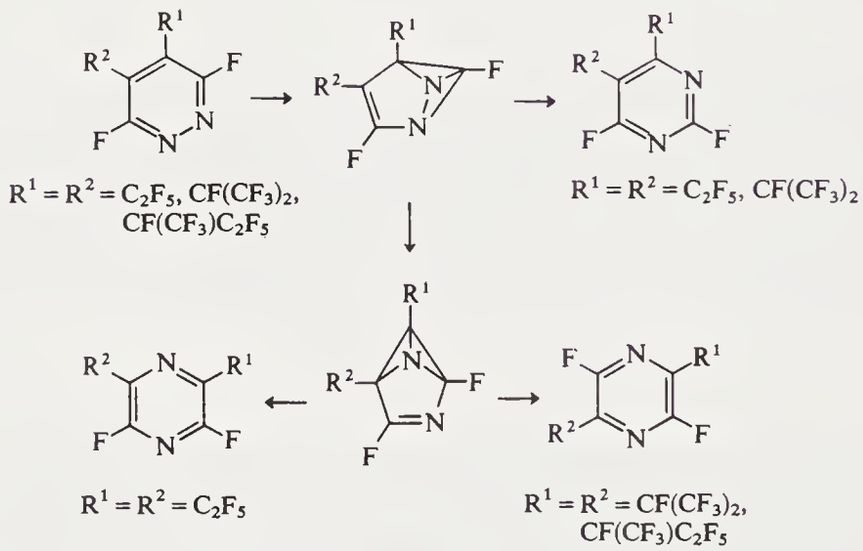
Photolysis of 1-methylpyridinium chloride (**37**→**39**) is considered to involve the azoniabenzvalene (**38**) as an intermediate, and similar behavior has been found in certain pyrylium cations (Schemes 3 and 4). Diazabenzvalenes are implicated in the rearrangement at 300 °C of certain perfluoropyridazines to pyrimidines and pyrazines (Scheme 5).



Scheme 3



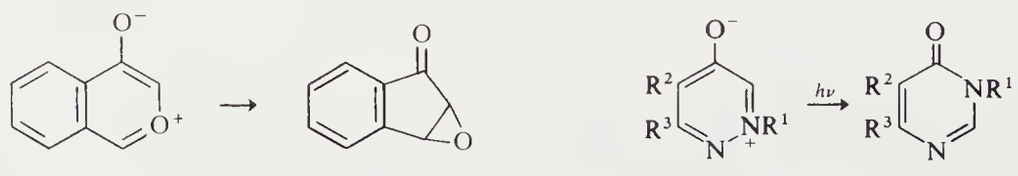
Scheme 4



Scheme 5

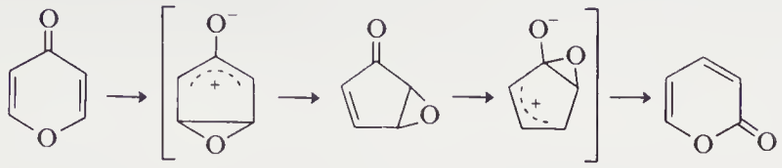
3.2.1.2.4 Rearrangement to or via *1,3-bridged heterocycles* (26)→(27)

3-Oxidopyridiniums (**26**; Z = NR, Y = O) are converted photochemically into the bicycle (**27**); corresponding 3-oxidopyryliums and especially 4-oxidoisochromyliums isomerize more easily (*cf.* **40**→**41**). 5-Oxidopyridazinium betaines are isomerized photochemically into corresponding pyrimidin-4-ones by a similar path (Scheme 6).



(**40**) (**41**) **Scheme 6**

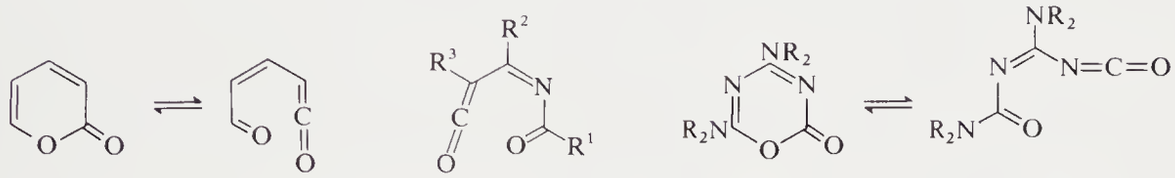
Photoisomerization of pyran-4-one and substituted derivatives to pyran-2-ones involves a zwitterionic intermediate of similar type (Scheme 7).



Scheme 7

3.2.1.2.5 Ring opening (28)→(29), (30)→(31)

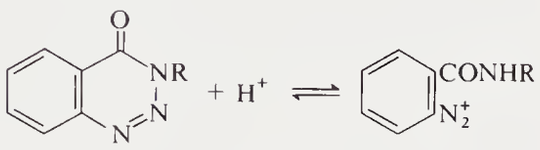
Irradiation of pyran-2-one gives the ketene (**42**) reversibly. Similar reactions are known for aza and diaza analogues. Thus, 1,3-oxazin-6-ones isomerize photochemically to ketene imines (**43**), and flash vacuum pyrolysis converts the oxadiazinone (**44**) reversibly into (**45**).



(**42**) (**43**) (**44**) (**45**)

2*H*-1,2-Oxazines and thiazines are unstable with respect to ring-opened isomers (*cf.* **30**→**31**).

1,2,3-Benzotriazin-4-ones on protonation undergo ring–chain tautomerism to yield diazonium ions (Scheme 8; see CHEC 2.18).



Scheme 8

3.2.1.3 Electrophilic Attack at Nitrogen

3.2.1.3.1 Introduction

Pyridines and azines behave as tertiary amines in their reactions with a wide range of electrophiles:

(i) proton acids give salts.
(ii) Lewis acids form coordination compounds.
(iii) transition metal ions form complex ions.
(iv) reactive halogen compounds give quaternary salts.
(v) activated alkenes (and alkynes) give quaternary salts (by Michael addition).
(vi) halogens form adducts.
(vii) certain oxidizing agents yield amine oxides.

The ease of such reactions depends on two major factors: the nucleophilicity of the nitrogen atom, dominated by its charge density, and the degree of steric hindrance. A minor factor is the juxtaposition of nitrogen lone pairs (the α-effect), which increases the reactivity at nitrogen in pyridazines, but not sufficiently to overcome the unfavorable electronic effect (see below).

The pK_a of a nitrogen is a convenient measure of its nucleophilicity: in proton addition steric effects are unimportant. All other types of electrophilic attack at nitrogen are sensitive in varying degrees to steric effects from α-substituents. (Exception: certain ring formation reactions as in metal chelation.)

Additional aza substitution decreases nitrogen charge density considerably, and the azines are all less nucleophilic than pyridine. Pyridine-like nitrogen atoms in cationic rings, *e.g.* diazinonium, oxazinium and thiazinium, are still less nucleophilic and few reactions with electrophiles are known, although diazines can be converted by reactive alkylating agents into diquaternary salts.

3.2.1.3.2 Effect of substituents

The electronic effects are summarized in (i)–(iii): these are quantified by the pK_a values of pyridines in Section 3.2.1.3.3. Steric effects (iv) are illustrated in Sections 3.2.1.3.4–3.2.1.3.11.

(i) Strongly electron-withdrawing substituents, *e.g.* NO_2, COR, Cl, make these reactions more difficult by decreasing the electron density on the nitrogen atom; the effect is largely inductive and therefore is particularly strong from the α-position.

(ii) Strongly electron-donating substituents, *e.g.* NH_2, OR, facilitate electrophilic attack by increasing the electron density on the nitrogen. This operates by the mesomeric effect and is strongest from the γ-position. From the α-position opposing inductive effects possessed by these same substituents can partially or wholly cancel the increase in reactivity caused by α-NH_2 or α-OR.

(iii) Fused benzene rings, aryl and alkyl groups, and other groups with relatively weak electronic effects have little influence.

(iv) Reactions other than proton addition are hindered by all types of α-group. The shape of the substituent is important: thus, Me, Et and Pr^i generally show rather similar effects (as Et and Pr^i can rotate) whereas Bu^t shows a much larger steric effect. However, buttressing and the 'gear effect' ⟨76JA2847⟩ can alter this situation. A fused five-membered ring is generally less hindering than a fused six-membered ring.

3.2.1.3.3 Orientation of reaction of azines

The position of attack in azines containing more than one ring nitrogen atom is determined by the substituents according to the above guidelines. Thus in 3-substituted pyridazines protonation will occur at position 2 only for strong electron donor substituents (effectively NR_2, O^-). All other protonations, and all other reactions with electrophiles occur predominantly at N-1. In 4-substituted pyridazines, where steric effects are unimportant and inductive effects of the substituent less important, reaction will occur at N-1 for electron donor and N-2 for electron acceptor substituents. In 3,6-disubstituted pyridazines, the less bulky and most activating substituent will direct the substitution α to it. In monocyclic 1,2,3-triazines, the 2-nitrogen atom is the site of electrophilic attack except in *N*-oxidation.

3.2.1.3.4 Proton acids

(i) Pyridine

Pyridines form stable salts with strong acids. Yellow ionic picrates are useful for characterization. Pyridine itself is often used to neutralize acid formed in a reaction and as a basic solvent. The basicity of pyridine (as measured by the dissociation constant of its conjugate acid, pK_a 5.2) is less than that of aliphatic amines (*cf.* NH_3, pK_a 9.5; NMe_3, pK_a 9.8). This reduced basicity is probably due to the changed bond hybridization of the nitrogen atom: in ammonia the lone electron pair is in an sp^3-orbital, but in pyridine it is in an sp^2-orbital. The higher the *s* character of an orbital, the more it is concentrated near the nucleus, and the less available for bond formation. Nitriles, where the lone electron pair is in an *sp*-orbital, are of low basicity.

(ii) Azines

The basicity of the diazines is sharply reduced from that of pyridine (pK_a 5.2): the pK_a of pyrazine is 0.4, pyrimidine is 1.1 and pyridazine is 2.1. The significantly higher basicity of pyridazine as compared to pyrazine, unexpected for mesomeric and inductive effects, is attributed to the lone pair–lone pair repulsion which is removed in the cation.

The basicities of triazines and tetrazines are undoubtedly considerably lower than those of the diazines, but few quantitative data are available.

A fused benzene ring has little effect on the pK_a values in the cases of quinoxaline (*ca.* 0.6) and cinnoline (2.6). Quinazoline has an apparent pK_a of 3.3 which makes it a much stronger base than pyrimidine, but this is due to covalent hydration of the quinazolinium cation (see Section 3.2.1.6.3); the true anhydrous pK_a for equilibrium between the anhydrous cation and anhydrous neutral species of quinazoline is 1.95 ⟨76AHC(20)128⟩.

(iii) Effects of substituents on basicity of pyridine

The ΔpK_a values of representative substituted pyridines as compared with pyridine itself are shown in Table 1. Substituent effects are in line with the discussion in Section 3.2.1.3.2.

(a) Methyl groups are weakly base strengthening due to hyperconjugative and inductive effects. The increase in pK_a is somewhat greater for α- and γ- than for β-methyl groups.

(b) Phenyl groups are weakly electron-withdrawing by the inductive effect but can release electrons by the mesomeric effect. The mesomeric effect does not operate for the *meta*-position, and 3-phenylpyridine has a reduced basicity. The inductive effect for the 4-position is weak leading to an increased basicity, whereas the two effects cancel in 2-phenylpyridine.

(c) Amino groups are strong mesomeric electron donors and hence base strengthening. The base strength is 4-amino > 2-amino (increased importance of opposing inductive effect) > 3-amino (small influence of mesomeric effect).

(d) Methoxy groups are mesomeric donors but inductive acceptors. The inductive effect is dominant for the 2-position, the mesomeric effect for the 4-position.

(e) Halogen atoms are strong inductive acceptors and weak mesomeric donors: they cause a marked decrease in basicity, especially from α-positions.

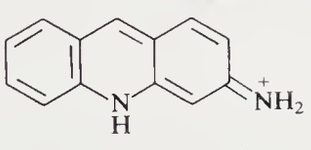
(f) The nitro group, strongly electron-withdrawing by both inductive and mesomeric effects, causes an especially large drop in basicity.

Table 1 ΔpK_a Values for Monosubstituted Pyridines (in H_2O)[a]

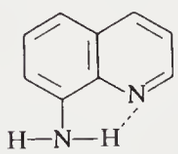
	Me	*Ph*	*NH_2*	*OMe*	*Cl*	*NO_2*
2-Position	0.8	0.1	1.7	−1.9	−4.5	−7.8
3-Position	0.5	−0.4	0.9	−0.3	−2.4	−4.4
4-Position	0.8	0.3	4.0	1.4	−1.4	−3.6

[a] *cf.* pyridine, pK_a 5.2.

(g) Fused benzene rings usually have little effect; *cf.* pK_a values: quinoline, 4.85; isoquinoline, 5.14; acridine, 5.6. Substituents on them usually have little effect on the basicity; however those which can lead to significant charge delocalization in the conjugate acid by a *p*-quinoid canonical form are base strengthening (*cf.* pK_a values: 7-aminoquinoline, 6.5; 3-aminoacridine (**46**), 8.04).



(**46**)



(**47**)

(h) Intramolecular hydrogen bond formation with the pyridine nitrogen atom is base weakening; *cf.* pK_a values: 8-aminoquinoline (**47**), 3.93; 4-aminoacridine, 4.40.

(i) Steric effects are usually unimportant; however in extreme cases as in 2,6-di-*t*-butylpyridine (pK_a 3.6) the pK_a does fall significantly below that of pyridine.

Much work has been done on the quantitative correlation of the basicity of pyridines with Hammett substituent constants. The best single parameter correlation for 4-substituents is with σ_p ⟨78AHC(22)81⟩.

(iv) Proton acids and azinone anions: acidity of azinones

Some pK_a values are collected in Table 2. Thiones are *ca.* 2 pK units more acidic than the corresponding azinones. Fused benzene rings have little effect except in the 3-substituted isoquinoline series where partial bond fixation lowers the acidity. Additional aza substitution increases the acidity significantly.

Table 2 Acidity of Azinones and Azinethiones[a]

Additional structure features	α-*Series*		γ-*Series*	
	$X=O$	$X=S$	$X=O$	$X=S$
—	11.7	9.97	11.09	8.83
3,4-Benzo	>11	10.82	—	—
4,5-Benzo	9.62	8.58	—	—
5,6-Benzo	>11	10.21	11.25	8.83
2N	—	—	8.68	6.54
3N	9.17	7.14	8.59	6.90
4N	8.23	6.32	—	—
5N	8.59	6.90	—	—
6N	10.46	8.30	—	—

[a] pK_a values in aqueous solution taken from ⟨63PMH(1)1⟩.

3.2.1.3.5 Metal ions

(i) Simple complexes

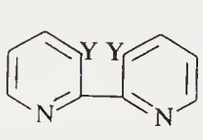
Many transition and B-subgroup metals form complex ions with pyridines in aqueous solution, *e.g.* $Ni^{2+} \rightarrow Ni(C_5H_5N)_4^{2+}$; $Ag^+ \rightarrow Ag(C_5H_5N)_2^+$; if certain anions are also present, uncharged complexes can result, *e.g.* $Cu^{2+} + 2OCN^- + 2C_5H_5N \rightarrow Cu(OCN)_2 \cdot (C_5H_5N)_2$, soluble in H_2O and $CHCl_3$; Ni^{2+}, Cd^{2+} and Zn^{2+} react similarly.

The diazines also form metal complexes. Thus pyrazine forms tetrahedral and octahedral complexes with Co^{II} and other transition metals: it functions as a monodentate and also as a bidentate bridging ligand to give polymeric complexes. The stability of these complexes is increased by back-bonding.

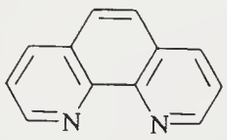
Pyridine and pyrazine can also replace up to three of the carbonyl groups in Group VI metal carbonyls to form compounds of type $Cr(CO)_3py_3$.

(ii) Chelate complexes

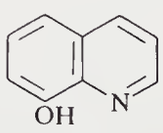
Chelate rings can be formed by pyridines containing α-substituents such as carboxyl or CH=NR. Important bicyclic chelating agents are 2,2′-bipyridyl (**48**; Y = H), *o*-phenanthroline (**49**) and 8-hydroxyquinoline (**50**), which all form bis- and tris-complexes with many metals. This type of complex formation has many analytical applications. Overlap between the *d*-orbitals of the metal atom and the pyridine π-orbitals is believed to increase the stability of many of these complexes. Steric effects can hinder complex formation as in (**48**; Y = Me).



(**48**)



(**49**)



(**50**)

Suitably substituted diazines also form chelate complexes, *e.g.* 2,3,5,6-tetrakis(α-pyridyl)-pyrazine yields red tridentate complexes with Fe^{II}.

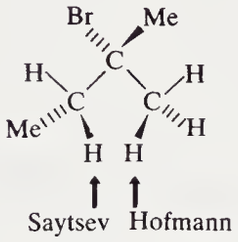
3.2.1.3.6 Alkyl and aryl halides and related compounds

(i) N-*Alkylation of pyridines*

Pyridines displace halide, sulfate, toluene-*p*-sulfonate and other ions from the corresponding alkyl compounds to form alkylpyridinium salts. These reactions are of the S_N2 type and are sensitive to steric changes in the pyridine or alkyl derivatives. Pyridine reacts exothermically with methyl iodide or dimethyl sulfate. Reactions involving pyridines with α-substituents of any type, electron-withdrawing β- or γ-substituents, or alkyl halides other than methyl, are slower and are often carried out by heating in a solvent of suitable high dielectric constant, such as acetonitrile, to promote ion formation. Alternatively a highly active alkylating agent can be used, such as an alkyl triflate.

The quantitative effects of α-substituents in decreasing the rates of these reactions are not additive and also depend considerably on solvent and alkylating agent. They are low in liquid sulfur dioxide as a solvent where solvation effects are small and the high dielectric constant increases the bond breaking in the transition state. For 3- and 4-substituted pyridines a Brönsted correlation exists between the rates of quaternization and the pK_a values ⟨78AHC(22)86⟩.

With tertiary halides, bimolecular elimination usually occurs; if isomeric alkenes can result, the proportions formed depend on the steric requirements of the pyridine because formation of the more substituted alkene (Saytsev Rule) is more sensitive to steric hindrance than formation of the less substituted alkene (Hofmann Rule). Pyridine and *t*-amyl bromide give 25% of 2-methylbut-1-ene (less substituted alkene), but 2,6-lutidine gives it in 45% yield (*cf.* **51**). However, pyridine and *t*-butyl bromide in the presence of $AgBF_4$ yield the 1-*t*-butylpyridinium ion.



(51)

(ii) Diazines and triazines

Alkyl halides react with diazines less readily than with pyridines. All the diazines are, nevertheless, more reactive toward methyl iodide than predicted by their pK_a values and the Brönsted relationship. The significant although modest rate enhancements found are considered to arise from interactions between the two lone pairs on the nitrogen atoms; this interaction is largest in pyridazine. Use of oxonium ions can convert the diazines into diquaternary salts. Quinoxalines and phenazines similarly yield diquaternary salts under forcing conditions.

The alkylation of pyridones and azinones is considered in Section 3.2.1.7.4.

(iii) N-*Arylation*

Only highly activated aryl halides react with pyridines. Thus, 2,4-dinitrochlorobenzene with pyridine forms 1-(2,4-dinitrophenyl)pyridinium chloride; active heteroaryl halides such as 2-chloropyrimidine react similarly. To phenylate pyridine, diphenyliodonium ions are needed: $Ph_2I^+BF_4^- +$ pyridine → 1-phenylpyridinium $BF_4^- +$ PhI. This reaction may involve initial electron transfer.

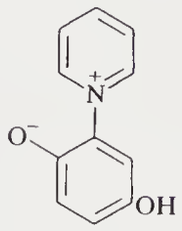
3.2.1.3.7 Acyl halides and related compounds and Michael-type reactions

Acyl and sulfonyl halides and anhydrides react instantaneously with pyridine to form quaternary salts. These salts are not usually isolated; they are excellent acylating and sulfonylating agents. The

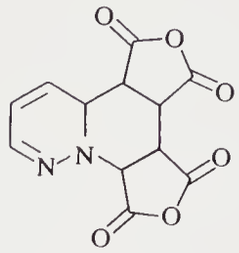
familiar use of pyridine as a solvent in such reactions reflects this. 4-Dimethylaminopyridine (DMAP) is very much more effective than pyridine in catalyzing acylation and related reactions, and in this case many of the highly reactive intermediates can be isolated.

Bromocyanogen and pyridine give 1-cyanopyridinium bromide, important for ring-opening reactions (see *e.g.* Section 3.2.1.6.3.iv).

Pyridines add to quinones in Michael-type reactions to give phenolbetaines (**52**). Many other Michael acceptors behave similarly, *e.g.* acrylate esters and acrylamides in the presence of acid yield quaternary ions $py^+CH_2CH_2COY$. Pyridazine at room temperature with maleic anhydride gives the 2:1 adduct (**53**).

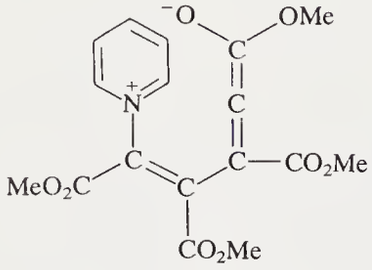


(52)

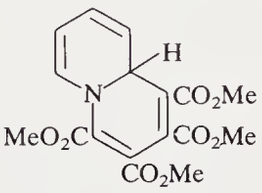


(53)

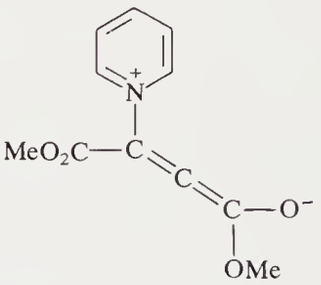
Such reactions occur readily with alkynic esters, but the products isolated are often complex. Thus the initial Michael adduct of type (**56**) from pyridine with acetylenedicarboxylic ester reacts with more alkynic ester to yield (**54**), (**55**) and other products. Quinoline and isoquinoline react similarly.



(54)



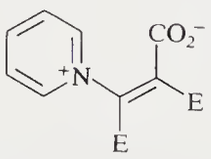
(55)



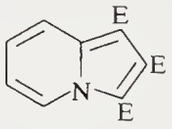
(56)

Ylide (**56**) can also be trapped by carbon dioxide to give (**57**). In the presence of water the reaction can take a different course and give the indolizine (**58**) ⟨78AHC(23)350⟩.

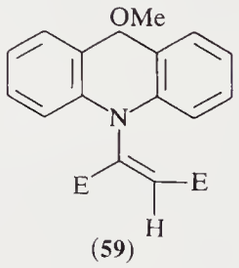
Acridine and dimethyl acetylenedicarboxylate in the presence of methanol yield the addition compound (**59**) ⟨63AHC(1)159⟩.



(57)



(58)

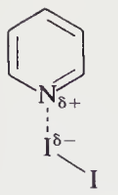


(59)

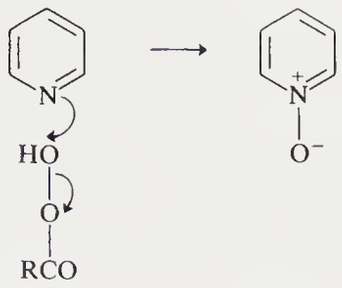
E = CO_2Me

3.2.1.3.8 Halogens

At room temperature pyridines react reversibly with halogens and interhalogens, *e.g.* ICl, to give unstable adducts, which behave as mild halogenating agents. X-Ray diffraction studies of the pyridine–iodine complex have given its structure (**60**).



(60)



(61) (62)

3.2.1.3.9 Peracids

Pyridine *N*-oxides are formed by the treatment of pyridines with peracids (**61–62**). Typical conditions are $MeCO_2H/H_2O_2$ at 100 °C or *m*-$ClC_6H_4CO_3H/CHCl_3$ at 0 °C. The pyridine nitrogen atom reacts less readily with peracids than do aliphatic tertiary amines, as expected. Large α-substituents and any electron-withdrawing substituents slow the reaction; thus the *N*-oxidation of 2,6-diphenylpyridine proceeds in poor yield, and efficient conversion of pentachloropyridine to the *N*-oxide requires a powerful oxidant such as peroxytrifluoroacetic acid.

The formation of *N*-oxides by peracid oxidation of azines proceeds less readily than in the pyridine series. Thus, although pyrimidine and its simple alkyl derivatives can be converted to the *N*-oxides, yields are usually low.

The orientation of *N*-oxide formation in diazines follows the rules outlined in Section 3.2.1.3.2. Thus, 3-aminopyridazines give mainly 2-oxides; other 3-substituted pyridazines form 1-oxides. However, the orientation of *N*-oxide formation in pyrazines can depend on the conditions: 2-chloropyrazine normally forms the 4-oxide as expected, but in strongly acidic conditions the 4-nitrogen atom is protonated, and *N*-oxide formation takes place at the 1-position. *N*-Oxidation of 1,2,3-triazines gives mainly the 1-oxides together with smaller amounts of the 2-oxides in fair overall yield.

Only pyrazine and its benzo derivatives are easily converted into di-*N*-oxides, although di-*N*-oxides have been reported, for example, in the pyridazine, pyrimidine and cinnoline series.

3.2.1.3.10 Aminating agents

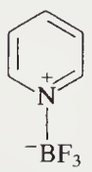
Hydroxylamine *O*-sulfonic acid converts pyridine into the 1-aminopyridinium cation. Pyridazines undergo *N*-amination readily.

Reactions with nitrenes, which also give *N*-amination, are considered in Section 3.2.1.8.1.

3.2.1.3.11 Other Lewis acids

Pyridine readily forms stable coordination compounds. Thus, boron, aluminum and gallium trihalides react at 0 °C in an inert solvent to give 1:1 adducts (*cf.* **63**). Steric factors are important, and α-substituents decrease the ease of reaction. This is illustrated by the heats of reaction of pyridine, 2-methylpyridine and 2,6-dimethylpyridine with boron trifluoride which are 101.3, 94.1 and 73.2 kJ mol^{-1}, respectively. The marked decrease in exothermicity here should be contrasted with the small steric requirement of the proton as shown by the pK_a values of substituted pyridines (see Section 3.2.1.3.4).

Sulfur trioxide gives the expected adduct, a sulfonating agent; similarly *N*-nitropyridinium tetrafluoroborate is formed with $NO_2^+ BF_4^-$.



(63)

3.2.1.4 Electrophilic Attack at Carbon

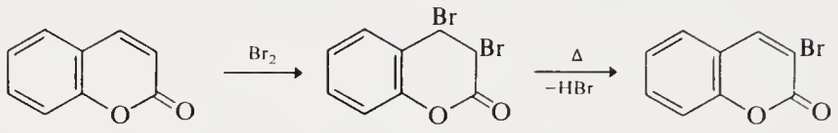
3.2.1.4.1 Species undergoing reaction and reaction mechanism

The intrinsic difficulty of electrophilic substitution of pyridines and azines is exacerbated because most of these reactions are carried out in acidic conditions where the pyridine nitrogen atom has become protonated. However, although electrophilic reagents react at the nitrogen atoms very readily, these reactions are often reversible, and even in strongly acidic solution there is a small proportion of the free base present. Thus, *a priori,* reaction is possible either on the conjugate acid majority species or on the minority free base species. In fact, considerable work has shown that some reactions occur on the pyridine or diazine free base, other reactions on conjugate acids.

The weaker the basicity of the pyridine nitrogen, the more likely it is that the reaction could occur on the free base. α-Halogen atoms are particularly effective, in that they sharply reduce basicity but not very much the susceptibility toward electrophilic substitution.

Halogenation of pyridines is easier than nitration or sulfonation because it can be carried out in non-acidic media and the pyridine–halogen adducts are appreciably dissociated. Dihalogenation can occur since one halogen atom causes little additional deactivation of the ring. The mercuration of pyridines (Section 3.2.1.4.9) probably involves coordination of the pyridine nitrogen to the mercury atom, and such coordination causes less ring deactivation than protonation.

In some instances, especially with the oxygen and sulfur heterocycles, the overall reaction leading to a substituted product does not involve an S_EAr mechanism but proceeds by an addition followed by elimination sequence, as outlined for the bromination of coumarin in equation (2). The choice of experimental conditions can affect the outcome of the reaction, as illustrated in the formation of (**88**) and (**89**) in Section 3.2.1.4.7.



(2)

3.2.1.4.2. Reactivity and effect of substituents

The reactivity of six-membered rings toward electrophilic substitution reactions can be summarized as follows:

(i) Triazines, diazines *without* strongly activating substituents (NH_2,OR) and pyridines *with* strongly deactivating substituents (NO_2,SO_3H,COR,*etc.*) do not react.

(ii) Pyridines without strong activation, diazines with a single strongly activating substituent and diazinones undergo nitration and sulfonation with difficulty (reactivity *ca.* that of *m*-dinitrobenzene) and halogenation somewhat more readily.

(iii) Pyridones, aminopyridines, and diazines with two strongly activating substituents readily undergo nitration, sulfonation and halogenation (reactivity *ca.* that of benzene).

(iv) Pyridines with two, and diazines with three strongly activating substituents are very reactive toward electrophilic substitution.

(v) Pyridines, pyridones and pyrones containing an amino or hydroxy group also undergo diazo coupling, nitrosation and Mannich reactions, as do their benzenoid analogues, phenol or aniline. Such reactions take place under conditions of relatively low acidity where less of the compounds is in the form of unreactive cations.

(vi) Alkyl groups and halogen atoms behave normally as weakly activating and deactivating substituents, respectively.

(vii) Fused benzene rings do not much affect the intrinsic reactivity, but electrophilic substitution frequently occurs in the benzene ring (see next section).

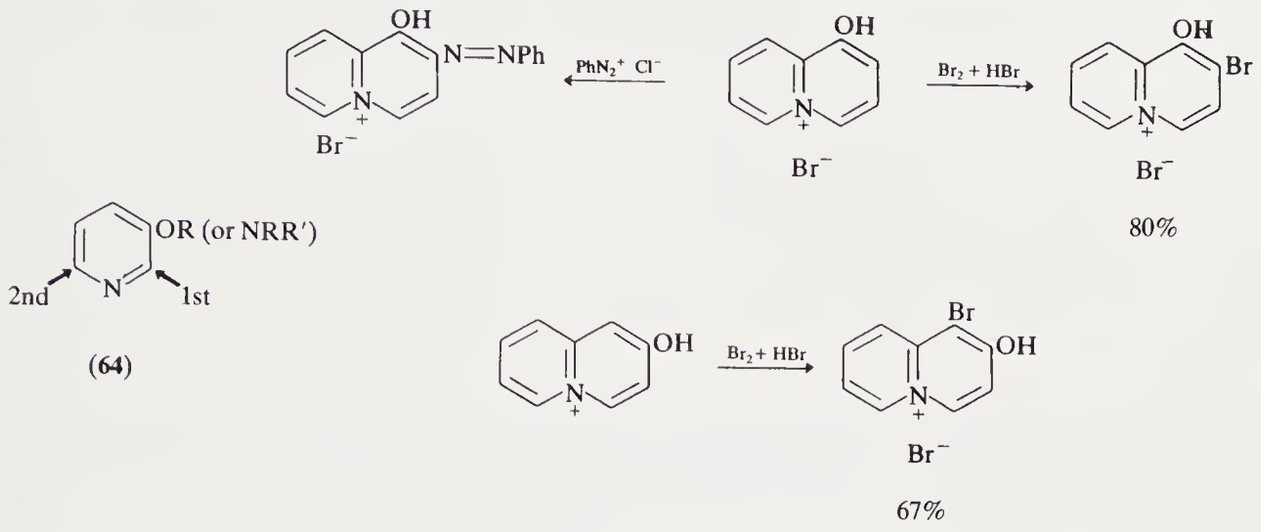
(viii) It follows from the above that the influence of substituent groups on the ease of electrophilic attack on ring carbon atoms can be largely predicted from a knowledge of benzene chemistry.

3.2.1.4.3 Orientation

Substituents exert their normal directive effects, and aza substitution directs *meta.* If there is conflict, then a strongly *para* directing substituent dominates. Thus, 3-hydroxypyridine reacts first

at the 2- and then at the 6-position. Pyridine 1-oxide is nitrated at position 4 as the free base but sulfonated at position 3 as the conjugate acid.

meta-Disubstituted benzenes containing one strongly *o,p*-directing and one strongly *m*-directing group are often further substituted between the two groups, and this may be compared with the orientation observed in (**64**). In the quinolizinium ion, amino or hydroxy groups in position 1 direct to the 2-position and those in position 2 direct to the 1-position (Scheme 9).



Scheme 9

In benzo- and phenyl-pyridines and in phenylpyridine 1-oxides, electrophilic substitution usually takes place in the benzene ring. In benzo-pyridones, -pyrones and -pyridine *N*-oxides, electrophilic substitution often occurs in either the benzene or the heterocyclic ring depending on the conditions; sometimes mixtures are formed (see Section 3.2.3.2.1).

3.2.1.4.4 Nitration

(i) Pyridines

Pyridine itself requires vigorous conditions for nitration (H_2SO_4–SO_3–KNO_3 at 300 °C); 3-nitropyridine is obtained only in poor yield. A single methyl group is insufficient activation; on attempted nitration, the picolines are extensively oxidized. However, 2,6-lutidine and 2,4,6-collidine afford the corresponding 3-nitro derivative in fair yield in milder conditions (H_2SO_4–SO_3–HNO_3 at 100 °C).

As expected, an amino group facilitates nitration strongly. 2-, 3- and 4-Aminopyridines are nitrated smoothly (H_2SO_4–HNO_3 at 40–70 °C to form mono- (5-, 2- and 3-, respectively) and di-nitro derivatives (3,5-, 2,6- and 3,5-, respectively) (Section 3.2.1.3.2). Alkylamino-, alkoxy- and 3-hydroxy-pyridines react analogously to the corresponding amino compounds.

Most nitrations of pyridines take place on the *N*-protonated species, and this includes the conversion of 2,6-dimethoxypyridine to the 3-nitro derivative. However, the further nitration of 2,6-dimethoxy-3-nitropyridine to the 3,5-dinitro derivative occurs on the free base. The introduction of the first nitro group reduces the basicity such that sufficient free base is now present for the reaction to take place through this minority species. 2,6-Dihalopyridines also undergo nitration as free base.

In general pyridines with $pK_a > 1$ nitrate as conjugate acids at the α- or β-position depending on the orientating effect of the attached substituents, while derivatives with $pK_a < -2.5$ nitrate as free bases. Those pyridines with intermediate pK_a values often show a mechanistic changeover, with change in pH (H_0).

(ii) Azines

Two or more electron-releasing substituents make 5-nitration in pyrimidines relatively easy: 2,4-diamino-6-chloropyrimidine yields the 5-nitro compound *via* a nitramine intermediate. Similarly,

4-amino-3,6-dimethoxypyridazine undergoes easy nitration to the corresponding 5-nitro compound. The less activated 3-methoxy-5-methylpyridazine requires more vigorous conditions, yielding 4-, 6- and 4,6-di-nitro derivatives.

(iii) Cationic rings

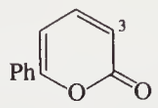
Few examples are known, but 1,2,4,6-tetramethylpyridinium can be nitrated to yield the 3-nitro derivative.

(iv) Pyridones, pyrones and azinones

2- and 4-Pyridone and their 1-alkyl derivatives are readily nitrated to form first the 3- or 5-mono- (H_2SO_4/HNO_3, 30 °C) and then the 3,5-di-nitro derivatives. These nitrations involve reactions of the neutral pyridone species. The proportions of 3- and 5-nitration in 2-pyridone vary with the conditions. 3-Nitration is favored at low acidity and high temperature and 5-nitration by the reverse.

Quinolin-2- and -4-ones can be nitrated in the 3-position (HNO_3, 100 °C); under conditions of higher acidity reaction occurs on the protonated species in the benzene ring (see Section 3.2.3.2.1).

Nitration of 6-phenyl-2-pyrone (**65**) depends on the conditions. The free base reacts at the 3-position, the conjugate acid at higher acidities in the *p*-position of the phenyl group.



(**65**)

Nitration of 4,5-dichloro-2-methylpyridazin-3-one occurs at position 6. Pyrimidin-2-one is nitrated under vigorous conditions to give the 5-nitro derivative, whereas 1-methylpyrimidine-2,4-dione yields the 5-nitro derivative at 25 °C.

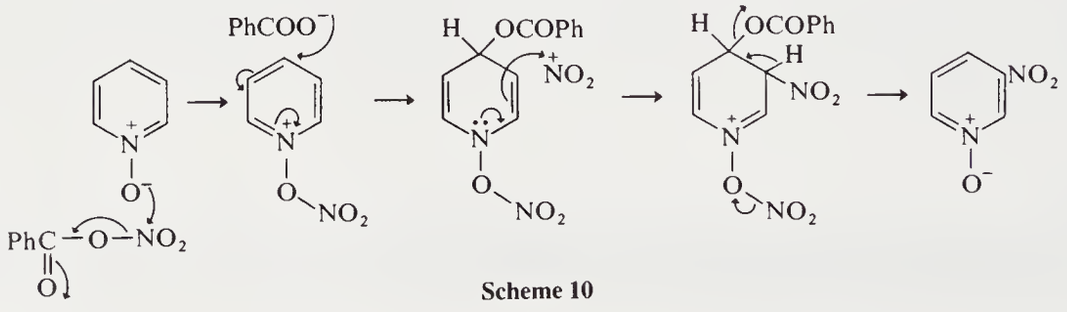
(v) Azine N*-oxides*

Pyridine 1-oxide is nitrated (H_2SO_4/HNO_3, 100 °C) to give the 4-nitro derivative in good yield. Substituted pyridine oxides such as the 2- and 3-methyl, -halo and -methoxy derivatives also give 4-nitro compounds in high yield. Quinoline 1-oxides are selectively nitrated in the 4-position at temperatures above *ca.* 80 °C whereas at lower temperatures nitration occurs in the benzo ring (Section 3.2.3.2.1).

Nitrations of pyridine 1-oxides in the 4-position take place on the neutral free base species. 2,6-Dimethoxypyridine 1-oxide is nitrated as the conjugate acid to yield the 3-nitro derivative; a second nitration to give the 3,5-dinitro analogue takes place on the free base.

Pyridazine 1-oxide and many of its substituted derivatives undergo nitration with nitric and sulfuric acids at position 4 to form the corresponding 4-nitropyridazine 1-oxides. If the 4-position is occupied nitration can occur at the 6-position.

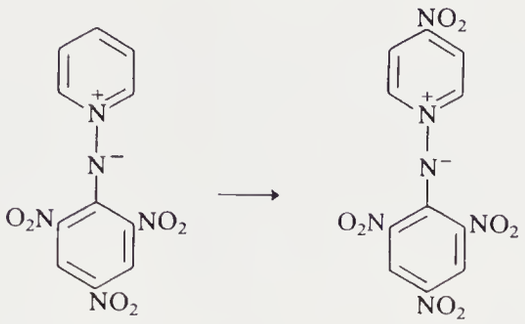
Reaction of pyridine 1-oxide with benzoyl nitrate leads to the 3-nitro derivative: the postulated mechanism is shown in Scheme 10.



Scheme 10

Nitration of pyridazine *N*-oxides with acyl nitrates prepared from acyl chlorides and silver nitrate also occurs at the β-position relative to the *N*-oxide group. Thus, pyridazine 1-oxide yields 3-nitropyridazine 1-oxide.

Pyridine-*N*-(2,4,6-trinitrophenyl)imine (**66**) can be nitrated in the 4-position (equation 3).



(3)

(**66**)

3.2.1.4.5 Sulfonation

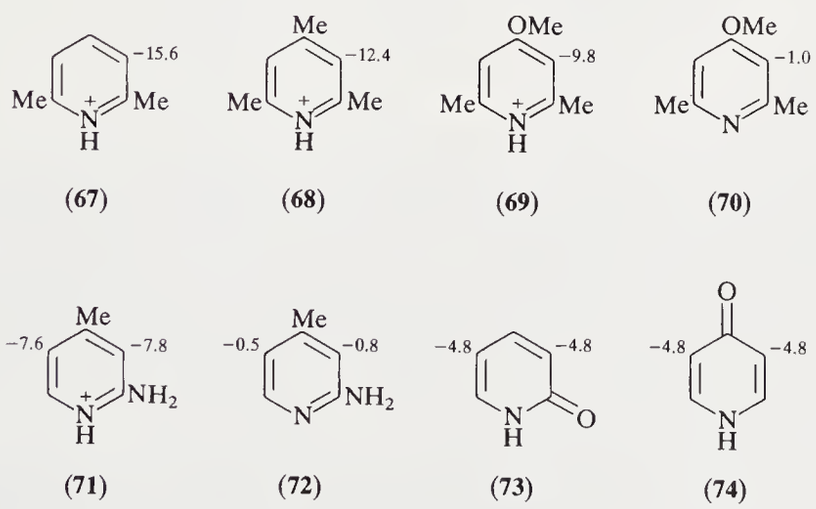
Sulfonation of pyridine affords the 3-sulfonic acid in 70% yield, but vigorous conditions (H_2SO_4–SO_3, 230 °C) and $HgSO_4$ catalyst are required. The picolines form β-sulfonic acids similarly. Sulfonation of pyridine at 360 °C gives a considerable amount of the 4-sulfonic acid. Heating the 3-sulfonic acid at this temperature produces a similar result; presumably, thermodynamic control takes over.

2-Aminopyridine and 1-methyl-2-pyridone are sulfonated under milder conditions (H_2SO_4–SO_3, 140 °C) in the 5-position. 2,6-Di-*t*-butylpyridine is converted into the 3-sulfonic acid under mild conditions (SO_2–SO_3, 0 °C) because reaction of SO_3 at the nitrogen atom is prevented sterically: thus reaction occurs on the free base species, under conditions where this is the majority species.

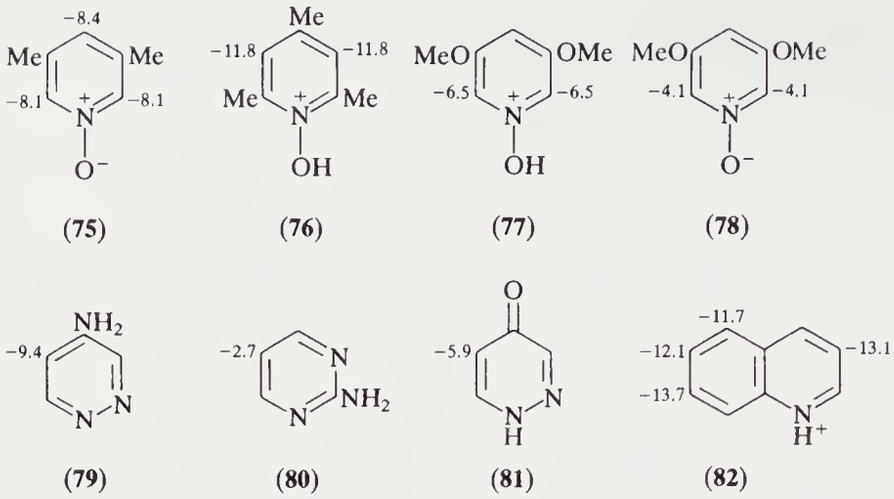
Sulfonation of pyridine 1-oxide requires vigorous conditions (H_2SO_4–SO_3–Hg^{2+}, 230 °C) and gives the 3-sulfonic acid (*cf.* Section 3.2.1.4.1).

3.2.1.4.6 Acid-catalyzed hydrogen exchange

Acid-catalyzed hydrogen exchange can be detected by isotopic labelling. Deuteration (followed by NMR) and tritiation (followed by radioactivity) rates of exchange at various ring positions at different acidities and temperatures have been investigated. By extrapolating all measurements to 100 °C and pH = 0, standardized rates of hydrogen exchange have been established for a large number of heterocycles, some of which are given in Scheme 11.



Scheme 11 Rates of hydrogen exchange standardized to 100°C and pH 0 (log k_0)



Scheme 11 Rates of hydrogen exchange standardized to 100°C and pH 0 (log k_0) (*continued*)

Compared to the rate for one position in benzene (log $k_0 = -11$), the large effect of the N^+ pole is apparent: from the *meta*-position it more than cancels the activating effect of three *o*/*p* methyl groups. A neutral nitrogen has a much smaller effect as is seen by the comparisons (**69**)/(**70**) and (**71**)/(**72**). In a protonated *N*-oxide, the rate-decreasing effect of N^+—OH is little different from N^+H [*cf.* (**68**)/(**76**)]; however, the neutral N^+—O^- group is much less deactivating at the 2- and 4-positions [*cf.* (**67**)/(**75**)]. Pyridones exchange rapidly as their neutral species.

Considerable work has also been done with activated derivatives of the diazines. 4-Aminopyridazine and pyridazin-2-one undergo exchange in the form of their free bases at position 5. Comparisons of (**72**) with (**79**) and (**80**) show the considerable effect of a *para*-N, while that of the *meta*-N is much less.

In the quinolinium cation, there is little difference in reactivity between position 3 and all the positions of the benzene ring (**82**).

Pyrimidin-2-one exchanges its 5-hydrogen much faster than the corresponding exchange in pyridin-2-one. However, this is due to the existence of a small proportion of the covalent hydrate (**83**) which undergoes rapid exchange.

(**83**)

3.2.1.4.7 Halogenation

(i) Pyridines

Pyridine with CoF_3–F_2 gives perfluoropiperidine; conversion of pyridine to mainly 2-fluoropyridine occurs with xenon difluoride.

Vapor phase chlorination at 150–200 °C and bromination at 300 °C of pyridine give fair yields of the 3-mono- and 3,5-di-halo derivatives. As the temperature is raised increasing amounts of α-substitution occur (Section 3.2.1.8.2). Vapor phase chlorination of quinoline yields first the 3-chloro derivatives which undergo further substitution, but alkylpyridines generally undergo side-chain halogenation (Section 3.2.3.3.3).

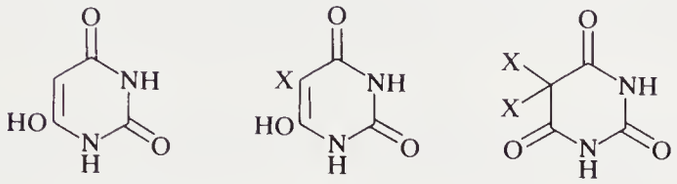
Chlorination and bromination of pyridine and some alkylpyridines in the β-position can be effected in the liquid phase at ~ 100 °C using excess $AlCl_3$ as catalyst. β-Bromination of pyridine and 2- and 4-picoline is conveniently effected in oleum at 80–120 °C. Bromination kinetics using HOBr in aqueous $HClO_4$ indicate that the partial rate factor for bromination of the pyridinium cation is $\sim 10^{-13}$, comparable to that for nitration.

Halogenation of 3-hydroxy- and 2-, 3- and 4-amino-pyridines proceeds under milder conditions (*e.g.* Cl_2, Br_2 or I_2 in EtOH or H_2O, 20–100 °C) to form the mono- and di-halo derivatives. The orientations of these products are *ortho* and *para* to the activating group, as expected.

(ii) Azines

Unsubstituted pyrimidine undergoes 5-halogenation under vigorous conditions; thus, bromination occurs at 230 °C. Pyrazine is chlorinated at 400 °C to give a mixture of mono-, di-, tri- and tetra-chloropyrazines, presumably by a free radical mechanism.

Halogenation of diazines containing one or more activating groups proceeds easily (Br_2 or Cl_2 in H_2O, AcOH, or $CHCl_3$, 20–100 °C). Sometimes 5,5-dihalo products are formed by ring de-aromatization, *e.g.* barbituric acid (**84**) gives successively (**85**) and (**86**).



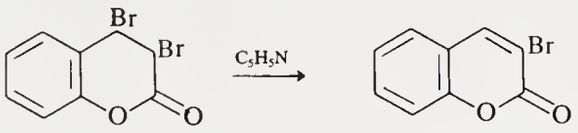
(**84**) (**85**) (**86**)

(iii) Pyridones, pyrones, azinones and N*-oxides*

2- and 4-Pyridones and 2- and 4-pyrones readily give their 3-mono- and 3,5-di-halo derivatives; even chelidamic acid (**87**) reacts in this way. Bromination of pyran-2-one gives the substitution product (**89**) or the addition product (**88**) depending on the conditions.

(**87**) (**88**) (**89**)

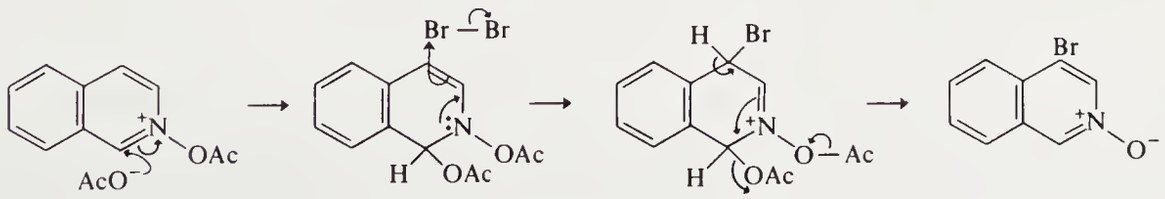
Quinolin-4-one forms a 3-bromo derivative, but coumarin gives the addition compound (**90**) which is easily re-aromatized (**90**→**91**). 4-Thiopyrones are halogenated in position 3. Pyridazinones and cinnolinones are also readily halogenated in the expected position.



(**90**) (**91**)

Halogenation of pyridine 1-oxide is not easy. Bromination in oleum gives the 3-bromo derivative, presumably *via* the conjugate acid, but only small yields of 4-bromopyridine 1-oxide have been obtained under less acidic conditions.

Quinoline 1-oxide gives a 4-bromo derivative (Br_2–H_2O, 100 °C). Isoquinoline 2-oxide is brominated in the 4-position by the mechanism of Scheme 12.



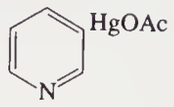
Scheme 12

3.2.1.4.8 Acylation and alkylation

Friedel–Crafts reactions are almost unknown in pyridine and azine chemistry.

3.2.1.4.9 Mercuration

Pyridine forms 3-acetoxymercuripyridine (**92**) ($Hg(OAc)_2 - H_2O$, 155°C); 2-amino- and 4-methyl-pyridine give the 5- and 3-acetoxymercuri compounds, respectively, at somewhat lower temperatures. Mercuric acetate mercurates 4-pyridone in the 3-position and 3-hydroxypyridine in the 2-position.



(**92**)

Isoquinoline forms a 4-acetoxymercuri derivative. Pyridine 1-oxide is mercurated predominantly in the 2-position, but increasing acidity increases the proportion of 3-mercuri product formed.

3.2.1.4.10 Nitrosation, diazo coupling, Mannich reaction, Kolbe reaction and reaction with aldehydes

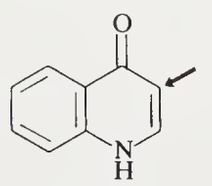
In general, only those pyridines containing hydroxy or amino groups, diazines with multiple amino or hydroxy substitution, and pyridones will undergo these reactions. Some examples are now given.

(i) Nitrosation

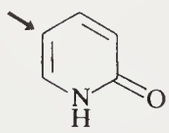
2,6-Diaminopyridine with nitrous acid forms the 3-nitroso derivatives. Nitrosation of pyrimidines occurs readily in the presence of three electron-releasing substituents; pyrimidine-4,6-diamine is also nitrosated to the blue 5-nitroso derivative.

(ii) Diazo coupling and Mannich reaction

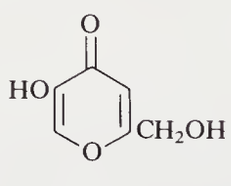
Quinol-4-one (**93**), 2-pyridone (**94**), kojic acid (**95**) and 4-hydroxycoumarin (**96**) couple with diazonium salts (to form azo compounds, *e.g.* **97**) and undergo Mannich reactions (*e.g.* with $HCHO + HNMe_2$ to form $—CH_2NMe_2$ derivatives) at the positions indicated. Chromones undergo the Mannich reaction to give for example (**98**).



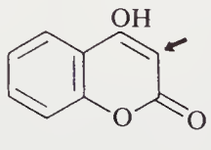
(**93**)



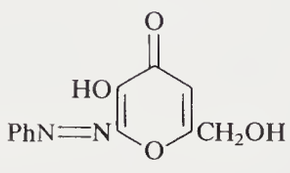
(**94**)



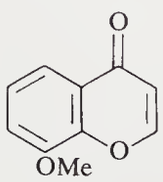
(**95**)

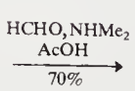


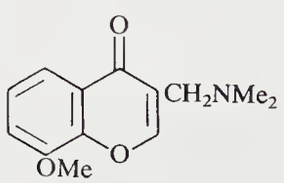
(**96**)



(**97**)







(**98**)

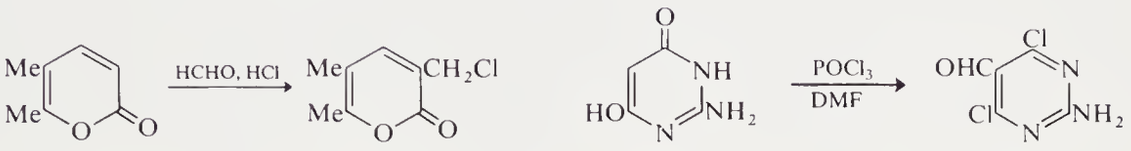
Mannich reactions and diazo coupling proceed readily in pyrimidines provided activating groups are present in each of the 2-, 4- and 6-positions.

(iii) Kolbe and Reimer–Tiemann reactions

3-Hydroxypyridine undergoes the Kolbe reaction (with carbon dioxide to give the carboxylic acid); the Na salt reacts mainly at the 2-, the K salt at the 6-position. Uracil undergoes the Reimer–Tiemann reaction with sodium hydroxide/chloroform to give 5-formyluracil.

(iv) Reactions with aldehydes

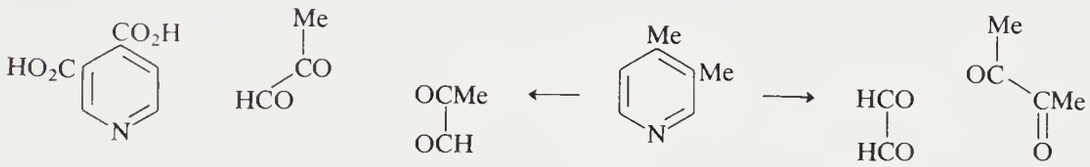
3-Hydroxypyridine and formaldehyde give 2-hydroxymethyl-3-hydroxypyridine. Pyrones can be chloromethylated, *e.g.* (**99**)→(**100**). Hydroxymethylation of the 5-position is possible in pyrimidines with at least two electron-releasing substituents. Under Vilsmeier–Haack conditions pyrimidones are converted into 5-formylchloropyrimidines; for example (**101**) gives (**102**).



(**99**) (**100**) (**101**) (**102**)

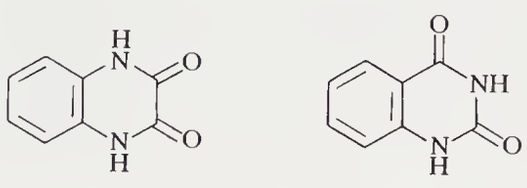
3.2.1.4.11 Oxidation

It is convenient to discuss oxidative attack at ring carbon here although this can involve radical as well as electrophilic oxidizing agents. Pyridine rings are generally very resistant to oxidation. CrO_3 dissolved in pyridine is used as a reagent to oxidize hydroxy groups, particularly in steroids. Many pyridine substituent groups can be selectively oxidized by $KMnO_4$, O_2 or $K_2Cr_2O_7$, especially under acid conditions. In alkaline media, some oxidative degradation of pyridine rings occurs; thus isoquinoline gives both cinchomeronic (**103**) and phthalic acids ($KMnO_4$–$NaOH$–H_2O) (Section 3.2.3.2.1). Ozone reacts with pyridines, although less readily than with benzenes; products corresponding to both Kekulé forms can be isolated, *e.g.* (**105**)→(**104**) + (**106**).



(**103**) (**104**) (**105**) (**106**)

Acridine is less stable toward oxidizing agents and yields acridone (with $Na_2Cr_2O_7$–HOAc). Some diazine derivatives are apparently oxidized directly to diazones: quinoxaline gives (**107**) (with $K_2S_2O_8$–H_2O) and quinazol-4-one yields (**108**) (with $KMnO_4$, CrO_3). These reactions probably involve nucleophilic attack of water followed by oxidation of the adduct (see Section 3.2.1.6.3).



(**107**) (**108**)

Highly activated rings are hydroxylated by $K_2S_2O_8$–$FeSO_4$: 2-pyridone and 3-hydroxypyridine are both hydroxylated *para* to the substituent; thus each gives the same compound (5-hydroxy-2-pyridone). 2-Pyrimidinone affords the 5-hydroxy derivative.

3.2.1.5 Attack at Sulfur

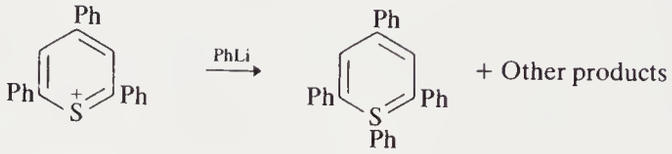
Reactions of this type are rare. Heterocyclic sulfur is usually electron deficient, which hinders the normal attack of electrophiles.

3.2.1.5.1 Reactions with electrophiles

Reactions take place in two circumstances:
(i) in formally 8 π-electron compounds (see Section 3.2.2.1.2.ii);
(ii) if the S atom is already in a higher oxidation state (see Section 3.2.2.2).

3.2.1.5.2 Reactions with nucleophiles

2,4,6-Thiinium cations react with lithium aryls to give complex mixtures containing some 1,2,4,6-tetrasubstituted thiabenzenes (**109**→**110**) (see CHEC 2.02.5.4.5).



(109) **(110)**

3.2.1.6 Nucleophilic Attack at Carbon

Before discussing nucleophilic attack specifically at ring carbon we enumerate five general pathways which have been distinguished for the attack of nucleophiles on heteroaromatic six-membered rings:

Path A: Nucleophilic attack at a hydrogen atom of a substituent with subsequent elimination (discussed under the relevant substituent in Section 3.2.3.1).

Path B: Attack at α- or γ-ring carbon, with subsequent reaction not involving ring opening (discussed in this section).

Path C: Nucleophilic attack at a substituent atom other than hydrogen (discussed under the relevant substituent in Section 3.2.3.1).

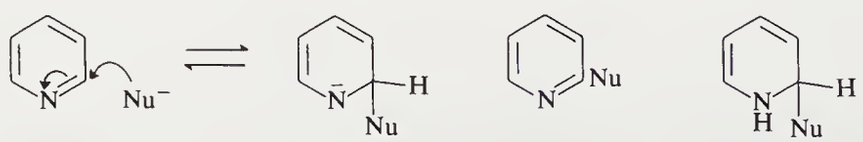
Path D: Attack at α-ring carbon followed by ring opening (discussed in this section).

Path E: Ylide formation by removal of a ring hydrogen atom followed by addition of an electrophile (discussed in Section 3.2.1.7).

3.2.1.6.1 Ease of reaction

(i) Pyridines

The electron displacement toward the nitrogen atom allows nucleophilic reagents to attack pyridines at the α-position (**111**), a type of reactivity shown in benzenoid chemistry only by derivatives with electron-withdrawing substituents. However, formation of the initial adduct (**112**) in an appreciable amount is difficult because this involves de-aromatization of the pyridine ring and, once formed, the adduct tends to re-aromatize by dissociation (**112**→**111**). Only very strong nucleophilic reagents (*e.g.* NH_2^-, LiR, $LiAlH_4$, Na/NH_3 and, at high temperatures, OH^-) react. The tiny proportion of adducts of type (**112**) formed by the addition of amide or hydroxide ions can also re-aromatize by hydride ion loss, thus gradually causing complete reaction (**112**→**113**). The adducts formed by the addition of hydride ions (from $LiAlH_4$) or carbanions (from LiR) are more stable; at low temperatures they are converted to dihydropyridines (**114**) by proton addition, but at higher temperatures re-aromatization occurs by hydride ion loss.



(111) **(112)** **(113)** **(114)**

(ii) Azines

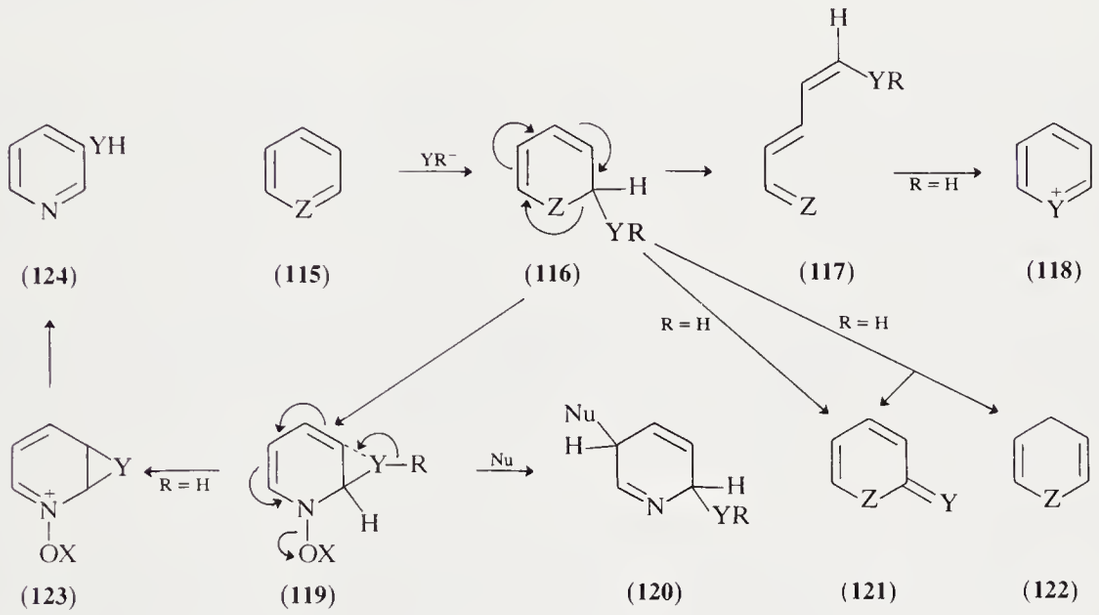
Diazines are considerably more reactive toward nucleophiles than pyridines and as the number of ring nitrogens increases the propensity for nucleophilic addition reactions increases still more. Many 1,2,4-triazines give addition products with various nucleophiles which are formally dihydrotriazines.

The limit is reached with 1,3,5-triazine. This reacts very easily with weak nucleophiles, and ring cleavage nearly always follows. Thus, it behaves as a formylating agent toward amines and other active hydrogen compounds.

Pteridines also undergo nucleophilic addition reactions particularly easily, such as covalent hydration, addition of bisulfite, *etc.*

(iii) Cationic rings

In a pyridinium ring the positive charge facilitates attack by nucleophilic reagents at positions α or γ to the heteroatom. Hydroxide, alkoxide, sulfide, cyanide and borohydride ions, certain carbanions and amines react, usually at the α-position, under mild conditions to give initial adducts of type (**116**). These non-aromatic adducts can be isolated in certain cases but undergo further reactions with alacrity. The most important of these include (a)–(d) below. If the group Z^+ of (**115**) is a nitrogen with a leaving group, usually N^+OX, then further possibilities (e)–(f) exist.



(a) Oxidation: *e.g.* (**116**; YR = OH)→pyridones (**121**); (**116**; YR = CH_2—heterocycle)→cyanine dyes.

(b) Disproportionation: *e.g.* (**116**; YR = OH)→pyridone (**121**) and dihydropyridine (**122**).

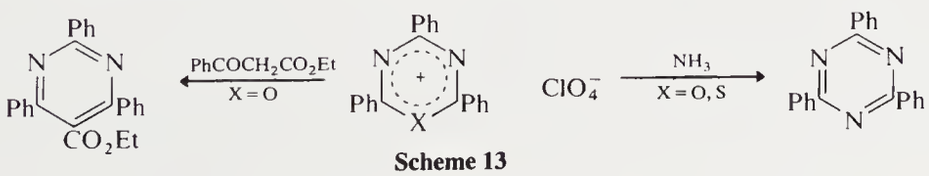
(c) Ring opening with subsequent closure (**115**→**118**): *e.g.* reaction of pyrylium salts with RNH_2 or S^{2-}.

(d) Ring opening without subsequent closure (**115**→**117**): *e.g.* reaction with OH^- of pyridinium salts carrying electron-withdrawing groups on nitrogen and pyrylium salts.

(e) Rearrangement of attacking group to the 3-position (**119**→**123**→**124**).

(f) Addition of a second mole of nucleophile (**119**→**120**).

Pyrylium and thiinium salts are very easily attacked by nucleophiles, particularly if there is an unsubstituted α- or γ-position, and 1,3,5-oxadiazinium and -thiadiazinium salts are still more susceptible (see Scheme 13).

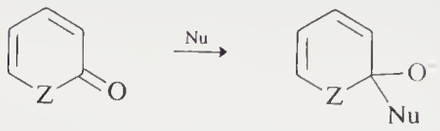


Scheme 13

(iv) Pyridones and azinones

(a) In both α- and γ-pyridones the carbon atom of the carbonyl group can be attacked by a powerful nucleophile (as in **125**). The reaction then proceeds by complete loss of the carbonyl oxygen atom and aromatization. These reactions, which also occur in α- and γ-pyrones, are all considered as substituent reactions in Section 3.2.3.7.2.

(b) Adducts (**125**) formed by reaction of α-pyrones at the carbonyl carbon atom can react further by ring opening as in the reactions with hydroxide ion, ammonia and amines (see Sections 3.2.1.6.3 and 3.2.1.6.4).



(125)

(v) N-*Oxides*

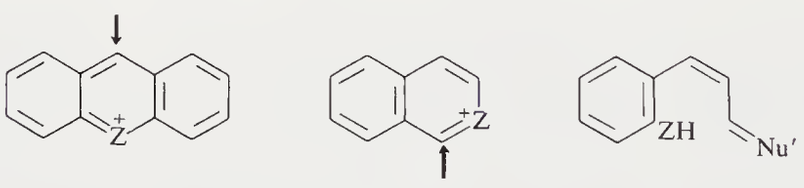
The intrinsic reactivity of pyridine 1-oxides toward nucleophiles is little greater than that of pyridine: only the strongest nucleophiles react. However, after initial reaction with an electrophile at the *N*-oxide oxygen, subsequent attack by nucleophiles is easy: see above discussion under 'cationic rings' (p. 167).

3.2.1.6.2 Effect of substituents

Nucleophilic attack on the ring carbon atoms of pyridines should be, and is, facilitated by electron-attracting substituents and hindered by electron-donating substituents. In pyridinium salts the effect of strongly electron-withdrawing substituents attached to the nitrogen atom, *e.g.* $—C_6H_3(NO_2)_2$, or —CN, is particularly marked and facilitates ring opening (Section 3.2.1.6) which is otherwise unusual.

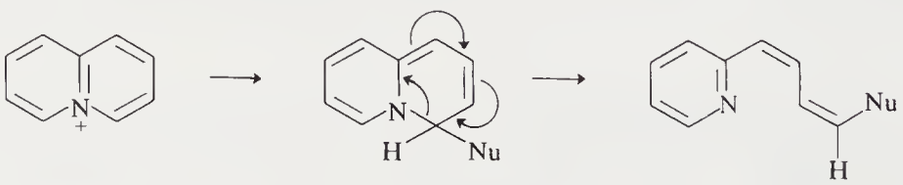
Fused benzene rings aid nucleophilic attack on pyridines, pyridinium and pyrylium ions, and pyrones; the loss of aromaticity involved in the formation of the initial adduct is less in monobenzo derivatives and still less in linear dibenzo derivatives than in monocyclic compounds. For the same reason, the tendency for this initial adduct to re-aromatize is less for benzopyridines. Fused benzene rings also influence the point of attack by nucleophilic reagents; attack rarely occurs on a carbon atom shared with a benzene ring. Thus, in linear dibenzo derivatives, nucleophilic attack is at the γ-position (**126**).

Similarly, reclosure to a new heterocyclic system after ring opening is possible in benzo[*c*] derivatives (**127**); in these last compounds initial attack is always in the α-position adjacent to the benzene ring because of partial double bond fixation. By contrast, ring opening of an αβ-benzo derivative gives a phenol or aniline (**128**) in which the Z—C bond is not easily broken.



(126) (127) (128)

However, in the quinolizinium ion (**129**) the fused ring increases the stability and makes it more difficult for nucleophilic attack, because now the aromaticity of both rings is lost in the intermediate addition product (**130**). Conversely, once the addition product is formed, ring opening is particularly easy (**131**).



(129) (130) (131)

3.2.1.6.3 Hydroxide ion

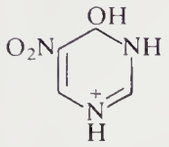
(i) Pyridine

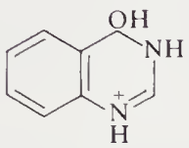
Uncharged pyridines are resistant to hydroxide ion at usual temperatures. Pyridine itself reacts with hydroxide ions under extreme conditions (KOH–air, 300 °C) to give 2-pyridone, the stable tautomer of 2-hydroxypyridine which is formed by oxidation of the initial adduct. As is expected, this reaction is facilitated by electron-withdrawing groups and fused benzene rings; quinoline and isoquinoline form 2-quinolone and 1-isoquinolone, respectively, rather more readily.

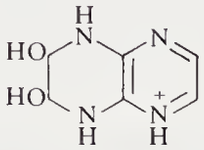
(ii) Other azines

Increasing numbers of nitrogen atoms increase not only the kinetic susceptibility toward attack but also the thermodynamic stability of the adducts. Pyrimidines with electron-withdrawing groups and most quinazolines show the phenomenon of 'covalent hydration'. Thus, in aqueous solution the cation of 5-nitropyrimidine exists as (**132**) and quinazoline cation largely as (**133**). These cations possess amidinium cation resonance. The neutral pteridine molecule is covalently hydrated in aqueous solution. The cation of 1,4,5,8-tetraazanaphthalene exists as a bis-covalent hydrate (**134**). The following factors help stabilize covalent hydrates ⟨65AHC(4)33⟩:

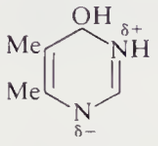
(1) amidine-type resonance, particularly in cationic (*e.g.* **135**) but also in neutral species (*e.g.* **136**);
(2) guanidinium-type resonance (**137**);
(3) urea-type resonance (*e.g.* **138**);
(4) 4-aminopyridinium-type resonance (**139**).

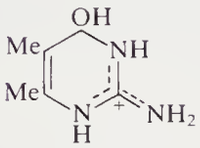

(**132**)

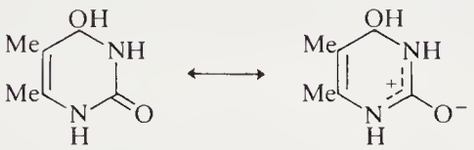

(**133**)

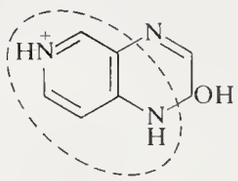

(**134**)


(**135**)


(**136**)


(**137**)

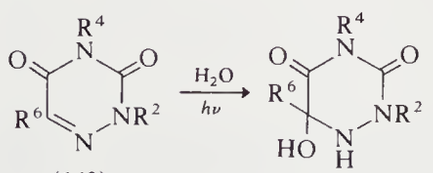

(**138**)

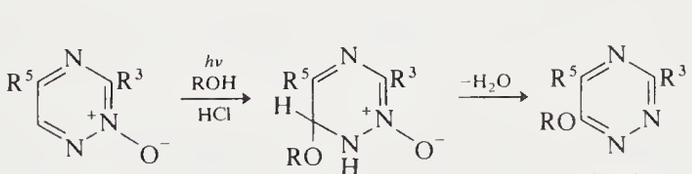

(**139**)

On irradiation uracil and related pyrimidines undergo photohydration across the 5,6-bond.

Many 1,2,4-triazine derivatives undergo photochemical hydration reactions, *e.g.* (**140**)→(**141**). Such reactions with 1,2,4-triazine 2-oxides are followed by loss of hydroxide ion to give overall substitution (**142**)→(**143**).

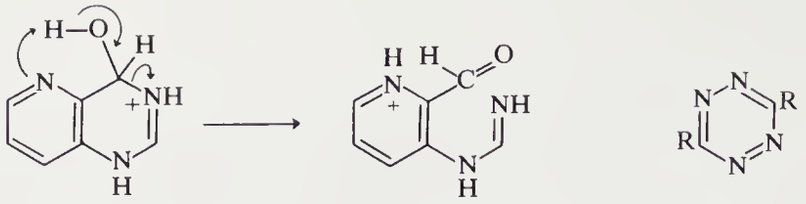
Insertion of a methyl group at the site where nucleophilic attack occurs during hydration considerably hinders the reaction and lowers the percentage of covalently hydrated species at equilibrium. Covalent hydrates are converted by mild oxidation into oxo compounds.


(**140**) (**141**)

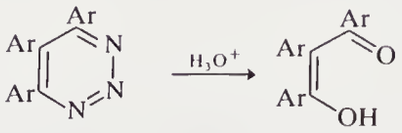

(**142**) (**143**)

Covalent hydrates can undergo ring opening especially in acidic media, for example the triazanaphthalene (**144**→**145**).

Polyaza rings suffer complete hydrolytic ring cleavage. Monocyclic 1,2,3-triazines are hydrolyzed by acid to yield 1,3-dicarbonyl compounds (Scheme 14). 1,2,3-Benzotriazines are easily converted into derivatives of 2-aminobenzaldehyde. 1,2,4,5-Tetrazines (**146**) are hydrolyzed in base to give aldehyde hydrazones, RCH=NNHCOR.



(144) (145) (146)



Scheme 14

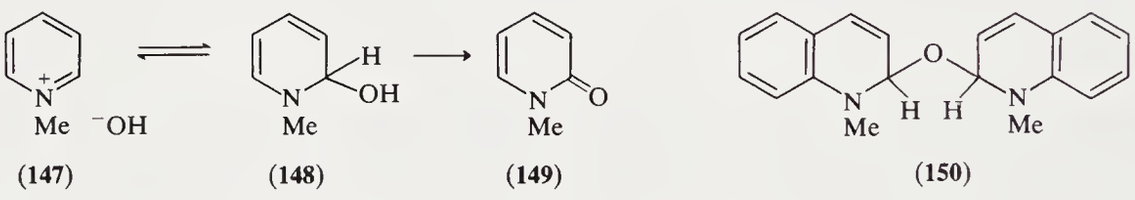
(iii) Alkylpyridinium cations

1-Methylpyridinium ions (**147**) react reversibly with hydroxide to form a small proportion of the pseudo-base (**148**).The term 'pseudo' is used to designate bases that react with acids measurably slowly, not instantaneously as for normal acid–base reactions. Fused benzene rings reduce the loss of resonance energy when the hetero ring loses its aromaticity and hence pseudo-bases are formed somewhat more readily by 1-methylquinolinium, 2-methylisoquinolinium and 10-methylphenanthridinium, and much more readily by 10-methylacridinium ions. Pseudo-bases carrying the hydroxy group in the α-position are usually formed preferentially, but acridinium ions react at the γ-position.

Pseudo-bases can undergo a number of further reactions:

(a) Oxidation. 1-Alkylpyridinium ions in alkaline solution are oxidized by $K_3Fe(CN)_6$ to give 2-pyridones (*e.g.* **149**). 2-Quinolones, 1-isoquinolones, 9-phenanthridones and 9-acridones can be prepared similarly.

(b) Many pseudo-bases disproportionate on standing to dihydropyridines and pyridones, *e.g.* (**151**)→(**152**) + (**153**). The mechanism shown is speculative, but resembles that for the Cannizzaro reaction.



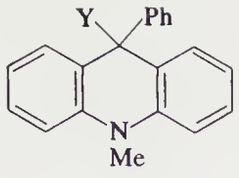
(147) (148) (149) (150)

(151) (152) (153)

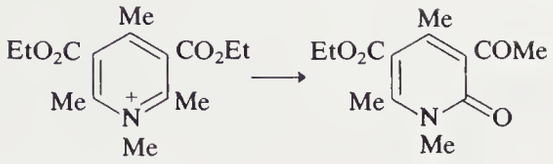
(c) Ether formation can occur. Recrystallization of (**154**; Y = OH) from ethanol forms (**154**; Y = OEt) *via* the acridinium ion. Pseudo-bases on keeping often lose water to give bimolecular products (*e.g.* **150**).

(d) Ring fission followed by closure to form a new heterocyclic or homocyclic ring can occur in pyridinium ions carrying suitable substituents. Examples are (**155**) + KOH + H_2O→(**156**) + EtOH, and also, under vigorous conditions (200 °C), (**157**) + NaOH→10% of (**158**).

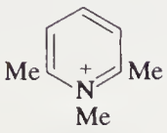
(e) Ring fission can be reversible as in for example, 1-methoxypyridinium (**159**) giving the glutaconic aldehyde derivative (**160**); this is followed by irreversible scission of the N—O bond (see Section 3.2.3.12.5).



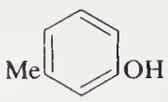
(154)



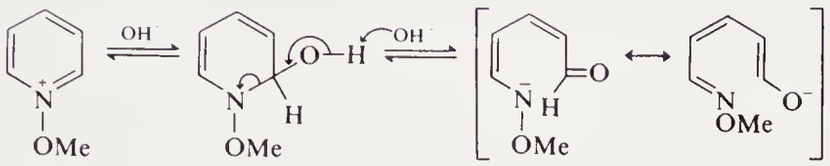
(155) (156)



(157)



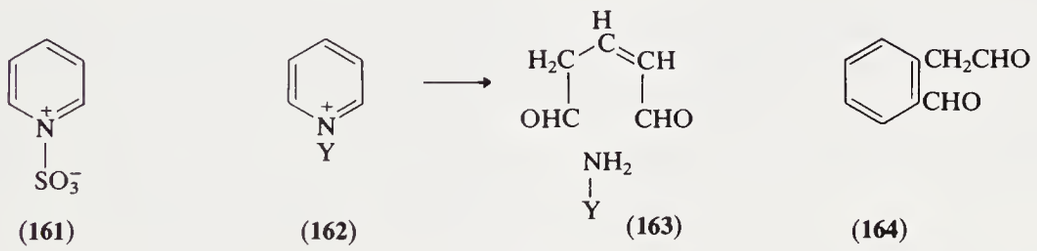
(158)



(159) (160)

(iv) Other pyridinium ions

Pseudo-bases derived from pyridinium ions carrying a strongly electron-withdrawing substituent on the nitrogen atom are unstable and undergo ring fission by hydroxide ions under mild conditions ($NaOH–H_2O$, 20 °C). Pyridine–sulfur trioxide (**161**) and 1-cyano- and 1-(4-pyridyl)-pyridinium ions all give glutaconic aldehyde (**162**→**163**); the other product is sulfamic acid, cyanamide (→$NH_3 + CO_2$) and 4-aminopyridine, respectively. Similarly, isoquinoline–sulfur trioxide gives homophthalaldehyde (**164**).

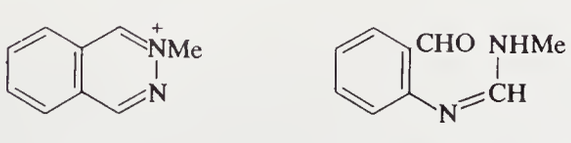


(161) (162) (163) (164)

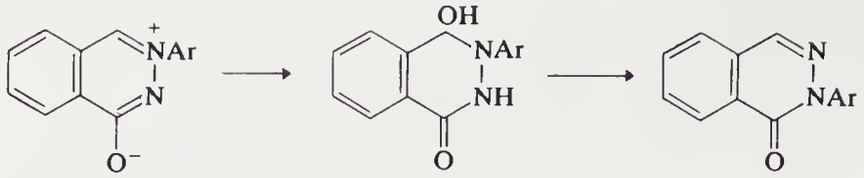
(v) Other cationic rings

Diazinium salts resemble pyridinium salts in their behavior. They form pseudo-bases with hydroxide ions which can disproportionate (*e.g.* 2-methylphthalazinium ion (**165**)→2-methylphthalaz-1-one + 2-methyl-1,2-dihydrophthalazine) or undergo ring fission (*e.g.* 3-methylquinazolinium ion→(**166**)). Aqueous acid converts (**167**) into (**168**), presumably by attack of a water molecule on a protonated species.

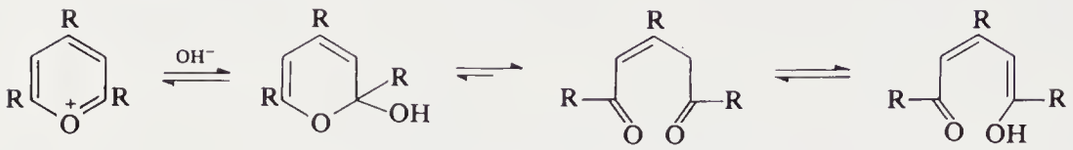
Pyrylium salts react with hydroxide ions in a complex series of equilibria involving the pseudo-base (**169**) and ring-opened forms (**170**) and (**171**).



(165) (166)

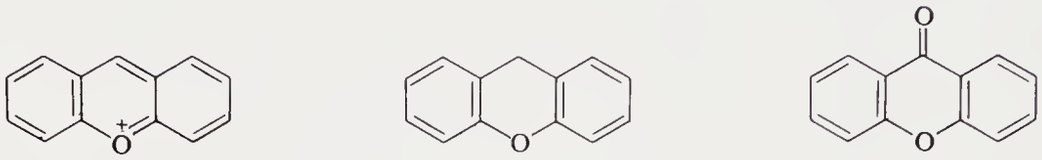


(167) (168)



(169) (170) (171)

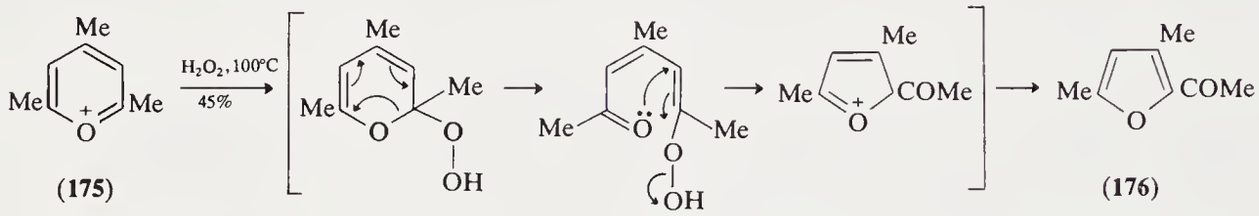
Some pseudo-bases do not ring open; the xanthylium ion (**172**) gives xanthydrol (**173**) which can be isolated or oxidized with dilute nitric acid to xanthone (**174**).



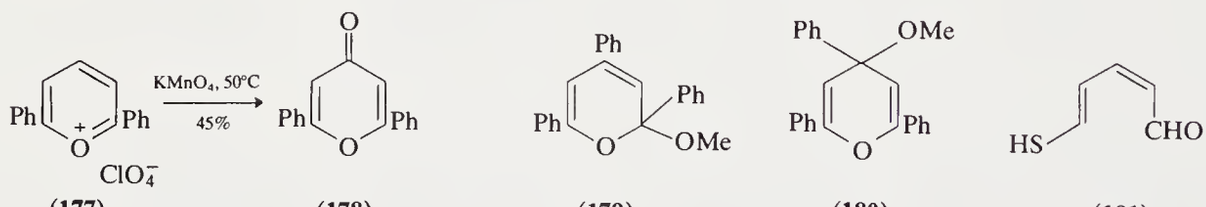
(172) (173) (174)

Hydrogen peroxide reacts with 2,4,6-trisubstituted pyrylium salts to cause ring contraction (**175**→**176**). If there is a free α- or γ-position, pyrylium salts can be oxidized to pyrones (**177**→**178**).

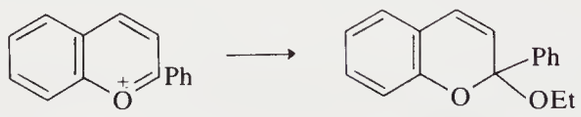
Methoxide ion attacks pyrylium salts to give methoxypyrans, *e.g.* (**179**), (**180**). Flavylium ion (**182**) gives (**183**) (with NaOAc–EtOH).



(175) (176)



(177) (178) (179) (180) (181)

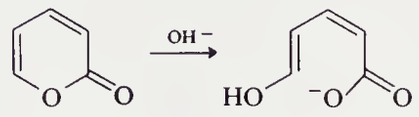


(182) (183)

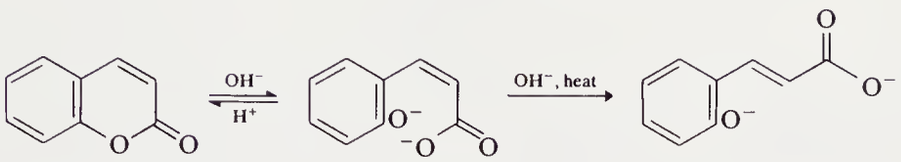
Unsubstituted thiinium cation is stable up to pH 6 in aqueous solution; at higher pH it ring opens to the aldehyde (**181**). Methoxide adds to 4-alkyl-2,6-diphenylthiinium cation to give a mixture of the 4-methoxy-4*H*- and 2-methoxy-2*H*-thiins under kinetic control (*cf.* **179**, **180**). The mixture then equilibrates toward the thermodynamically favored 2*H*-system.

(vi) Pyridones, pyrones, azinones, etc.

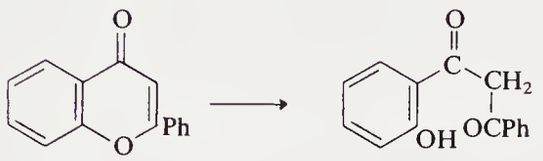
Although pyridones are usually resistant to alkali, pyrone rings are often easily opened. Pyran-2-ones are reversibly ring-opened by aqueous alkali to acid anions (**184**). Hydroxide ions convert coumarins (**185**) reversibly into salts of coumarinic acids (**186**) which can be converted into the *trans* isomers (**187**), and chromones (**188**) into β-dicarbonyl compounds (**189**).



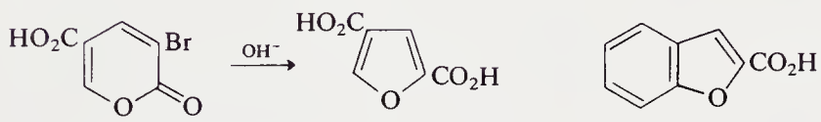
(**184**)



(**185**) (**186**) (**187**)



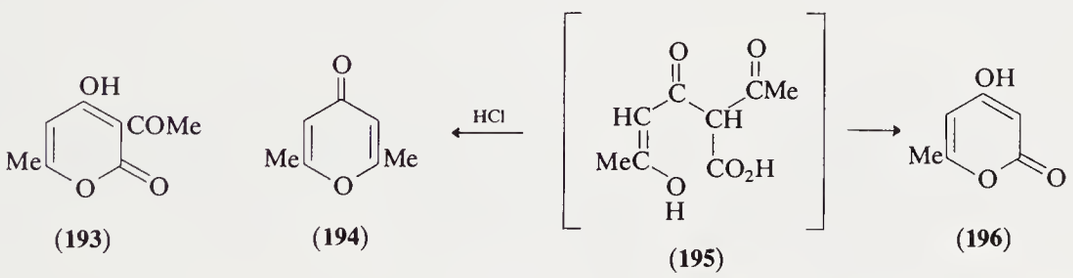
(**188**) (**189**)



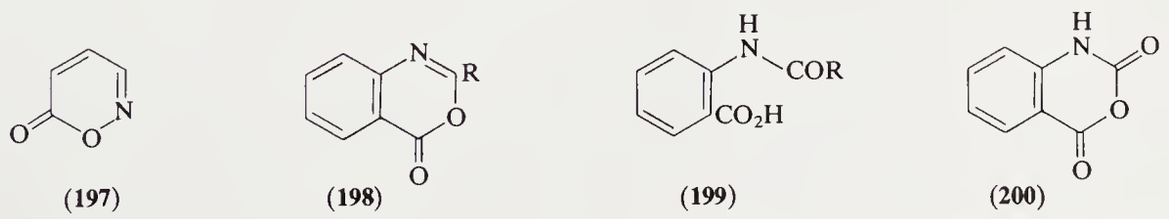
(**190**) (**191**) (**192**)

3-Bromo-2-pyrones and 3-bromocoumarins give furan- and benzofuran-2-carboxylic acids by ring fission and subsequent closure, *e.g.* (**190**)→(**191**); (**90**) or (**91**) [p. 163]→(**192**). Pyrone rings are opened by aqueous acid in some cases, probably by successive protonation and attack of a water molecule, *e.g.* dehydroacetic acid (**193**) gives (**195**) which immediately forms (**194**) or (**196**) with HCl or H_2SO_4, respectively.

Oxazinone rings, *e.g.* (**197**) and (**198**), and oxazinedione rings, *e.g.* isatoic anhydride (**200**), are rapidly cleaved by alkali as expected. Thus (**198**) yields (**199**).



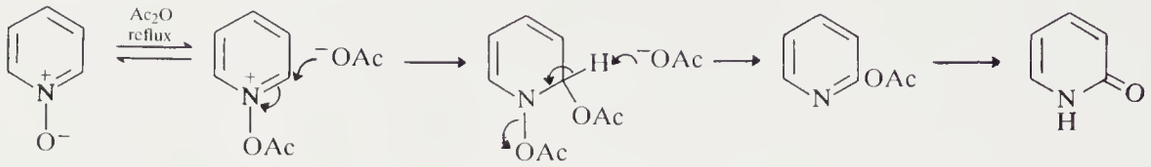
(**193**) (**194**) (**195**) (**196**)



(**197**) (**198**) (**199**) (**200**)

(vii) N-*Oxides*

N-Oxides are normally resistant to hydroxide attack. However, acetic anhydride converts the *N*-oxide group to *N*-acetoxy, and such compounds can be attacked by acetate anions. Thus, the reaction of acetic anhydride with pyridine *N*-oxide gives 2-pyridone (Scheme 15). This is a very general reaction; thus, for example, pyridazine 1-oxides unsubstituted at position 6 rearrange in the presence of acetic anhydride to the pyridazin-6-ones.



Scheme 15

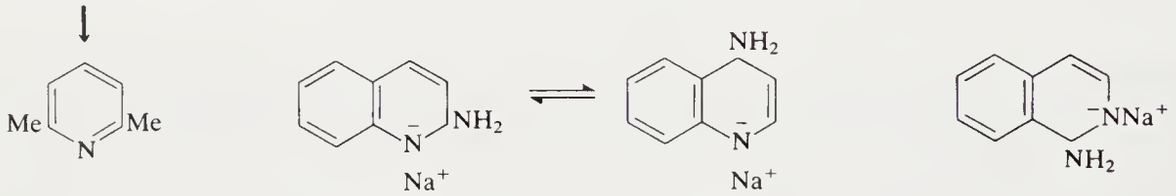
3.2.1.6.4 Amines and amide ions

(i) Pyridines and azines

Amines are insufficiently nucleophilic to react with pyridines, and the stronger nucleophile NH_2^- is required. When treated with amide ions ($NaNH_2 \rightarrow PhMe$), pyridine itself gives successively 2-aminopyridine (at 110 °C), 2,6-diaminopyridine (at 170 °C) or 2,4,6-triaminopyridine (at 200 °C, poor yield). The deactivating influence of electron-donating amino groups on subsequent stages of this reaction is evident.

This is the Chichibabin reaction and it occurs with substituted pyridines at an α-position unless both are blocked; thus, 2,6-lutidine (**201**), 2-methylquinoline and acridine give γ-amino derivatives. 3-Alkylpyridines react mainly at the 2-position. Isoquinoline reacts in the 1-position. Methyl sodamide ($Na^+ NHMe^-$) converts pyridine into its 2-methylamino derivative.

In liquid ammonia, sodamide forms addition complexes with quinoline (**202**, **203**) and isoquinoline (**204**) and the mechanism of the Chichibabin reaction is usually represented as the loss of H^- from such intermediates. However, in the heterogeneous conditions usually employed, electron transfer may be important. These intermediates correspond to the covalent hydrates described in Section 3.2.1.6.3.

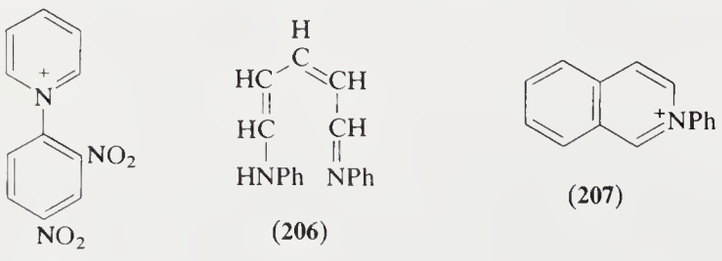


(**201**) (**202**) (**203**) (**204**)

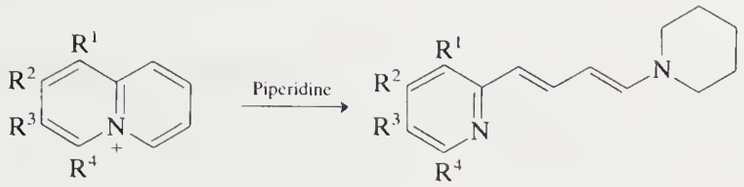
Amide ions react with diazines. Sodamide converts 4-methylpyrimidine successively into the 2-mono- and 2,6-di-amino derivatives, and pyrazine gives 2-aminopyrazine.

(ii) Pyridinium ions

The charged rings are sufficiently reactive to be attacked by amines. Pyridinium ions carrying strongly electron-withdrawing substituents on the nitrogen react to give open-chain products. Thus, 1-(2,4-dinitrophenyl)pyridinium ion (**205**) gives glutaconic dialdehyde dianil (**206**) and 2,4-dinitroaniline ($PhNH_2$, 100 °C) in the so-called Zinke reaction. Pyridine–sulfur trioxide, 1-(4-pyridyl)pyridinium and 1-cyanopyridinium ion react similarly.



(**205**) (**206**) (**207**)

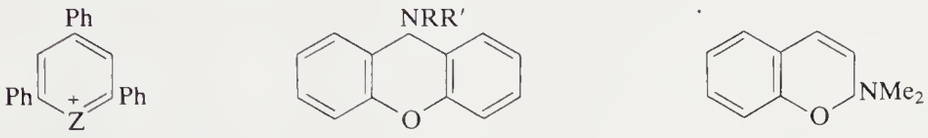


(208) (209)

Quinolizinium ions (**208**) react with piperidine to give the ring-opened products (**209**). Subsequent closure of the ring can also occur; *e.g.* 2-(2,4-dinitrophenyl)isoquinolinium ion with $PhNH_2$ at 190 °C forms (**207**).

(iii) Other cationic rings

Pyrylium cations form pyridines with ammonia and pyridinium salts with primary amines. For example, 2,4,6-triphenylpyrylium cation (**210**; Z = O) yields 2,4,6-triphenylpyridine with ammonia, the corresponding 1-methylpyridinium salt with methylamine, and pyridine 1-arylimines with phenylhydrazine. Xanthylium ions (**172**), where ring opening cannot readily occur, form adducts (**211**) with ammonia, amines, amides, ureas, sulfonamides and imides. Similar adducts (*e.g.* **212**) are formed by benzo[*b*]pyrylium ions.



(210) (211) (212)

Amines also react with thiinium salts to give pyridinium salts, but reaction goes less easily than with the pyrylium analogues. 1,3-Oxazinium and -thiazinium cations react with ammonia and amino derivatives to give pyrimidines.

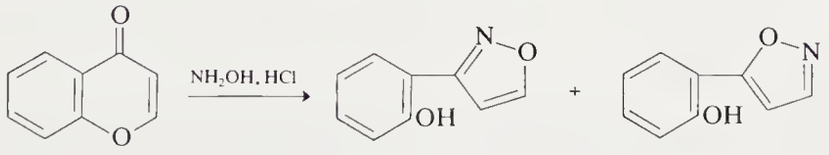
(iv) Pyridones, pyrones and azinones

2- and 4-Pyridone both undergo the Chichibabin reaction to give the 6- and 2-amino derivatives, respectively.

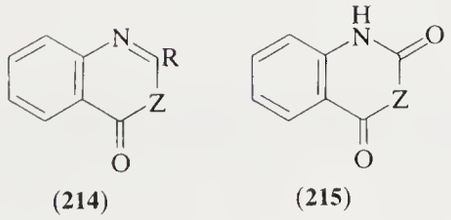
Pyran-4-ones react with ammonia and amines to give ring-opened products, which reclose to yield pyridones. Pyran-2-ones are similarly converted by ammonia or amines into 2-pyridones. Isocoumarins form isoquinolones on treatment with ammonia or primary amines.

However, chromones react differently, because the phenolic hydroxy group in the ring-opened intermediate is unreactive. Thus isoxazoles (**213**) result from the reaction with hydroxylamine, and a pyrazole is formed with hydrazine. γ-Pyrones also give pyrazoles with hydrazine.

Oxazones in which the heteroatoms are not adjacent react with ammonia and amines to give diazones, *e.g.* (**214**, **215**; Z = O) yield (**214**, **215**; Z = NR).



(213a) (213b)



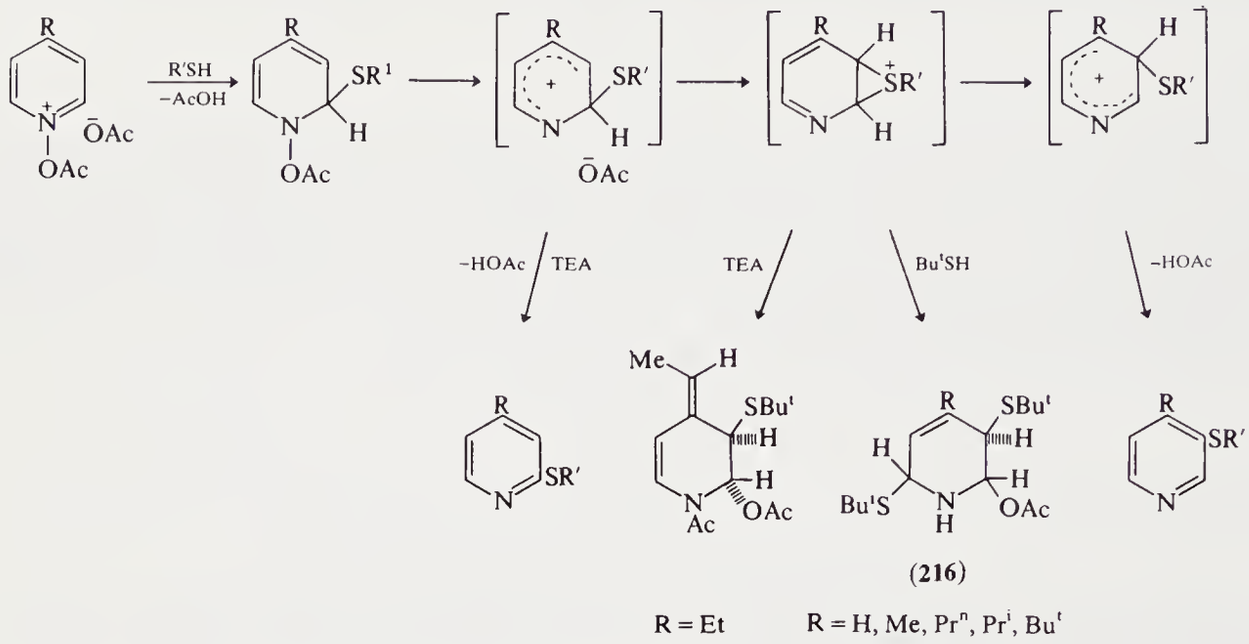
(214) (215)

3.2.1.6.5 Sulfur nucleophiles

Neutral pyridines do not normally react with sulfur nucleophiles. Such reactions are known, however, for *N*-oxides and cationic rings.

Pyridine 1-oxide and methyl analogues undergo thioalkylation at the α- and γ-positions with alkanethiols in acetic anhydride (Scheme 16). Some β-substitution occurs under these conditions probably *via* episulfonium intermediates, evidence for which comes in the isolation of tetrahydropyridines, *e.g.* (**216**).

Pyrylium salts are converted by sodium sulfide into thiinium salts, *e.g.* (**210**; Z = O)→(**210**; Z = S).

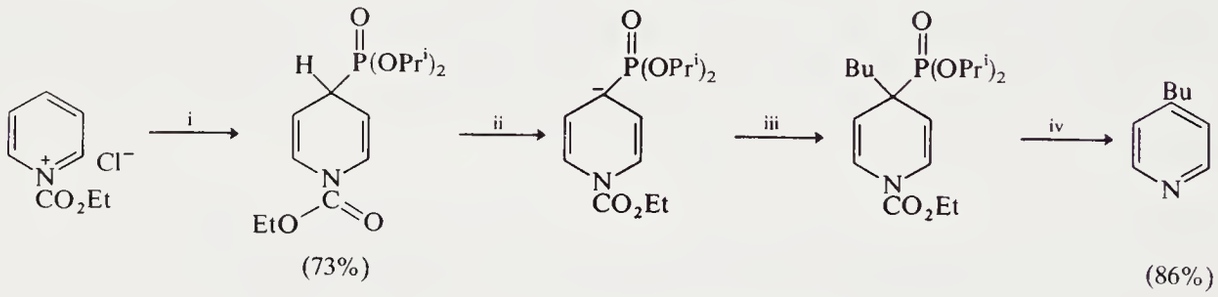


Scheme 16

3.2.1.6.6 Phosphorus nucleophiles

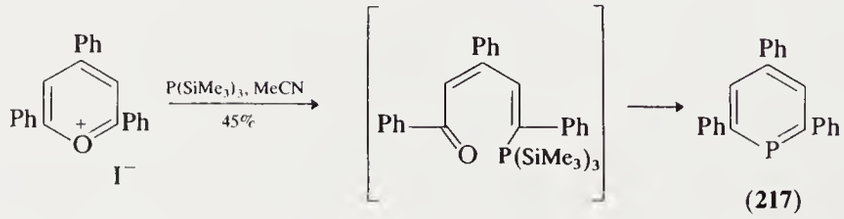
1-Ethoxycarbonylpyridinium cations are attacked by phosphites (Scheme 17). The intermediates can be further reacted to give 4-alkylpyridines as shown.

Pyrylium salts with nucleophilic phosphines yield phosphinines (**217**).



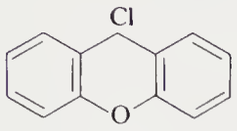
i, $P(OPr^i)_3$; ii, BuLi, THF, −78 °C; iii, BuBr; iv, BuLi (2 equiv.)

Scheme 17

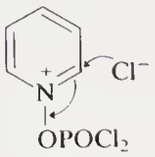


3.2.1.6.7 Halide ions

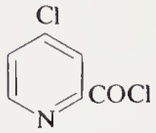
Chloride ions are comparatively weak nucleophiles, and do not react with pyridines. In general, there is also no interaction with pyridinium and pyrylium compounds, but xanthylium chloride is in equilibrium with an appreciable amount of (**218**), this being a particularly favorable case with little loss of resonance energy on adduct formation.



(**218**)



(**219**)



(**220**)

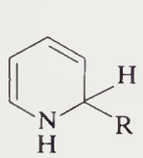
Pyridine and quinoline *N*-oxides react with phosphorus oxychloride or sulfuryl chloride to form mixtures of the corresponding α- and γ-chloropyridines. The reaction sequence involves first formation of a nucleophilic complex (*e.g.* **219**), then attack of chloride ions on this, followed by re-aromatization (see also Section 3.2.3.12.5) involving the loss of the *N*-oxide oxygen. Treatment of pyridazine 1-oxides with phosphorus oxychloride also results in an α-chlorination with respect to the *N*-oxide groups with simultaneous deoxygenation. If the α-position is blocked substitution occurs at the γ-position. Thionyl chloride chlorinates the nucleus of certain pyridine carboxylic acids, *e.g.* picolinic acid→(**220**), probably by a similar mechanism.

3.2.1.6.8 Carbon nucleophiles

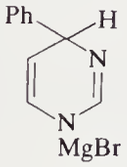
(i) Organometallic compounds

Pyridine reacts with lithium alkyls and aryls under rather vigorous conditions (*e.g.* xylene at 100 °C) to afford 2-alkyl- and 2-aryl-pyridines. The reaction proceeds by way of the corresponding dihydropyridines (**221** or a tautomer), and these may be isolated at lower temperatures. The less reactive Grignard reagents give poorer yields of the same products. In 3-substituted pyridines, attack at C-2 is favored over C-6 unless the C-3 substituent or the attacking alkyl group is very large.

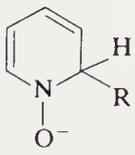
In the presence of free magnesium, considerable 4-substitution is also observed, and when pyridine is reacted with, for example, *n*-butyl chloride and magnesium directly, 4-*n*-butylpyridine is formed without appreciable contamination by the 2-isomer. Possible reasons for this change in orientation are discussed in CHEC 2.05. Reaction of pyridine with lithium dialkyl cuprate and a suitable electrophile gives almost exclusively the 1,4-dihydro product, *e.g.* (**224**)→(**225**).



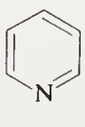
(**221**)



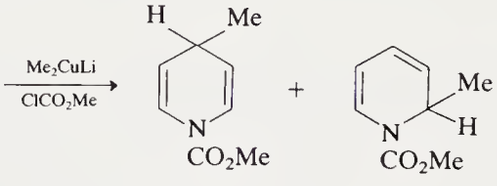
(**222**)



(**223**)



(**224**)



81% overall

(**225**)

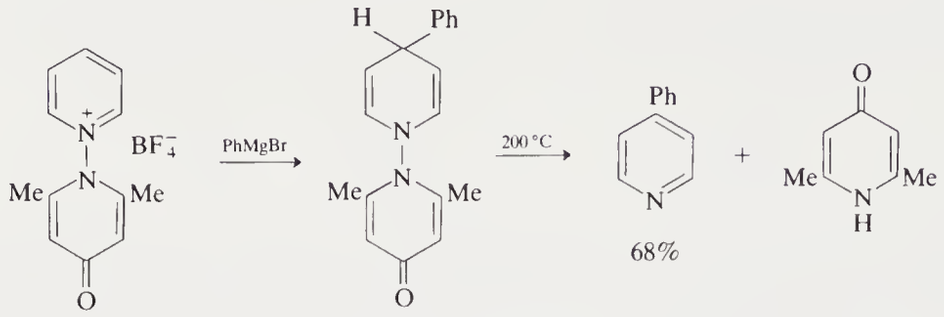
Benzopyridines are attacked by organometallic compounds at an α-position (to the nitrogen) unless both are blocked. The dihydro derivatives of quinolines and isoquinolines are more stable and less easily aromatized than those from pyridine, and are hence more frequently isolated.

Diazines also react more readily than pyridine. Thus, pyrimidine and phenylmagnesium bromide give adduct (**222**), which can be oxidized to 4-phenylpyrimidine.

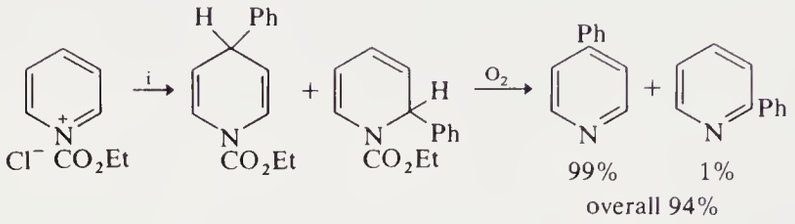
2,4-Dimethylpyrazine and lithium aryls afford the 3-aryl derivatives.

Corresponding reactions with *N*-oxides give α-substituted aromatic products by the loss of hydroxide ions from intermediates of type (**223**). However, yields are poor, both because the *N*-oxide also acts as an oxidizing agent toward the organometallic compound and because ring opening can occur.

Cationic rings react readily with organometallic compounds: Grignard reagents with *N*-alkylpyridinium salts generally give 1,2-dihydropyridines. If the size of the *N*-substituent is increased, then the orientation can be directed to the 4-position. If the *N*-substituent is also a leaving group, then re-aromatization can occur (Scheme 18). 1-Ethoxycarbonylpyridinium salts are attacked in the 4-position by Grignard reagents in the presence of copper salts and BF_3 (Scheme 19); this is essentially the same reaction as shown in (**224**)→(**225**).



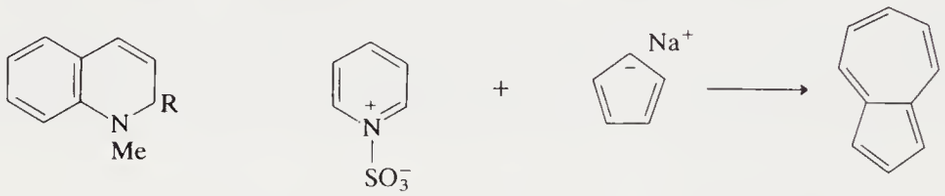
Scheme 18



i, CuI, PhMgBr, Mg, $BF_3{\cdot}OEt_2$, THF, −78 °C

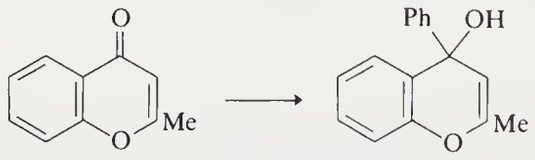
Scheme 19

With a Grignard reagent, 1-methylquinolinium ions give products of type (**226**). A notable reaction of this class is that between the pyridine–sulfur trioxide complex and sodium cyclopentadienide (**227**) which forms azulene (**228**) by a sequence involving opening of the pyridinium ring and subsequent closure to the seven-membered carbocyclic ring.



(**226**) (**227**) (**228**)

Pyran-4-ones with Grignard reagents give pseudo-bases which form the pyrylium salt with acid, *e.g.* (**229**) + PhMgBr→(**230**).

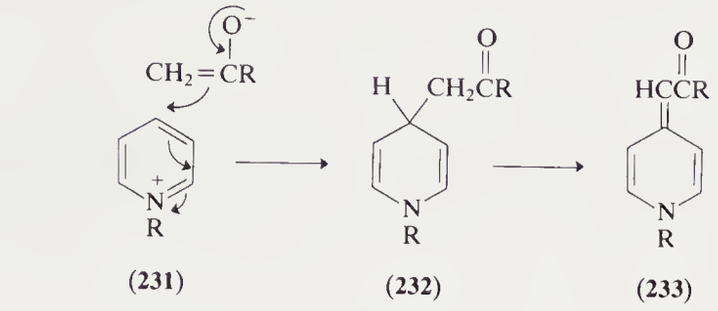


(**229**) (**230**)

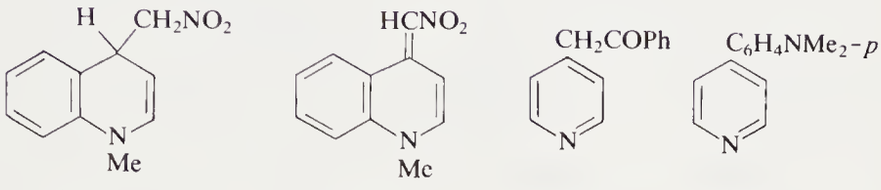
(ii) Activated methyl and methylene carbanions

The mesomeric anions of activated methyl and methylene compounds react with pyridinium and pyrylium cations, generally at a γ-position. Pyridinium ions combine with ketones as in (**231**) to give products of type (**232**) which can be isolated or oxidized *in situ* to mesomeric anhydro-bases (**233**) [*cf.* (**517**)↔(**518**), Section 3.2.3.3.5]. Quinolinium, isoquinolinium and acridinium ions give

similar adducts of stability increasing in the order given. Aliphatic nitro compounds react analogously, *e.g.* 1-methylquinolinium ion gives successively (**234**) and (**235**) (with $MeNO_2$–piperidine). 1-Benzoylpyridinium ions react similarly with acetophenone and dimethylaniline to give, after oxidation, aromatized products (**236**) and (**237**).

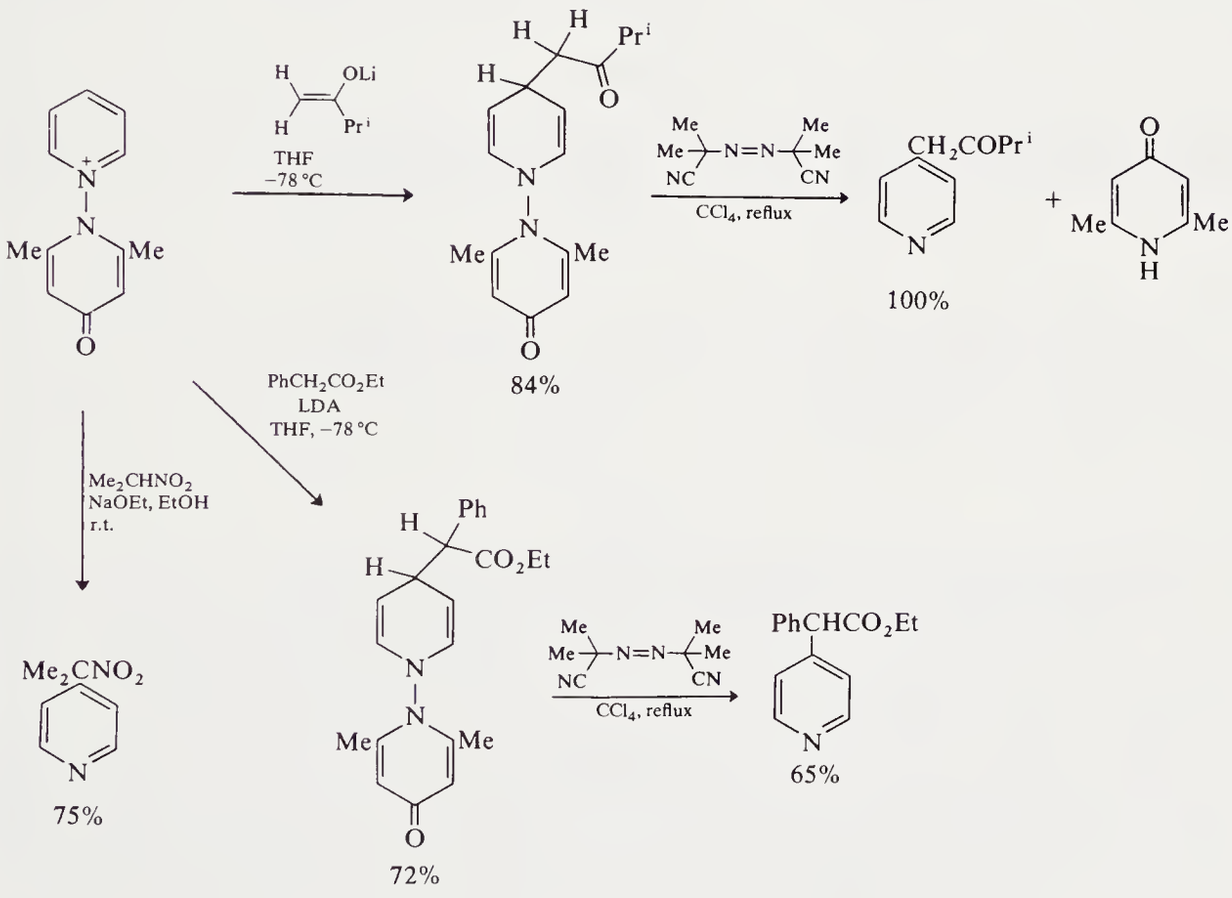


(**231**) (**232**) (**233**)



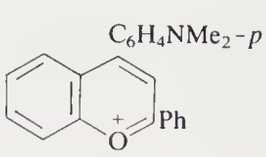
(**234**) (**235**) (**236**) (**237**)

The application of *N*—*N*-linked pyridinium salts to induce reaction with active hydrogen compounds in the 4-position is illustrated in Scheme 20.

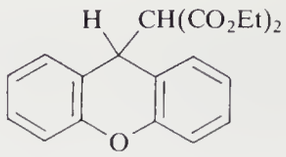


Scheme 20

Pyrylium salts with a free α- or γ-position react in a similar way without ring fission, *e.g.* flavylium ions (**182**) add dimethylaniline and the product aromatizes to give (**238**); xanthylium ions (**172**) form adducts at the 9-position with β-diketones, β-keto esters and malonic esters (*e.g.* **239**).

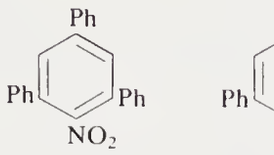


(238)

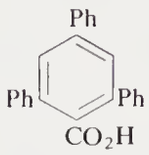


(239)

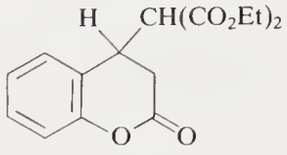
However, 2,4,6-trisubstituted pyrylium salts with certain active methyl and methylene compounds undergo ring fission and subsequent cyclization to benzenoid products. 2,4,6-Triphenylpyrylium ion (**210**; Z = O) in this way forms 2,4,6-triphenylnitrobenzene (**240**) with nitromethane and the substituted benzoic acid (**241**) with malonic acid, the latter reaction also involving a decarboxylation. In reactions of this type, 1,3-oxazinium salts react with active hydrogen compounds to give pyridines (Scheme 21).



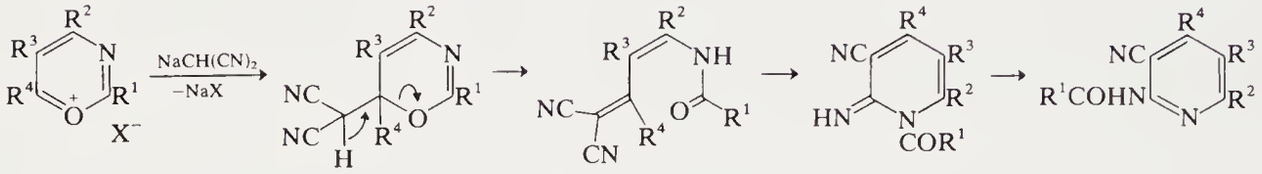
(240)



(241)

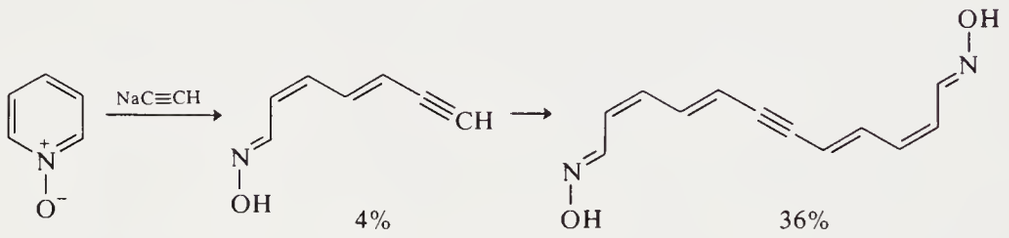


(242)

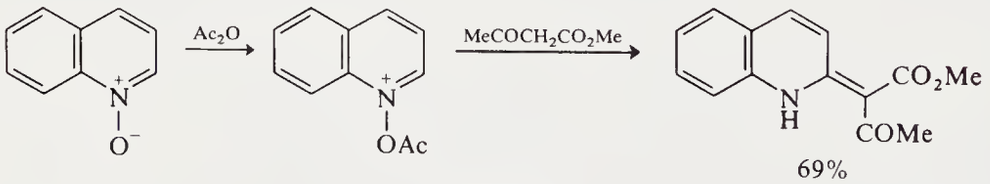


Scheme 21

Sodium acetylide reacts with pyridine 1-oxide to give ring-opened products (Scheme 22). However, in general *N*-oxides react only after quaternization (Scheme 23).



Scheme 22

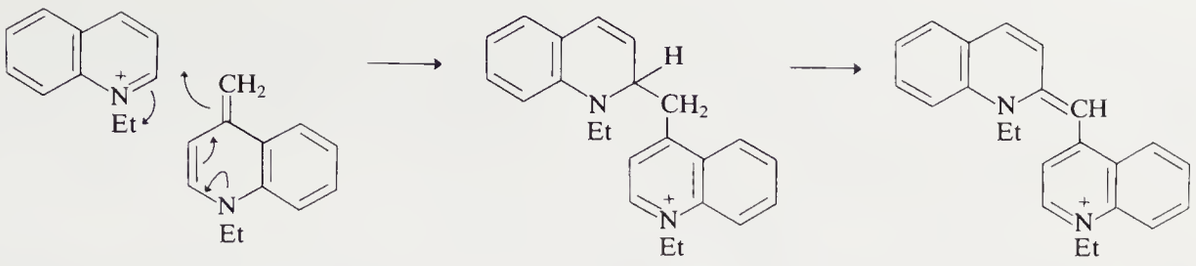


Scheme 23

Certain pyrones react with active hydrogen compounds in a quite different way: they display their alkenic character by a Michael reaction. Thus coumarin yields (**242**) with malonic ester.

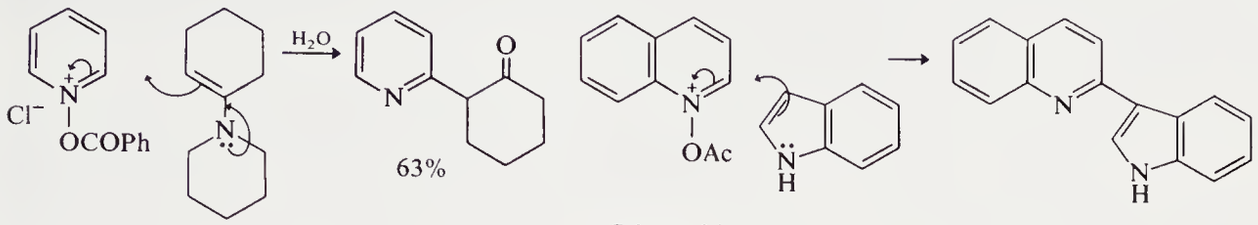
(iii) Anhydro-bases amd enamines

Anhydro-bases with cationic rings give adducts (*e.g.* **243**→**244**) which are spontaneously oxidized to cyanine dyes (**245**).



(243) (244) (245)

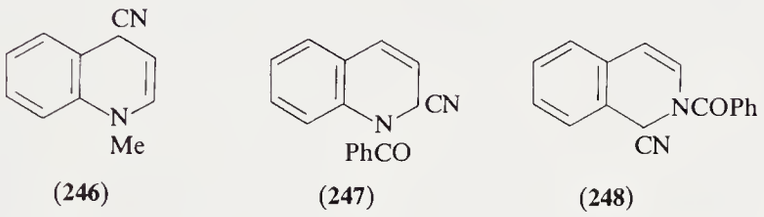
Pyridine *N*-oxides in the presence of acyl halides react with enamines as shown (Scheme 24).



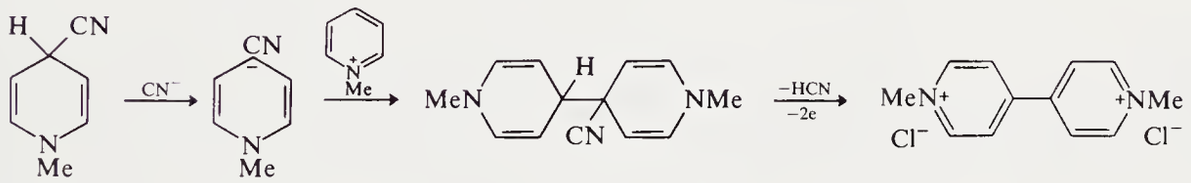
Scheme 24

(iv) Cyanide ions

So-called 'pseudocyanides', analogous to pseudo-bases, are formed by reaction of cyanide anions with benzopyridinium cations. Thus, 1-methylquinolinium ions give the pseudocyanide (**246**). Such pseudocyanides are important intermediates in the conversion of 1-alkylpyridines into 4,4′-bipyridyl diquaternary salts (Scheme 25).



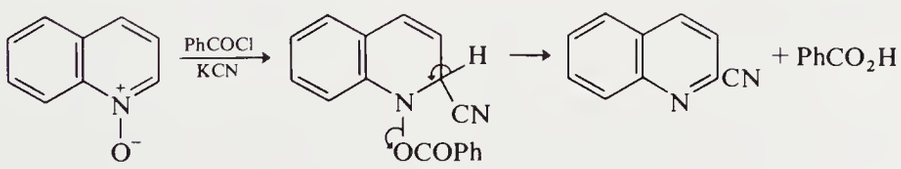
(246) (247) (248)



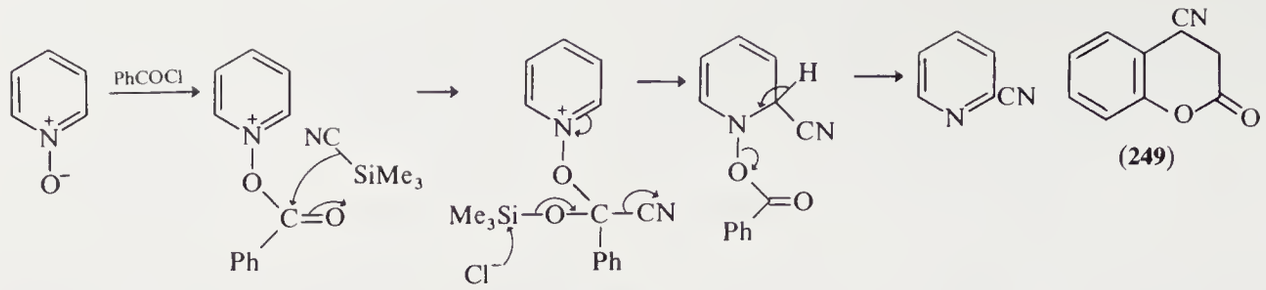
Scheme 25

In the Reissert reaction, 1-benzoylquinolinium ions (formed *in situ* from quinolines and PhCOCl) and cyanide ions give 'Reissert compounds'; thus quinoline itself forms (**247**). These Reissert compounds are hydrolyzed by dilute alkali to quinoline-2-carboxylic acids, for example, and benzaldehyde. Isoquinolines also form Reissert compounds (*e.g.* **248**).

In the Reissert–Henze reaction, quinoline 1-oxide reacts with benzoyl chloride and potassium cyanide to give 2-cyanoquinoline in good yield (Scheme 26). Pyridine 1-oxides undergo the Reissert–Henze reaction readily when the reaction is carried out in non-aqueous medium using $PhCOCl–Me_3SiCN$ (Scheme 27). Pyrimidine *N*-oxides also undergo Reissert–Henze reactions.



Scheme 26



Scheme 27

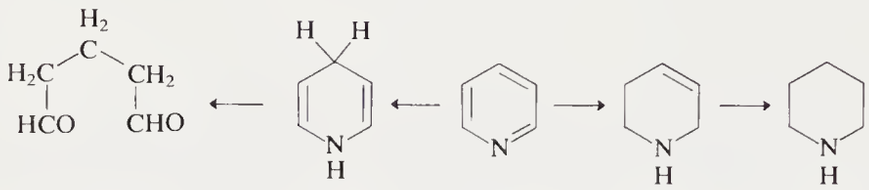
1-Alkoxypyridinium and 1-methoxypyridazinium salts yield cyanopyridines and cyanopyridazines, respectively, on treatment with potassium cyanide; the cyano group enters the α-position with respect to the *N*-oxide of the starting material.

Coumarin gives compound (**249**) by Michael addition of hydrogen cyanide.

3.2.1.6.9 Chemical reduction

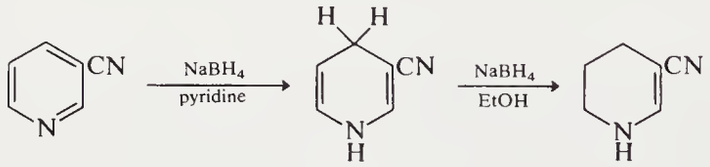
(i) Pyridines

Pyridines are more susceptible to reduction than benzenes. Sodium in ethanol or in liquid ammonia evidently reduces pyridine to 1,4-dihydropyridine (or a tautomer) because hydrolysis of the reaction mixture affords glutaric dialdehyde (**252**→**251**→**250**). Reduction of pyridines with sodium and ethanol can proceed past the dihydro stages to Δ^3-tetrahydropyridines and piperidines (**252**→**253** and **254**).



(**250**) (**251**) (**252**) (**253**) (**254**)

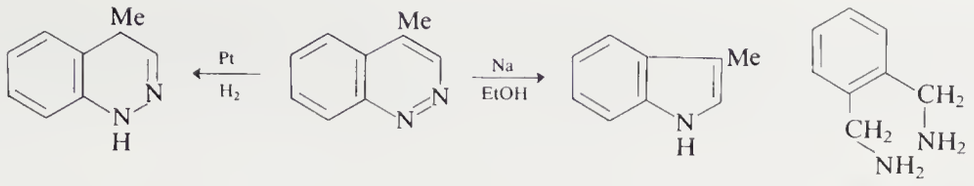
Pyridine and lithium aluminum hydride form a complex which contains 1,2- and 1,4-dihydropyridine rings. Reduction of quinoline with lithium aluminum hydride gives 1,2-dihydroquinoline. Neutral pyridines bearing electron-withdrawing substituents are also reduced by sodium borohydride (Scheme 28).



Scheme 28

(ii) Azines

Diazines are readily reduced. The ring can be cleaved when the two nitrogens are adjacent: thus pyridazine gives tetramethylenediamine as well as partially hydrogenated products on reduction with sodium and ethanol. Cinnolines form either dihydro derivatives, *e.g.* (**256**)→(**255**), or indoles by ring opening and reclosure, *e.g.* (**256**)→(**257**). Phthalazine gives 1,2,3,4-tetrahydrophthalazine (with Na/Hg) or the ring-opened product (**258**) (with Zn–HCl). Pyrazines and pyrimidines are normally reduced to hexahydro derivatives, whereas quinazolines and quinoxalines usually give 1,2,3,4-tetrahydro derivatives (*e.g.* with Na–EtOH).

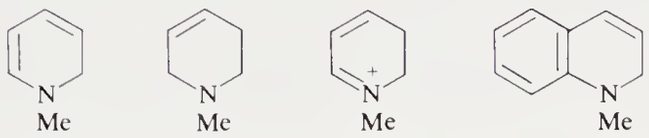


(255) (256) (257) (258)

Lithium aluminum hydride converts pyrimidines to di- or tetra-hydro derivatives. 1,2,4,5-Tetrazines with mild reducing agents give dihydro derivatives.

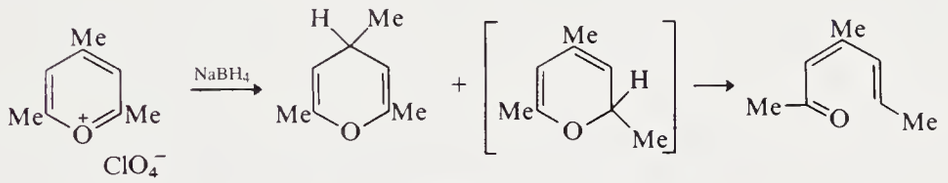
(iii) Cationic rings

Cationic rings are readily reduced under relatively mild conditions. 1-Methylpyridinium ion with sodium borohydride (in H_2O, 15 °C) gives the 1,2-dihydro derivative (**259**) at pH > 7 and the 1,2,3,6-tetrahydro derivative (**260**) at pH 2–5. The tetrahydro compound is probably formed *via* (**261**) which results from proton addition to (**259**). Pyridine cations are also reduced to 1,2-dihydropyridines by dissolving metals, *e.g.* Na/Hg.



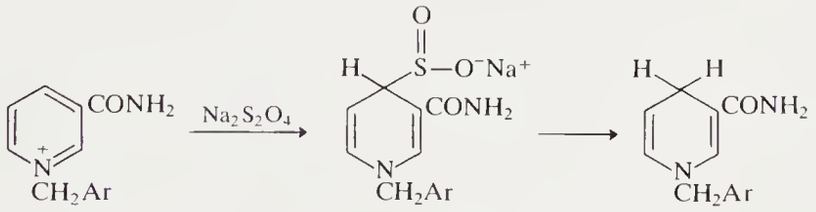
(259) (260) (261) (262)

Complex hydride reduction ($NaBH_4$ or $LiAlH_4$) of 1-methylquinolinium ions proceeds analogously to 1,2-dihydro compounds (*e.g.* **262**). 1-Methylisoquinolinium ions give the corresponding 1,2-dihydro compounds. Borohydride reduces pyrylium salts to mixtures of 2*H*- and 4*H*-pyrans; the former immediately ring opens to form the dienone (Scheme 29).

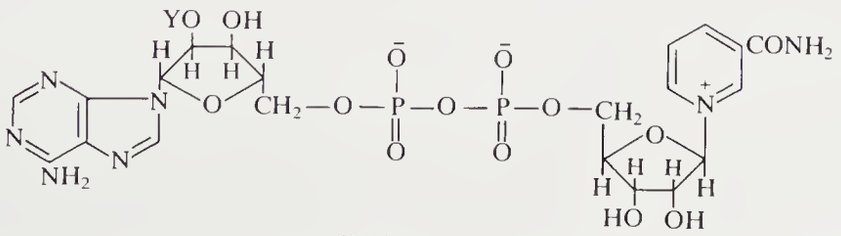


Scheme 29

Reduction of pyridinium ions with sodium dithionite ($Na_2S_2O_4$–H_2O–Na_2CO_3) gives 1,4-dihydro products. The mechanism involves initial formation of a sodium sulfinate intermediate which is stable in alkaline solution, but which decomposes as shown in Scheme 30 in acid or neutral solution.



Scheme 30



(263)

Vigorous chemical reduction (*e.g.* Sn–HCl or Zn–HCl) effects complete reduction of the heterocyclic ring, *e.g.* 1-methylquinolinium ion yields 1-methyl-1,2,3,4-tetrahydroquinoline. Reversible reduction of the pyridinium ring of coenzymes I and II (**263**; Y = H and PO_3H_2, respectively) is important physiologically.

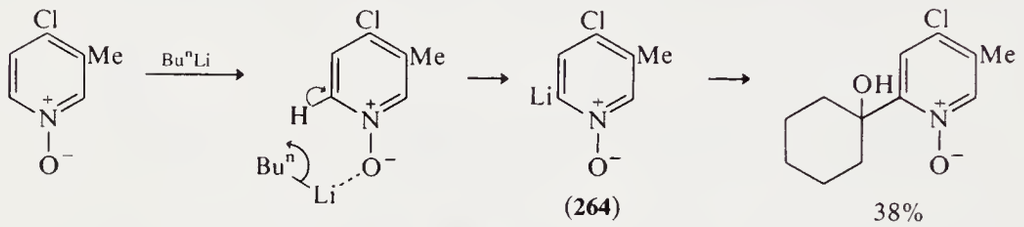
3.2.1.7 Nucleophilic Attack at Hydrogen attached to Ring Carbon or Ring Nitrogen

Hydrogen attached to ring carbon atoms of neutral azines, and especially azinium cations, is acidic and can be removed by bases as protons. The anions from azine *N*-oxides and some neutral azines can be stabilized as lithium derivatives. In other cases, the anion again adds a proton and hydrogen isotopic exchange can result. If the anion contains a halogen atom, then this can be eliminated to form a pyridyne or similar compound (see Section 3.2.3.10.1).

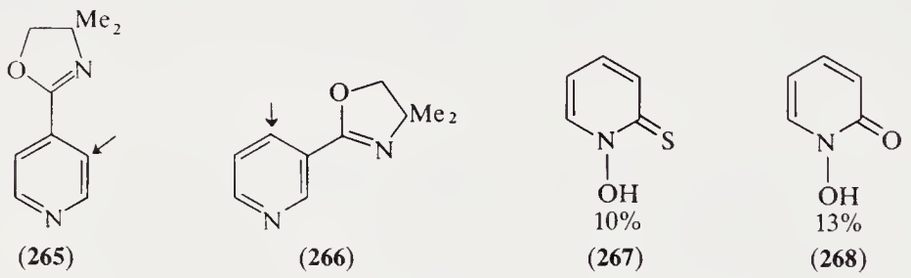
3.2.1.7.1 Metallation at a ring carbon atom

Direct ring metallation of azines generally requires some additional activating substituent. The oxazoline group directs lithiation: the 2-(4-pyridyl) derivative (**265**) is metallated at C-3 with methyllithium while the 3-isomer (**266**) reacts at C-4 with lithium tetramethylpiperidide ⟨82JOC2633⟩. Treatment of 3-ethoxy- or 3-butoxy-pyridine with butyllithium in the presence of TMEDA results in apparently exclusive metallation at the 2-position ⟨82S235⟩. The lithio products show normal reactivity. 3-Halopyridines are also lithiated regiospecifically at C-4, but pyridyne formation is then rapid.

Ring metallation generally succeeds with *N*-oxides. α-Lithio derivatives (**264**) can be generated in non-protic conditions by treating pyridine 1-oxides with *n*-butyllithium. These may be intercepted by various electrophiles such as cyclohexanone (Scheme 31). Reaction of substituted lithio *N*-oxides with carbon dioxide gives carboxylic acids; with sulfur and oxygen (**267**) and (**268**) are produced.



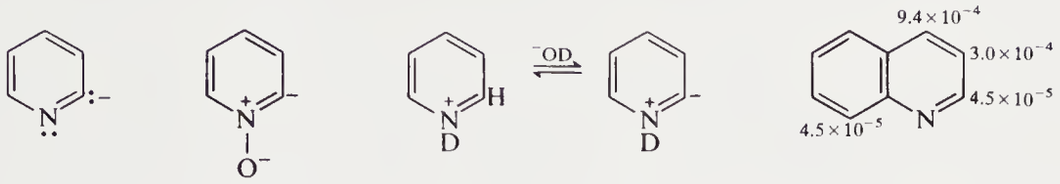
Scheme 31



3.2.1.7.2 Hydrogen exchange at ring carbon in neutral azines, N-oxides and azinones

Pyridine undergoes base-catalyzed hydrogen–deuterium exchange much more readily than benzene, resulting in eventual replacement of all hydrogen atoms by deprotonation followed by rapid deuteration of the intermediate negatively charged species in a sequential manner. The reactivity order $\gamma > \beta > \alpha$ is found for exchange in NaOMe–MeOD at 160 °C, NaOD–D_2O at 200 °C and $NaND_2$–ND_3 at −25 °C. The low reactivity of the 2-position reflects the unfavorable lone pair–lone pair interaction in the intermediate carbanion (**269**). Pyridine *N*-oxides exchange all protons, but now the C-2 protons react the most readily *via* the anion (**270**). In aqueous solution at

low pH, base-catalyzed hydrogen–deuterium exchange of pyridine can involve the pyridinium ion (**271**) and ylide (**272**) ⟨74AHC(16)1⟩. The exchange is facilitated by electron-withdrawing groups; in particular an electron-withdrawing group at the 3-position of pyridine accelerates exchange at the 4-position and *vice versa*. Quinoline undergoes hydrogen–deuterium exchange in NaOMe–MeOD, at 190.6 °C at the 2-, 3-, 4- and 8-positions (**273**) ⟨73JA3928⟩.



(**269**) (**270**) (**271**) (**272**) (**273**)

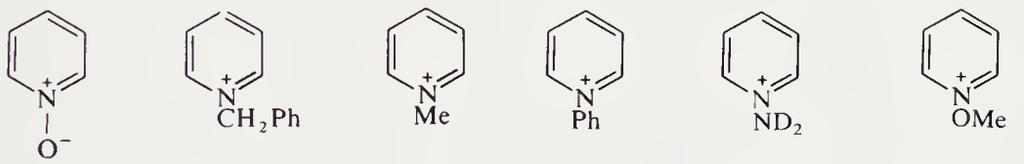
In pyridazines, base-catalyzed hydrogen–deuterium exchange takes place at positions 4 and 5 more easily than at positions 3 and 6. Pyridazine 1-oxide reacts first at positions 5 and 6 and then at positions 3 and 4. Pyrimidine exchanges as expected most readily at the 5-position, next at the 4-, and least readily at the 2-position. In pyrimidine 1-oxide, the reactivity order is $2 > 6 > 4 \gg 5$. 1,2,4-Triazines easily undergo base-catalyzed hydrogen exchange in the 2-position.

1-Methylpyridin-4-one (and 1-methylpyridin-2-one) undergoes H–D exchange at the 2- and 6-positions in basic D_2O at 100 °C.

3.2.1.7.3 Hydrogen exchange at ring carbon in azinium cations

Hydrogen isotope exchange is facile at the α-position in pyridinium salts. 3-Methyl- and 3-cyano-pyridinium methiodides undergo exchange in the order $2 > 6 \gg 4, 5$ in 0.01 M NaOD–D_2O. The relative rates of H–D exchange for the α-, β- and γ-positions in 1-methylpyridinium chloride are 3400:3:1.

The rates of H–D exchange at the α-positions for a series of *N*-substituted pyridinium cations and pyridine 1-oxide derivatives in D_2O at 75 °C (Scheme 32) ⟨70JA7547⟩ correlate well with the Taft inductive parameter σ_I ($\rho_I = 15$). A positively charged nitrogen in a ring is estimated to activate the α-position toward deprotonation and ylide formation by a factor of 10^{15}.

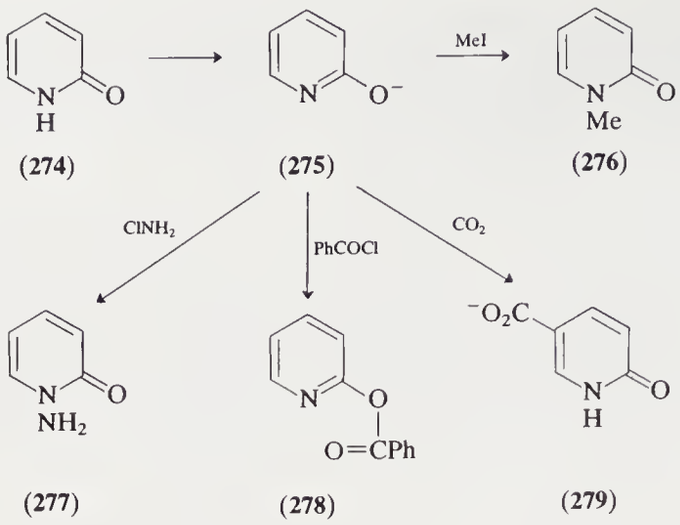


1.0 110 140 530 2700 1.3×10^6

Scheme 32

3.2.1.7.4 Proton loss from a ring nitrogen atom

Pyridones and azinones are weak acids of pK_a *ca.* 11 (see Section 3.2.1.3.4. iv). They form mesomeric anions (*cf.* **274**→**275**) which react very readily with electrophilic reagents at the nitrogen, oxygen or carbon atom, depending on the circumstances (see Section 3.2.3.7.2). The anion (**275**) from 2-pyridone is alkylated and aminated mainly on nitrogen (**275**→**276**, **277**), acylated on oxygen (**275**→**278**) and reacts at a ring carbon atom in the Kolbe reaction (**275**→**279**). Attack on the pyridone anion (*cf.* **275**) is probably involved in certain other electrophilic substitutions, *e.g.* the diazo coupling of 4-quinolone (see Section 3.2.1.4.10).



The position of alkylation can depend on counter ion, solvent and reagent. Thus, Ag salts tend to give *O*-alkylation, whereas Na or K salts predominantly undergo *N*-alkylation (see CHEC 2.05.2.5).

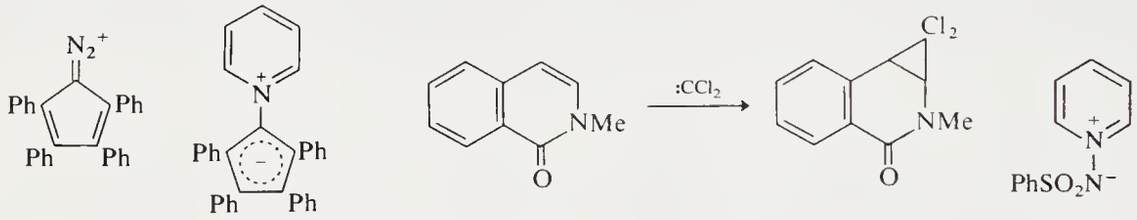
Reaction of pyridones with diazoalkanes involves deprotonation as the first step, forming an alkyldiazonium cation which then rapidly alkylates the pyridone anion; 2-pyridone gives mainly *O*-methyl derivatives, but 4-pyridone gives mixed *O*- and *N*-methyl derivatives.

The reactivity pattern of azinones containing an NH group is similar to that of the pyridones just discussed. Thus, for example, the alkylation of pyridazinones under basic conditions also gives mixtures of *N*- and *O*-substitution products.

3.2.1.8 Reactions with Radicals and with Electron-deficient Species; Reactions at Surfaces

3.2.1.8.1 Carbenes and nitrenes

Attack generally occurs at a pyridine nitrogen atom for both carbenes and nitrenes. Ylide (**281**) has been obtained by heating (**280**) in pyridine. However, the isoquinolone (**282**) undergoes attack at the isoquinoline double bond to give (**283**).



Sulfonyl azides react with pyridine to give pyridine 1-sulfonylimides (*e.g.* **284**). However, the analogous reaction with 2,4,6-trimethylpyridine gives some 3-(phenylsulfonylamino) derivative together with the 1-sulfonylimide. Nitrenes derived from photolysis of acyl azides also add to the nitrogen atom to form the corresponding pyridine-*N*-imines ⟨74AHC(17)220⟩.

3.2.1.8.2 Free radical attack at ring carbon atoms

(i) Halogen atoms

Vapor phase halogenation of pyridine at high temperatures gives mixtures of 2- and 2,6-di-bromopyridine (Br_2, 500 °C or CuBr–Br_2, 350 °C) and 2- and 2,6-di-chloropyridine (Cl_2, 270 °C). Presumably these reactions involve attack by free halogen atoms as distinct from the ionic halogenation at lower temperatures which gives β-orientation (*cf.* Section 3.2.1.4.7). Under similar conditions (Br_2, 450 °C) quinoline gives 2-bromoquinoline.

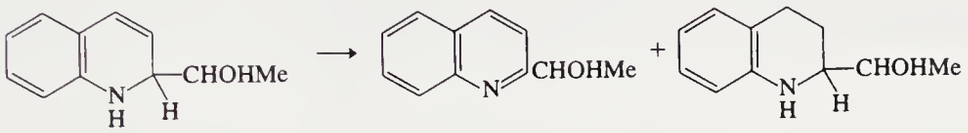
(ii) Alkyl radicals

Alkyl radicals, prepared *in situ* by electrolysis ($RCO_2^- \rightarrow RCO_2\cdot + R\cdot + CO_2$) or thermal decomposition [$(RCO_2)_2 \rightarrow 2R\cdot + 2CO_2$; $Pb(OAc)_4 \rightarrow Pb(OAc)_2 + 2CO_2 + 2Me\cdot$], react with pyridine to form mainly 2-alkyl derivatives. Although these and other homolytic alkylations of neutral heteroaromatics usually proceed in poor yields, if protonated heteroaromatic bases are used, many of the side reactions are minimized, selectivity is high and yields are good. Selectivity is increased because the alkyl radicals are nucleophilic in character and thus selectively attack the α-position.

Alkyl radicals for such reactions are available from many sources such as acyl peroxides, alkyl hydroperoxides, particularly by the oxidative decarboxylation of carboxylic acids using peroxydisulfate catalyzed by silver. Pyridine and various substituted pyridines have been alkylated in the 2-position in high yield by these methods. Quinoline similarly reacts in the 2-, isoquinoline in the 1-, and acridine in the 9-position. Pyrazine and quinoxaline also give high yields of 2-substituted alkyl derivatives ⟨74AHC(16)123⟩.

(iii) α-Hydroxyalkyl radicals

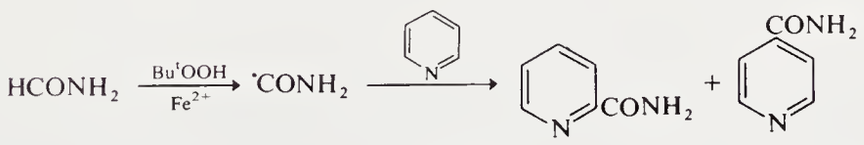
Hydrogen abstraction from a position α to the oxygen of alcohols and ethers gives α-oxyalkyl radicals which add readily to electron-deficient heterocycles: for example, quinoline reacts as shown in Scheme 33. Pyridine is hydroxymethylated at C-2 and C-4 using methanol and ammonium persulfate; 4-methylquinoline yields the 2-CH_2OH derivative with $NH_2OSO_3H + MeOH + FeCl_3$ ⟨83CC916⟩.



Scheme 33

(iv) Acyl radicals

Acyl radicals obtained by the oxidation of aldehydes or the oxidative decarboxylation of α-keto acids proceed with complete selectivity to the α- or γ-position of the protonated heterocyclic nitrogen. Pyridines, quinolines, pyrazines and quinoxalines all react as expected; yields are typically 40 to 70%. Similarly, pyridines can be carbamoylated in acid media at C-2 (Scheme 34). This reaction also succeeds with diazines.



Scheme 34

(v) Aryl radicals

In sharp contrast, homolytic arylation is unselective and gives low yields. Phenyl radicals attack pyridine unselectively to form a mixture of 2-, 3- and 4-phenylpyridines in proportions of *ca.* 53, 33 and 14%, respectively. The phenyl radicals may be prepared from the normal precursors: PhN(NO)COMe, $Pb(OCOPh)_4$, $(PhCO_2)_2$ or $PhI(OCOPh)_2$. Substituted phenyl radicals react similarly.

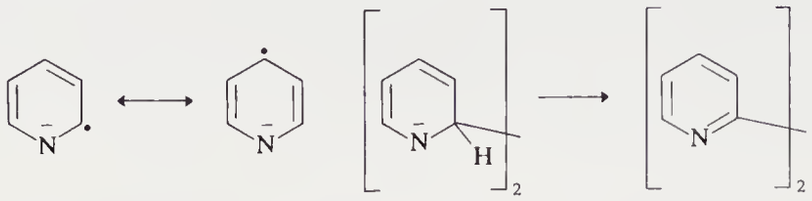
(vi) Hydrogen atoms

As for any other organic molecules containing CH bonds, heteroaromatics can be labelled with tritium by reaction with energetic tritium atoms from neutron irradiation.

3.2.1.8.3 ***Electrochemical reactions and reactions with free electrons*** (See also Section 3.2.1.6.9 – Chemical reduction)

(i) Neutral species: reactions with metals

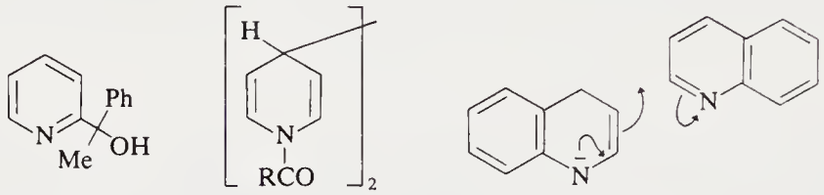
Certain metals (*e.g.* Na, Zn) add one electron to pyridine to form a radical anion (**285**↔**286**) which can dimerize by reaction at the α- or γ-position; these dimers form bipyridyls by hydride ion loss. On treatment with sodium at 20 °C, pyridine forms mixtures of 2,2′-, 2,3′-, 2,4′- and 4,4′-bipyridyl, probably by aromatization of intermediate dihydro compounds (**287**→**288**). The reaction can be directed to give largely 4,4′-bipyridyl, a product of commercial importance.



(**285**) (**286**) (**287**) (**288**)

Pyridine is converted by a modified Raney nickel catalyst into 2,2′-bipyridyl, and the reaction has been extended to many substituted pyridines and quinolines. 2-Substituted pyridines give the 6,6′-bipyridyls. 3-Methylpyridine gives 5,5′-dimethyl-2,2′-bipyridyl, but none of the other isomers.

These dimerizations are analogous to those of the radical anions $R_2\dot{C}—O^-$ which are intermediates in the reduction of ketones to pinacols. Indeed, in the presence of magnesium amalgam, pyridine condenses with a ketone to give an alcohol (**289**) by oxidation of the intermediate dihydropyridine. In a similar reaction type, pyridine with zinc and acetic anhydride or ethyl chloroformate yields (**290**; R = Me and OEt, respectively).



(**289**) (**290**) (**291**)

Treatment of quinoline with sodium gives mainly 2,3′-biquinolyl, the formation of which can possibly be explained as initial reduction followed by reaction of the dihydroquinoline anion with another molecule of quinoline (**291**).

(ii) Neutral species: electrochemical reduction

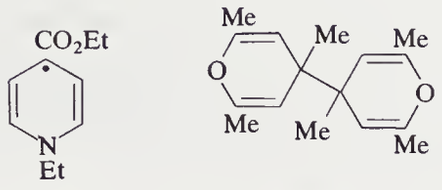
Pyridine is not reduced at the mercury electrode, but with difficulty it can give piperidine at a lead cathode. Electron-attracting substituents facilitate electrochemical reduction. The reduction potentials for the polarographic reduction of quinoline and isoquinoline derivatives are much less negative than those for the pyridine analogues. Diazines are reduced electrochemically stepwise, usually as far as tetrahydro derivatives ⟨70AHC(12)262⟩.

(iii) Cationic rings

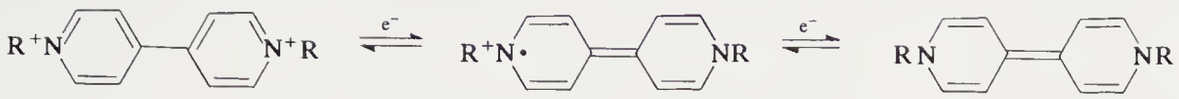
Pyridinium cations are reduced electrochemically or by metals to neutral radicals of considerable stability, especially when merostabilization by an α- or γ-substituent occurs; thus (**292**) has been isolated. Bispyridinium compounds are particularly readily reduced to radical cations, such as (**294**). Radical (**294**; R = Me) is the active species of the herbicide paraquat.

Pyridyl radicals without such stabilization dimerize and form bispyridinium compounds by oxidation.

One-electron reduction of pyrylium salts, with dissolving metals or electrochemically, gives dimers (*e.g.* **293**) *via* pyranyl radicals ⟨80AHC(27)46⟩.



(292) (293)



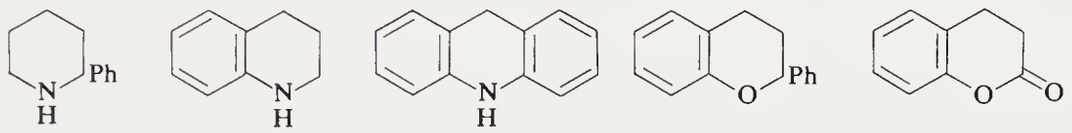
(294)

3.2.1.8.4 Other reactions at surfaces

(i) Catalytic hydrogenation

Pyridines are readily hydrogenated to piperidines over Raney nickel at 120 °C. Reductions with noble metal catalysts proceed smoothly (at 20 °C) when the bases are in the form of hydrochlorides; the free bases tend to poison the catalyst. A pyridine ring is reduced more easily than a benzene ring; thus, 2-phenylpyridine→2-phenylpiperidine (**295**), quinoline→1,2,3,4-tetrahydroquinoline (**296**) and acridine→9,10-dihydroacridine (**297**).

Pyridinium and pyrylium ions, pyridones and pyrones are all readily hydrogenated; *e.g.* flavylium ion (**182**) and coumarin yield (**298**) and (**299**), respectively.



(295) (296) (297) (298) (299)

(ii) Isotopic hydrogen exchange

Transition metals also catalyze isotopic exchange reactions. Platinum is the most active catalyst for most heterocycles. The mechanism may involve metallation, addition, σ-addition and π-complex formation. α-Hydrogen exchange in pyridine is favored over β- and γ-positions, particularly by a cobalt catalyst whereas platinum is much less selective. In isoquinoline both the 1- and 3-position protons are exchanged at almost the same rates with very little exchange at any other position. In 3-substituted pyridines exchange is preferred at the 6-position, the more so as the size of the 3-substituent increases ⟨73AHC(15)140⟩.

3.2.1.9 Intermolecular Reactions with Cyclic Transition States

3.2.1.9.1 Introduction

Reactions of this type are characteristic of compounds with low aromaticity. While rare in pyridine, they are favored by the following structural modifications which lower the aromatic stabilization energy:

(i) Benzo ring-fusion, especially three or more rings linearly fused.

(ii) Polyhetero rings and especially two adjacent ring nitrogens or a ring oxygen.

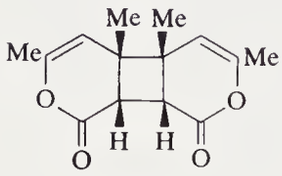
(iii) Exocyclic carbonyl groups and especially betaine structures.

We classify these reactions according to the number of π-electrons contributed by the heterocycle (usually four, but sometimes two, six or even eight) and by the other component.

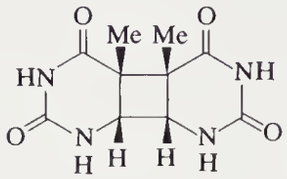
3.2.1.9.2 *Heterocycles as 2π component in [2 + 2] cycloaddition*

[2 + 2] Photodimers (*e.g.* **300**) are formed from 2-pyranones (note: 2-pyranones can also form [2 + 4] photodimers; see next section), uracil, thymine (**301**) and coumarins.

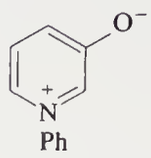
Irradiation of 1-phenyl-3-oxidopyridinium (**302**) yields the symmetrical dimer (**303**): this can be considered as a [2 + 2] or [6 + 6] cycloaddition.



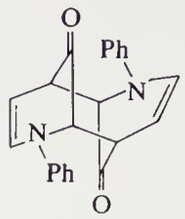
(**300**)



(**301**)

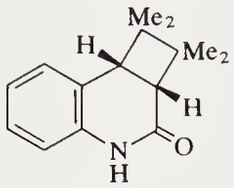


(**302**)

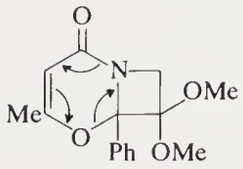


(**303**)

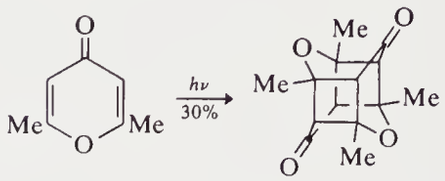
2-Quinolone undergoes photochemical addition of tetramethylethylene to give (**304**) ⟨70AHC(11)50⟩, 1,3-oxazin-4-ones photocycloadd ketene acetals to give (**305**), and irradiation of 2,6-dimethylpyran-4-one yields the cage dimer (**306**).



(**304**)



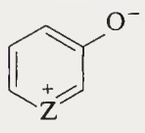
(**305**)



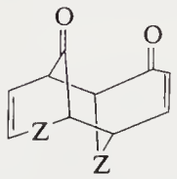
(**306**)

3.2.1.9.3 *Heterocycles as both 2π and 4π components in [2 + 4] cyclodimerization*

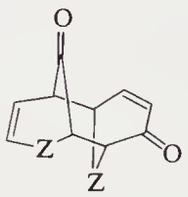
3-Oxidopyridiniums with a strong electron-withdrawing substituent at the 1-position (such as 2-pyrimidinyl) spontaneously dimerize (**307**→**308** + **309**); 3-oxidopyryliums and 3-oxidothiiniums behave similarly. These cyclodimerizations are reversible.



(**307**)

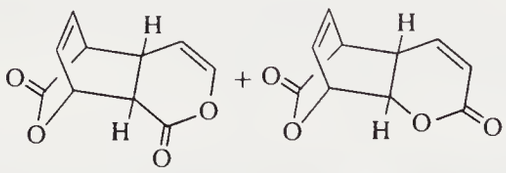


(**308**)

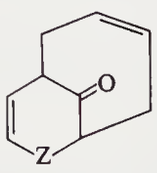


(**309**)

Pyran-2-ones can give unsymmetrical dimers (**310** and **311**).



(**310**) (**311**)



(**312**)

3.2.1.9.4 *Heterocycles as 2π component in [2 + 4] cycloaddition*

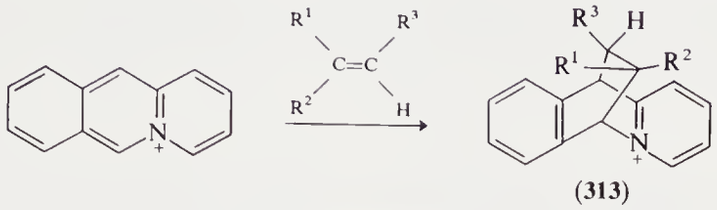
3-Oxidopyridiniums and 3-oxidopyryliums (**307**) react with a variety of dienes to give adducts of type (**312**).

3.2.1.9.5 Heterocycles as 4π component in [2 + 4] cycloaddition

In accordance with the discussion in the introduction (Section 3.2.1.9.1), heterocycles with the following characteristics undergo these reactions.

(i) Benzo ring fusions

The acridizinium ion adds to various dienophiles to give products of the type (**313**; Scheme 35).

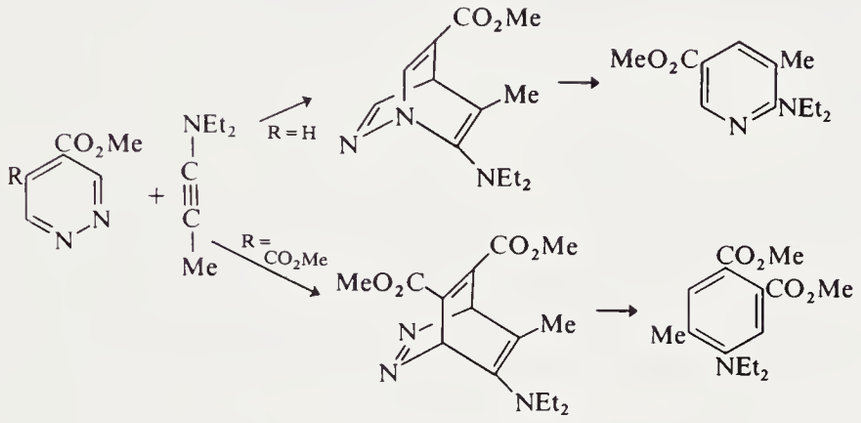


(**313**)

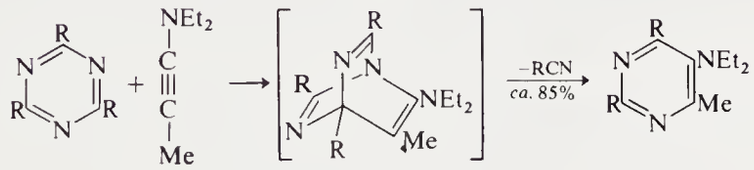
Scheme 35

(ii) Polyheteroatoms

Pyridazinecarboxylic esters undergo cycloaddition reactions as in Scheme 36. 1,3,5-Triazines react with dienophiles in Diels–Alder reactions (equation 4).



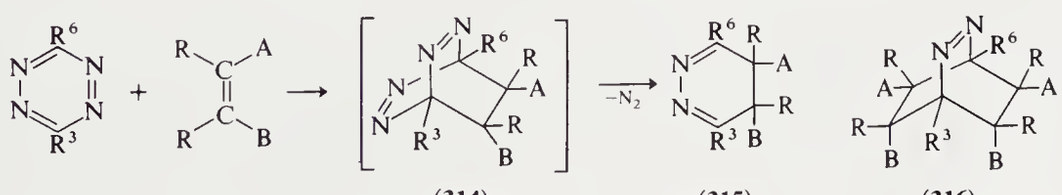
Scheme 36



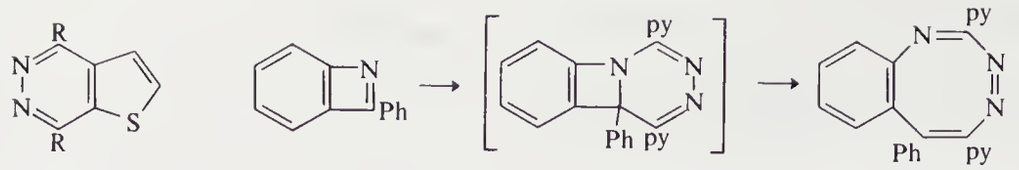
(4)

R = H, Me, CO_2Et, *etc.*

1,2,4,5-Tetrazines react with alkenes to give bicycles (**314**) which lose nitrogen to give the 4,5-dihydropyridazine (**315**). This can either tautomerize to a 1,4-dihydropyridazine, be oxidized to the aromatic pyridazine, or undergo a second Diels–Alder reaction to give (**316**). Many heterocycles act as the dienophile in such reactions; for example thiophene gives (**317**). The reaction is also used to trap unstable compounds, for example, 2-phenylbenzazete (**318**) as compound (**319**).



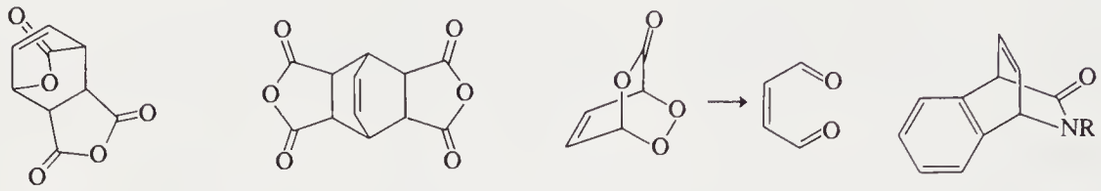
(**314**) (**315**) (**316**)



(317) (318) (319)

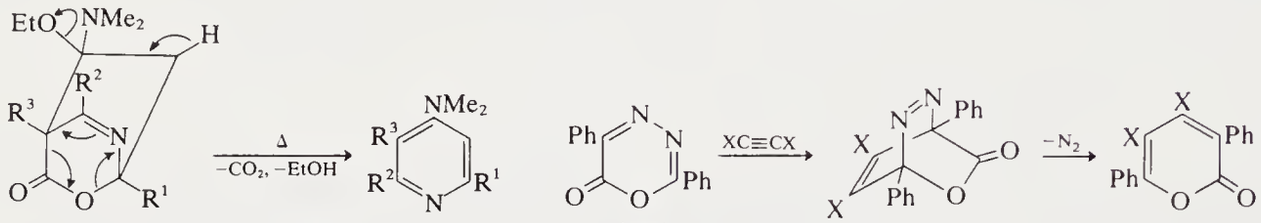
(iii) Ring carbonyl group

α-Pyranones undergo Diels–Alder reactions: with maleic anhydride adducts of type (**320**) are formed which can lose carbon dioxide and react with more anhydride to give (**321**). 2-Pyranones also react with singlet oxygen to give endoperoxides (**322**). Benzyne reacts with 1-methyl-2-pyridone to give (**323**).



(320) (321) (322) (323) R = Me

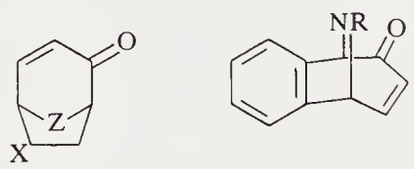
1,3-Oxazin-6-ones with electron-rich dienophiles give cycloadducts which lose CO_2 on heating (Scheme 37). The oxadiazinone (**324**) also reacts as a diene.



Scheme 37 (324)

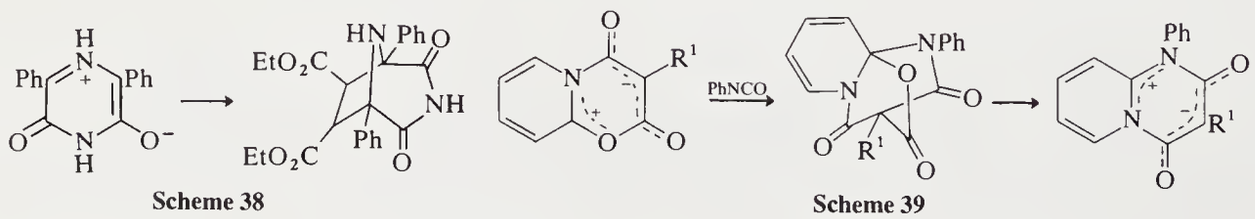
(iv) Betaine structures

3-Oxido-pyridiniums and -pyryliums react readily with dienophiles to yield cycloadducts of type (**325**). For Z = NMe, an electron-withdrawing X group is required in the dienophile, but with Z = O or *N*-(2-pyridyl) even unactivated alkenes react. 1-Phenyl-3-oxidopyridinium and benzyne give (**326**).



(325) (326) R = Ph

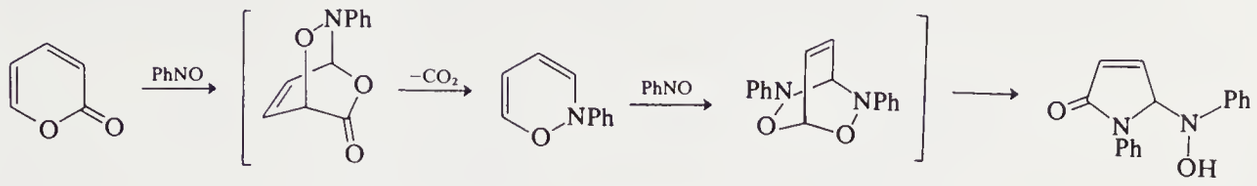
2,6-Dihydroxypyrazine betaines react to give bridged rings, *e.g.* with diethyl maleate (Scheme 38). Bicyclic 1,3-oxazine and 1,3-thiazine betaines form cycloadducts which fragment to restore the aromaticity (Scheme 39).



Scheme 38 Scheme 39

(v) Antiaromatic ring

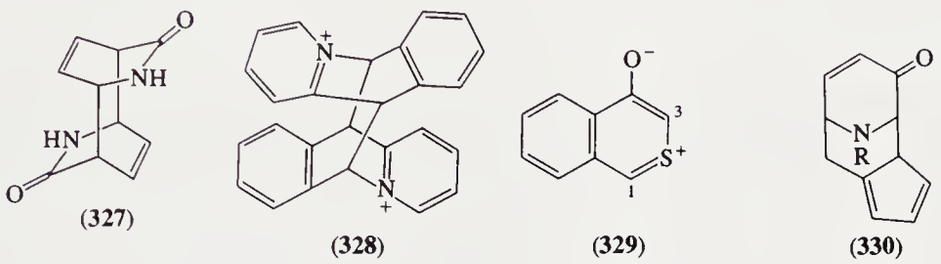
2-Phenyl-1,2-oxazine, formed as a transient intermediate, appears to undergo cycloaddition immediately (Scheme 40).



Scheme 40

3.2.1.9.6 Heterocycles as 4π component in [4 + 4] cycloaddition

2-Pyridone on irradiation in concentrated solution gives the dimer (**327**); 2-aminopyridine behaves similarly. The acridizinium ion (see Scheme 25) like anthracene undergoes [4 + 4] photocycloaddition to yield (**328**). 4-Oxido-2-benzothiinium (**329**) gives a thermal dimer across the 2,4-positions.



(**327**) (**328**) (**329**) (**330**)

3.2.1.9.7 Heterocycles as 4π component in [4 + 6] cycloaddition

3-Oxidopyridiniums (**307**; Z = NR) react with fulvenes to form adducts across the 2,6-positions (**330**).

3.2.2 REACTIONS OF NON-AROMATIC COMPOUNDS

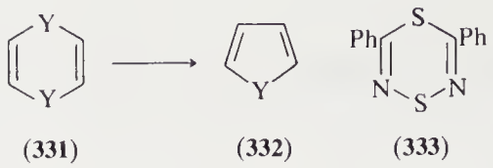
We classify these compounds according to their degree of unsaturation. There is a class of eight-π-electron systems containing two O, S or NR atoms in the ring which possess considerable stability. We then consider the thiabenzenes, which behave as cyclic sulfonium betaines, and related compounds.

Among the hydrogenated derivatives, we distinguish dihydro from the tetrahydro/hexahydro class, as the former bear an intimate relationship to their aromatic analogues.

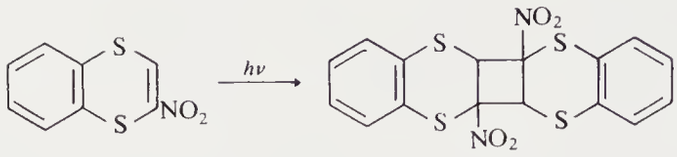
3.2.2.1 Eight-π-electron Systems: 1,2- and 1,4-Dioxins, -Oxathiins and -Dithiins

3.2.2.1.1 Intramolecular thermolysis and photolysis reactions

Substituted 1,4-dioxins thermolyze and photolyze to complex mixtures (see CHEC 2.26.3.1.2). By contrast 1,4-dithiins and the corresponding sulfoxides generally extrude sulfur or sulfur monoxide to give the corresponding thiophene [(**331**)→(**332**); Y = S]. 1,4,2,6-Dithiadiazines (*e.g.* **333**) similarly extrude sulfur to give 1,2,5-thiadiazoles. 2-Nitro-1,4-benzodithiin undergoes photochemical dimerization (equation 5) ⟨70AHC(11)63⟩. The dibenzo-fused systems are rather stable.



(331) (332) (333)



(5)

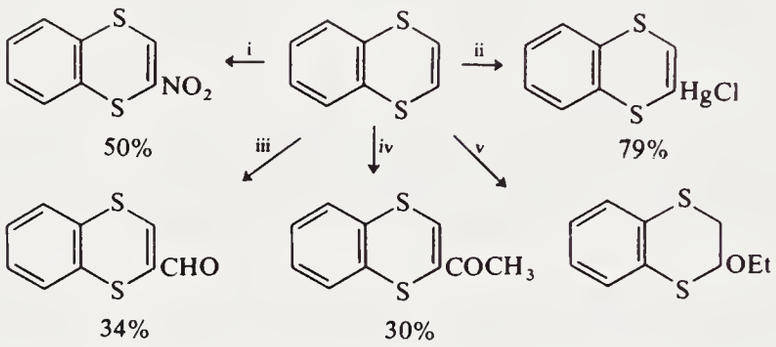
3.2.2.1.2 Reaction with electrophiles

(i) By addition to C=C double bonds

1,4-Dioxin and 1,4-dithiin both undergo easy electrophilic addition reactions, *e.g.* of halogens to the double bonds. Alcohols under acid catalysis form ketal addition products.

(ii) By electrophilic substitution

Substitution products can be obtained from some 1,4-dithiins. Thus, 2,5-diphenyldithiin is formylated under Vilsmeier conditions, and mono- or di-nitrated and brominated in the heterocyclic ring. 1,4-Benzodithiin shows similar properties (see Scheme 41).



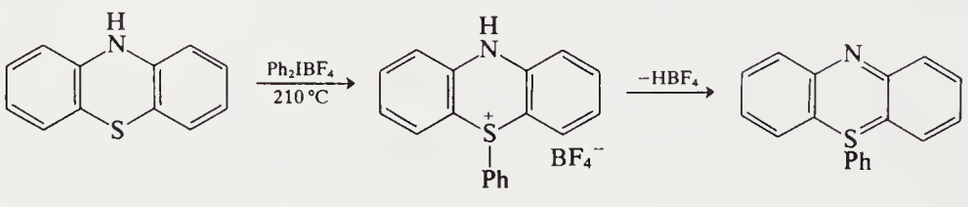
i, HNO_3, AcOH; ii, $HgCl_2$; iii, PhNMeCHO, $POCl_3$; iv, Ac_2O, H_3PO_4; v, EtOH, H^+

Scheme 41

(iii) By reaction at sulfur

1,4-Dithiins react readily at sulfur with peracids, alkyl halides and hydroxylamine *O*-sulfonic acid to give sulfoxides, thiinium salts and sulfilimines, respectively. Similar reactions are known for 1,4-benzodithiins.

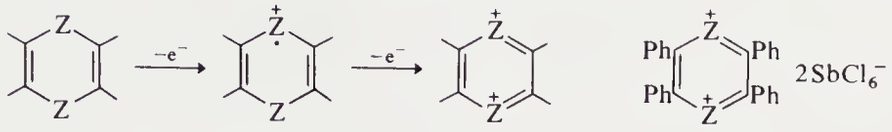
N-Alkylphenothiazines are oxidized to *S*-monoxides and *S,S*-dioxides with hydrogen peroxide in acetic acid. Phenothiazone can also be *S*-phenylated to form a phenothiazinium cation (**334**), which loses HBF_4 to give (**335**).



(334) (335)

(iv) By electron loss

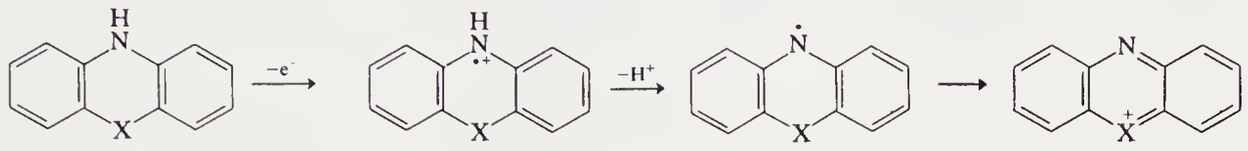
These compounds undergo one-electron oxidations to give radical cations and further loss of a second electron to give a six-π-electron dication (see Scheme 42). These reactions can be carried out electrochemically or chemically. Dication salts such as (**336**) and (**337**) have been isolated.



Scheme 42

(**336**) Z = O
(**337**) Z = S

Phenoxazines and phenothiazines (**338**; X = O, S) may be oxidized to phenoxazonium and phenothiazinium salts (**339**; X = O, S). Radical cations are intermediates; these lose H^+ to form a neutral radical followed by another electron to form the six-π-electron system (Scheme 43).



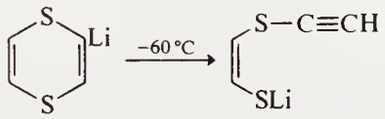
(**338**) (**339**)

Scheme 43

3.2.2.1.3 Reactions with nucleophiles

These electron-rich systems usually show little tendency to react with nucleophiles, but 1,2-dithiins suffer nucleophilic attack at sulfur followed by ring cleavage.

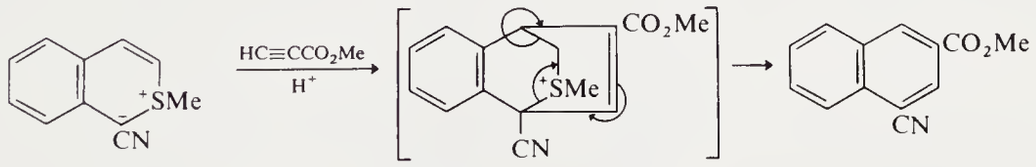
1,4-Dithiin is readily metallated at the 2-position by *n*-butyllithium at −110 °C, and (**340**) can be trapped at this temperature. At −60 °C ring opening occurs to give (**341**).



(**340**) (**341**)

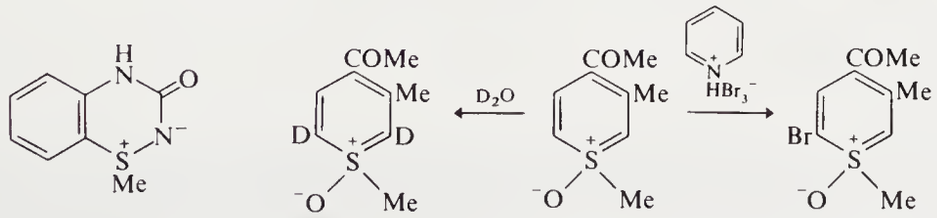
3.2.2.2 Thiabenzenes and Related Compounds

Thiabenzenes should be considered as sulfonium betaines. They react readily with acids to give mixtures of 2*H*- and 4*H*-thiinium salts, behave as dienes with dienophiles (equation 6), and can be oxidized to sulfoxides. The sulfimide (**342**) is an aza analogue of a thiabenzene and it is oxidized by $KMnO_4$ to the corresponding sulfoximide.



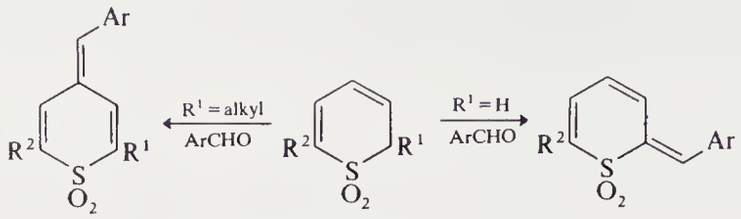
(6)

Thiabenzene sulfoxides can be nitrated and brominated; thus, (**343**) gives (**344**) and (**345**).



(**342**) (**345**) (**343**) (**344**)

2*H*-Thiin dioxides form anions which appear to have some homoaromatic stability. The anions react with aldehydes (Scheme 44).



Scheme 44

3.2.2.3 Dihydro Compounds

3.2.2.3.1 Introduction

We consider as 'dihydro derivatives' those rings which contain either one or two sp^3-hybridized carbon atoms. According to this definition, all reactions of the aromatic compounds with electrophiles, nucleophiles or free radicals involve dihydro intermediates. Such reactions with electrophiles afford Wheland intermediates which usually easily lose H^+ to re-aromatize. However, nucleophilic substitution (in the absence of a leaving group such as halogen) gives an intermediate which must lose H^-; such intermediates often possess considerable stability. Radical attack at ring carbon affords another radical which usually reacts further rapidly. In this section we consider the reactions of isolable dihydro compounds; it is obvious that much of the discussion on the aromatic compounds is concerned with dihydro derivatives as intermediates.

The reactions of the dihydro compounds are of two main classes. The reactions to regain aromaticity which depend intrinsically on the 'dihydro six-membered heterocyclic' structure can in turn be subdivided into four groups, of which the first is by far the most important:

(i) Loss of a group attached to an sp^3-hybridized ring carbon with its electrons to regain aromaticity.

(ii) Electrocyclic ring opening.

(iii) Loss of a group attached to an sp^3-hybridized ring carbon without its electron to form an eight-π-electron conjugated ring.

(iv) Loss of an electron or H· from a radical cation or neutral radical.

The other class of reactions includes those which are common to alicyclic analogues: reactions with electrophiles and nucleophiles and through cyclic transition states.

We discuss these in turn, but first consider tautomeric structures.

3.2.2.3.2 Tautomerism

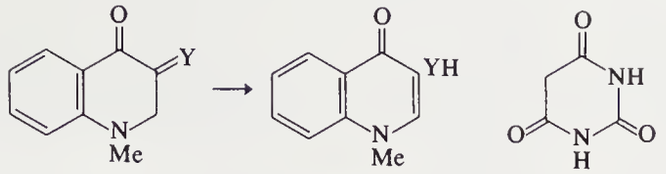
N-Unsubstituted dihydropyridines can exist in at least five tautomeric forms (Section 2.2.5.2). At least for *N*-substituted compounds 1,4-dihydropyridines (*cf.* **345**) are generally more stable, by *ca.* 9 kJ mol^{-1}, than the 3,4-dihydro and the 1,2-dihydro isomers (*cf.* **346**). By contrast 2*H*-pyrans appear to be thermodynamically more stable than 4*H*-pyrans. All three types of 1,3-oxazine are known.

(345) **(346)**

3.2.2.3.3 Aromatization

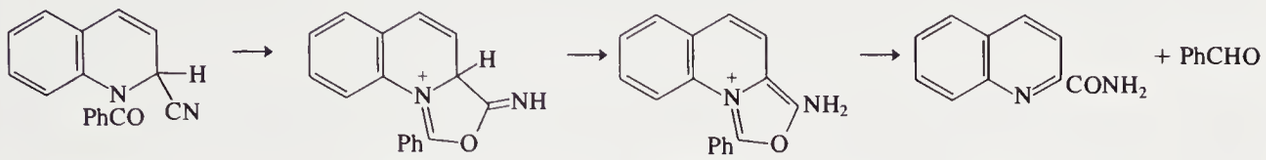
(i) By tautomerism

Compounds of type (**347**) can aromatize by isomerization [(**347**)→(**348**), Y = CHR, NR]. In a few cases such tautomerism is reversible: barbituric acid (**349**) exists mainly in the trioxo form whereas the anion is aromatic.



(347) (348) (349)

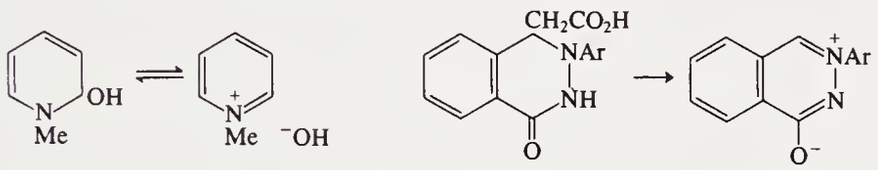
1-Benzoyl-2-cyano-1,2-dihydroquinolines and the corresponding isoquinolines (Reissert compounds) (*cf.* Section 3.2.1.6.8.iv) are cleaved by acid into aldehydes plus 2-quinoline- or 1-isoquinoline-carboxamides. The mechanism of this reaction involves the sequence (**350**)→(**353**); note the aromatization step (**351**)→(**352**).



(350) (351) (352) (353)

(ii) By loss of attached leaving groups with bonding electrons

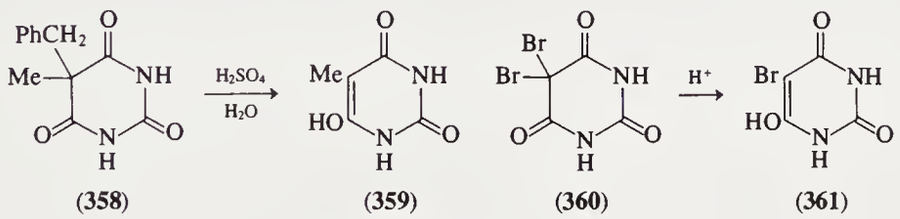
Those dihydro compounds which carry a leaving group attached to their single sp^3-hybridized carbon atom exist in equilibrium with the corresponding aromatic compounds (*e.g.* the pseudo-bases **354**⇌**355**; see Section 3.2.1.6.3.iv). Another similar example is that of the covalently hydrated cations of neutral azines (see Section 3.2.1.6.3). A somewhat less obvious example is the acid-catalyzed cleavage (**356**)→(**357**) with the loss of $MeCO_2H$.



(354) (355) (356) (357)

(iii) By loss of attached group without bonding electrons

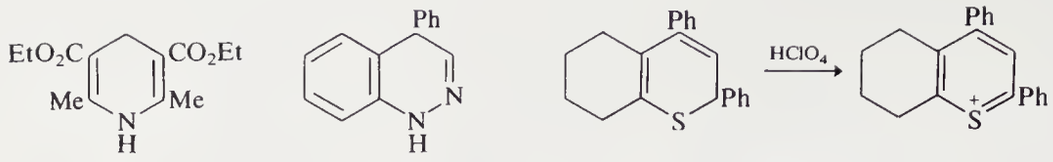
This includes expulsion of a carbonium ion (*e.g.* **358**→**359** + $PhCH_2OH$) or nucleophilic removal of a positive halogen atom (**360**→**361** + Br^+).



(358) (359) (360) (361)

(iv) By disproportionation

These compounds often disproportionate (*e.g.* **362**→2 moles of the corresponding pyridine + 1 mole of the piperidine). Some dihydrodiazines disproportionate: the dihydrocinnoline (**363**) on treatment with hydrochloric acid gives 4-phenylcinnoline and 4-phenyl-1,2,3,4-tetrahydrocinnoline.



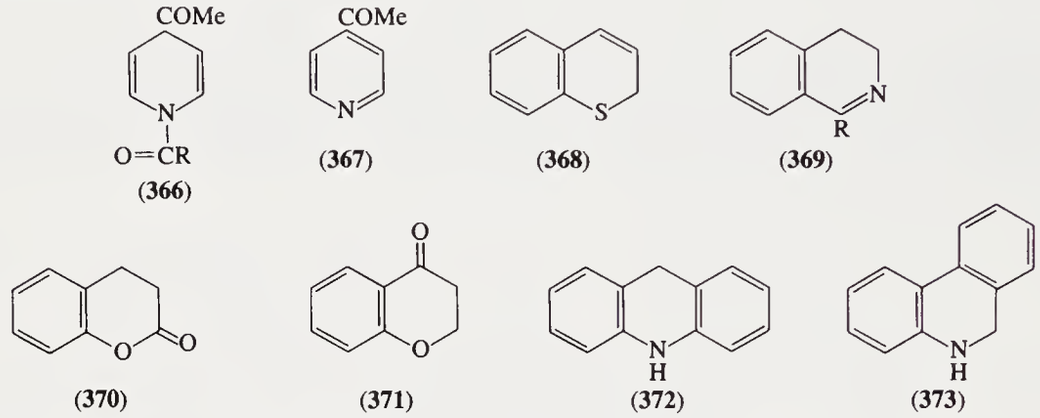
(362) (363) (364) (365)

2*H*- (*e.g.* **364**) and 4*H*-Thiins on treatment with acid disproportionate into thiinium salts (**365**) and the corresponding tetrahydrothiin.

(v) By oxidation or dehydrogenation

Dihydropyridines, 1,2-dihydro-quinolines and -isoquinolines, pyrans and chromenes are very easily oxidized. Syntheses which should afford the dihydro compounds often proceed direct to fully aromatic products (*cf.* Section 4.2.3.4.2). 1-Substituted dihydropyridines can be aromatized in various ways, *e.g.* with nitrous fumes ($NO–N_2O_4$). Compound (**366**) is converted into (**367**) by sulfur, or to 4-ethylpyridine by Zn–HOAc. The oxidation of 1,4-dihydropyridines by hydride transfer to give pyridinium cations has been extensively studied; some workers consider electron transfer to be the first step.

Pyrans and thiins are also easily aromatized, *e.g.* (**368**) + S_2Cl_2 → 1-benzothiinium ion. 2*H*-Thiins are aromatized by hydride acceptors such as triphenylmethyl cations to give thiinium salts, and similar conversions produce pyrylium salts from pyrans.

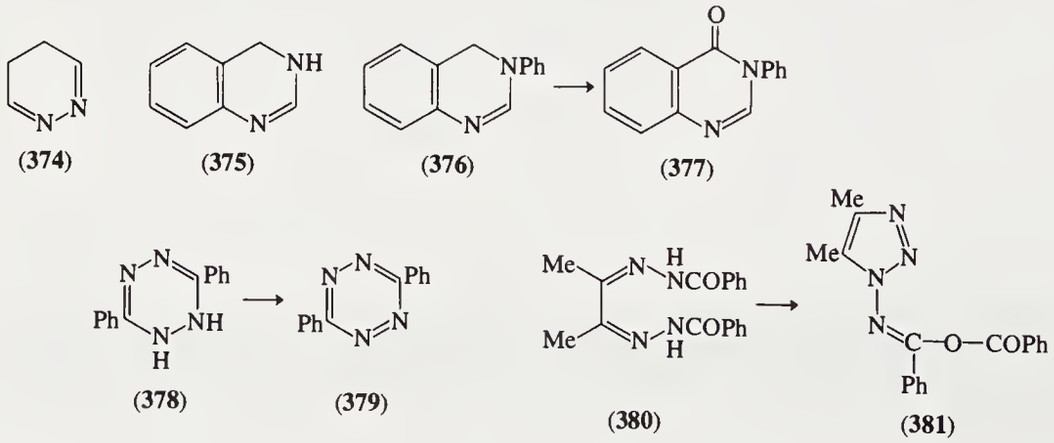


(366) (367) (368) (369)

(370) (371) (372) (373)

3,4-Dihydroisoquinolines (*e.g.* **369**), 3,4-dihydrocoumarins (*e.g.* **370**) and 2,3-dihydrochromones (*e.g.* **371**) are aromatized by either oxidation or dehydrogenation with S or Se at 300 °C or Pd at 200 °C. 9,10-Dihydroacridines (*e.g.* **372**) and 5,6-dihydrophenanthridines (*e.g.* **373**) with NH groups are oxidized to the fully aromatic compounds on exposure to air or by other oxidizing agents such as chromic oxide.

Dihydrodiazines are readily aromatized by oxidizing agents: 4,5-dihydropyridazine (**374**) yields pyridazine (CrO_3–AcOH), and 3,4-dihydroquinazoline (**375**) is converted by $K_3Fe(CN)_6$ into quinazoline. Some dihydrodiazines are oxidized directly to diazinones (*e.g.* **376**→**377** with $KMnO_4 - OH^-$). Dihydro-triazines and -tetrazines also readily yield the corresponding aromatic azine (*e.g.* **378** + Br_2 or O_2 →**379**).



(374) (375) (376) (377)

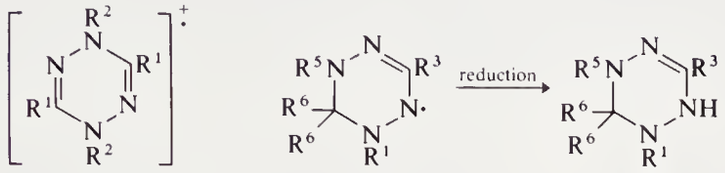
(378) (379) (380) (381)

(vi) By ring contraction

Oxidation of 1,2-bishydrazones (**380**) is now known to give triazoles (**381**) and not dihydro-1,2,3,4-tetrazines. Possibly the latter are intermediates but are aromatized by ring contraction.

3.2.2.3.4 Electron loss to form radicals

The formation of a radical cation by electron loss, or a neutral radical by successive loss of e^- and H^+ is probably an important pathway in many of the oxidative and other reactions of these dihydro compounds. In most cases, the radical is merely a transient intermediate, but 1,4-dihydro-1,2,4,5-tetrazines are electrochemically oxidized to stable radical cations (**382**) or to neutral verdazyls (**383**). In turn, verdazyls are easily reduced to 1,2,3,4-tetrahydrotetrazines (**384**).

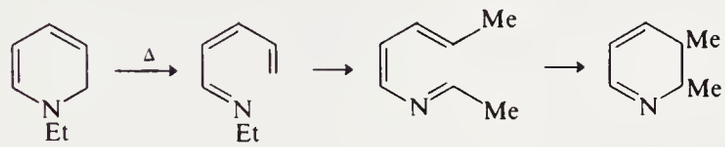


(**382**) (**383**) (**384**)

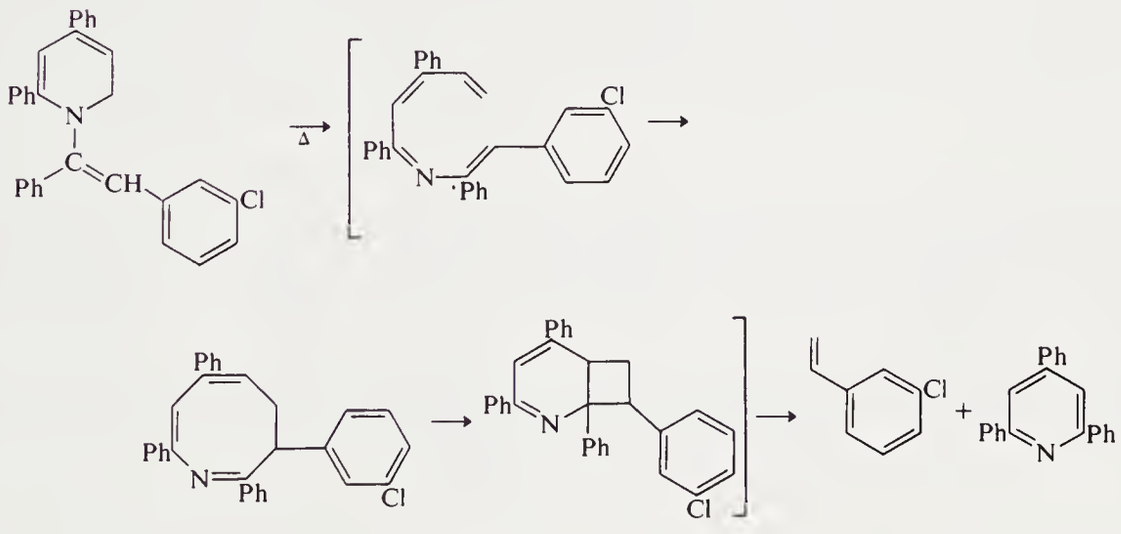
3.2.2.3.5 Electrocyclic ring opening

The concept of electrocyclic ring opening of a 1,2-dihydro six-membered heterocycle is familiar from the numerous examples found after nucleophilic attack, especially on cationic rings.

Similar reactions occur with isolated 1,2-dihydro derivatives. Dihydropyridines can undergo isomerization by electrocyclic ring opening (see equation 7). 1-Vinyl-1,2-dihydropyridines in a somewhat similar sequence yield pyridines *via* azacyclooctatrienes (equation 8).

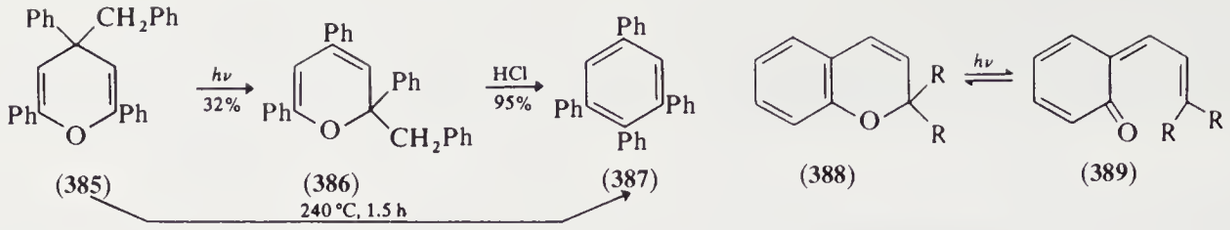


(7)



(8)

The 4-benzylpyran (**385**) rearranges on irradiation or thermally into the 2-benzyl isomer (**386**) which yields the benzene (**387**) *via* electrocyclic ring opening. Irradiation of 2*H*-chromenes (**388**) gives an intense red color due to the quininoid photoproduct (**389**).

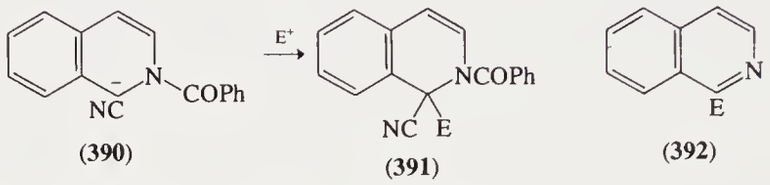


(385) (386) (387) (388) (389)

3.2.2.3.6 *Proton loss to an eight-π-electron conjugated system*

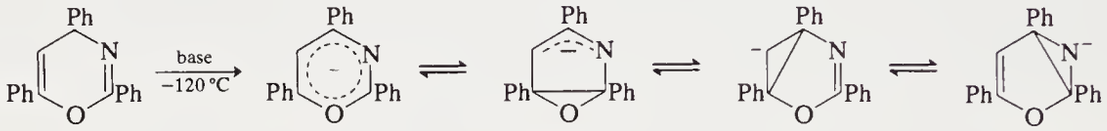
Very strong bases can extract a proton from the 1,2- or 1,4-dihydropyridine ring giving a fully conjugated eight-π-electron antiaromatic system, which can be trapped by electrophiles.

Reissert compounds (*cf.* Section 3.2.1.6.8.iv) can be deprotonated ($NaH/HCONMe_2$) to give anions (*e.g.* **390**) which react with electrophiles to give intermediates (**391**) which can be hydrolyzed to substituted heterocycles (**392**). Electrophiles utilized include alkyl and reactive aryl halides and carbonyl compounds.



(390) (391) (392)

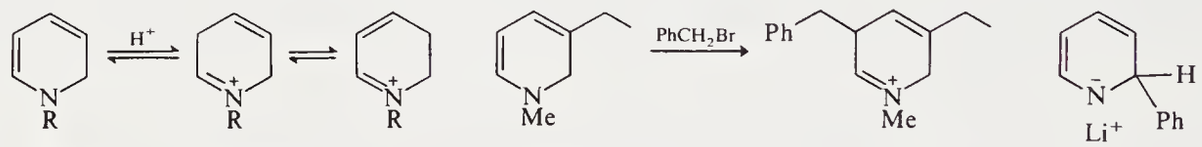
Oxazinyl anions obtained from 4*H*-1,3-oxazines are considered to exist in equilibrium with valence bond tautomers (Scheme 45).



Scheme 45

3.2.2.3.7 *Electrophilic substitution*

1,2-Dihydropyridines (**393**) are susceptible to electrophilic attack. The β-carbon is the kinetic site of protonation giving a 2,5-dihydropyridinium cation (**394**) which slowly rearranges to the thermodynamically more stable 2,3-dihydropyridinium ion (**395**). Alkylation of a 1,2-dihydropyridine at the 3-position can be carried out under phase-transfer conditions (**396**→**397**).

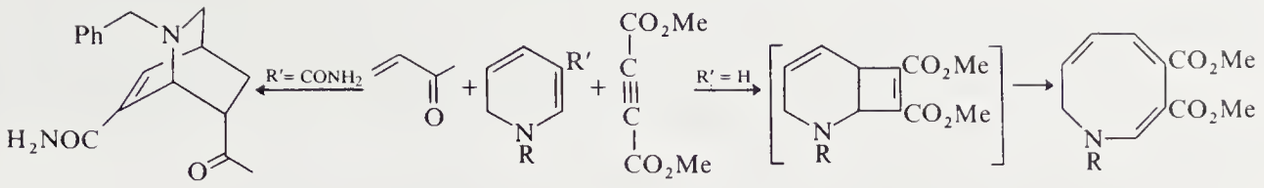


(393) (394) (395) (396) (397) (398)

The *N*-lithio-2-phenyl-1,2-dihydro adduct (**398**) (Section 3.2.1.6.8.i) is a useful synthetic intermediate that reacts with alkyl halides, bromine ⟨70CC478⟩, carbon dioxide ⟨70TL3371⟩ and benzophenone ⟨70CC921⟩ to give 2,5-disubstituted derivatives.

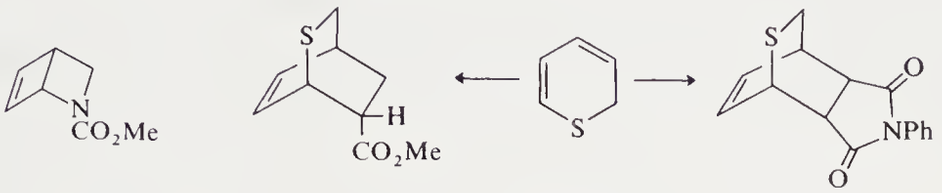
3.2.2.3.8 *Cycloaddition reactions*

The 1,2-dihydropyridine ring can be a four-electron component in a Diels–Alder reaction and also undergo [2 + 2] cycloadditions with alkynes (Scheme 46).



Scheme 46

1,2-Dihydropyridines are isomerized photochemically to 2-azabicyclohexenes (**399**).
2*H*-Thiins behave as dienes in Diels–Alder reactions (Scheme 47).



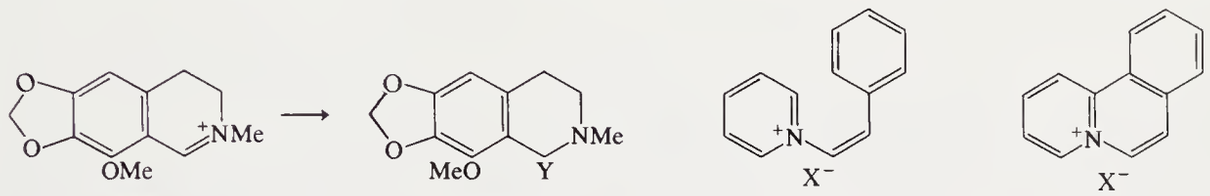
(**399**)

Scheme 47

3.2.2.3.9 Other reactions

3,4-Dihydroisoquinolines, *e.g.* (**369**), are basic and form quaternary salts, *e.g.* (**400**). With alkali these salts form carbinolamine pseudo-bases, *e.g.* cotarnine (**401**; Y = OH), which can be oxidized to lactams or which disproportionate on standing. The quaternary ions can also react with other nucleophilic reagents, *e.g.* (**400**) + RMgBr → (**401**; Y = R); (**400**) + MeCOMe → (**401**; Y = CO_2Me); (**400**) + CN^- → (**401**; Y = CN); (**400**) + RNH_2 → (**401**; Y = NHR). The pseudo-bases are in equilibrium with open-chain compounds since aldehyde derivatives can be prepared.

Reduction of dihydro compounds to the tetra- or hexa-hydro derivatives is usually possible. For example, dihydroisoquinolines of type (**369**) form the corresponding tetrahydroisoquinoline with H_2/Pd or with Na/Hg–EtOH.



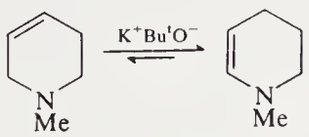
(**400**) (**401**) (**402**) (**403**)

C-Styrylpyridines undergo photocyclization to give azaphenanthrenes and *N*-styrylpyridinium cation forms an azoniaphenanthrene (**402** → **403**).

3.2.2.4 Tetra- and Hexa-hydro Compounds

3.2.2.4.1 Tautomeric equilibria

Tetrahydro compounds still contain one ring double bond and thus can exist in several tautomeric forms (*cf.* Section 2.2.5.2). Little systematic work is available regarding the position of such equilibria, but 1-methyl-Δ^2-piperideine is more stable than the Δ^3-isomer by 16 kJ mol^{-1} (equation 9).



(9)

3.2.2.4.2 Aromatization

Tetra- and hexa-hydro compounds can often be aromatized, but this is more difficult than in the corresponding dihydro series. Thus, the conversion of piperidines to pyridines typically requires dehydrogenation with Pd at 250 °C.

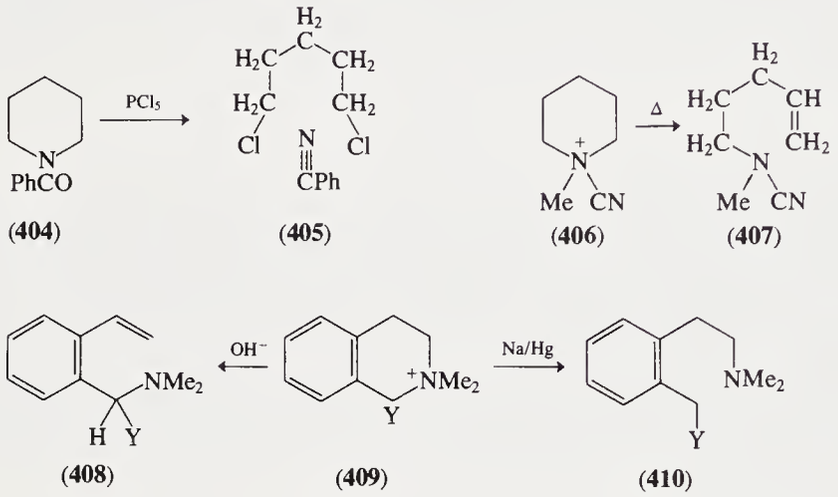
3.2.2.4.3 Ring fission

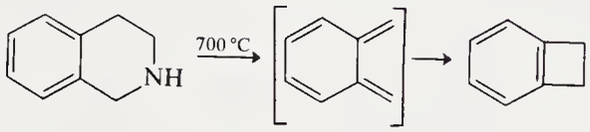
Cleavage of a saturated heterocyclic ring is accomplished using degradative procedures which are also applicable to corresponding aliphatic compounds. Thus, a nitrogen-containing ring is opened by:

(i) the von Braun amide and PCl_5 method for NH compounds, *e.g.* (**404**)→(**405**);
(ii) the von Braun cyano-ammonium route for tertiary amines, (**406**)→(**407**);
(iii) Hofmann exhaustive methylation for tertiary amines, *e.g.* (**409**)→(**408**);
(iv) the Emde reaction, specifically for tetrahydroisoquinolines, *e.g.* (**409**; Y = Me)→(**410**, **408**; Y = Me).

The rings of cyclic ethers are opened more readily than in the acyclic series; *e.g.* tetrahydropyran with aqueous hydrochloric acid at 100 °C gives $Cl(CH_2)_5Cl$.

1,2,3,4-Tetrahydroisoquinoline undergoes a thermal retro-Diels–Alder reaction to give *o*-quinodimethane (equation 10).





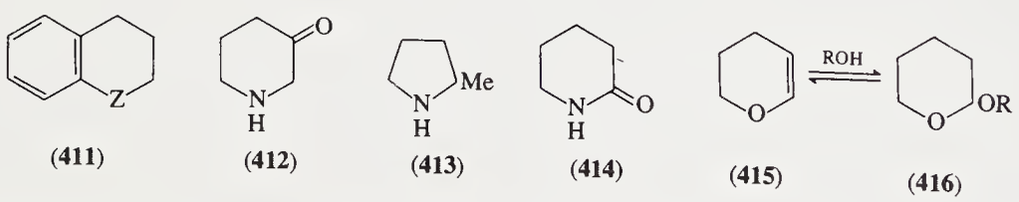
(10)

3.2.2.4.4 Other reactions

These compounds usually show other reactions typical of their aliphatic analogues. 1,2,3,4-Tetrahydroquinoline (**411**; Z = NH) is thus an *N*-alkylaniline; chroman (**411**; Z = O) is an alkyl aryl ether.

3-Piperidone (**412**) behaves as an amino ketone, although on Clemmensen reduction it gives 2-methylpyrrolidine (**413**). 2-Piperidone (**414**) is a lactam.

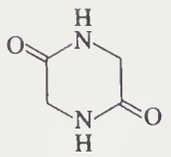
Δ^2-Dihydropyran (**415**) is an enol ether and as such adds hydroxy compounds (hydroxy groups are thus 'protected') to give adducts (**416**) which dissociate on heating.



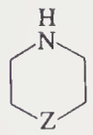
N-Methylpiperidine is a tertiary amine, and as such it is converted by mercuric acetate into 1-methyl-Δ^2-tetrahydropyridine.

1,3-Dioxane behaves as an acetal, 1,4-dioxane as a bis-ether, and 2,5-dioxopiperazine (**417**) as a bis-lactam.

Piperazine (**418**; Z = NH) and morpholine (**418**; Z = O) show typical aliphatic secondary amine properties, but their pK_a values, 9.8 and 8.4, respectively (*cf.* piperidine pK_a 11.2), reflect the inductive effect of the second heteroatom.



(**417**)



(**418**)

3.2.2.4.5 Stereochemistry

Steric effects can alter the reactivity of a heterocyclic compound as compared to its aliphatic analogue. For example, piperidine is less sterically hindered and more strongly nucleophilic than diethylamine.

Conformations of these compounds are discussed elsewhere (Section 2.2.4.3).

3.2.3 REACTIONS OF SUBSTITUENTS

3.2.3.1 General Survey of Reactivity of Substituents on Ring Carbon Atoms

We consider here substituents attached to carbon (see Section 3.2.3.12.1 for general discussion of substituents attached to nitrogen).

The differences in the reactivities of the same substituents on heteroaromatic nuclei and on benzene rings are a measure of the influence of the heteroatom(s). For six-membered heteroaromatic rings, the typical effect of the heteroatom(s) is to attract electrons away from the carbon atoms of the ring. This influence is relatively small when the heteroatom is β to the substituent, but large for the α- and γ-orientations.

3.2.3.1.1 The carbonyl analogy

The reactions of many of the typical functional groups of organic chemistry are influenced to a large extent by an adjacent carbonyl group because of the conjugative electron-withdrawing effect. As would be expected from the discussion in the preceding section, the reactions of substituents in six-membered heterocyclic rings can be similarly influenced. It is therefore helpful to consider systematically the familiar effects on substituents attached to carbonyl groups in aliphatic chemistry. These can be classified into six groups.

(i) Groups which can form anions are readily displaced by nucleophilic reagents (**419**).

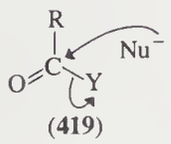
(ii) α-Hydrogen atoms are easily lost as protons (**420**).

(iii) As a consequence of (ii) tautomerism is possible (**421**⇌**422**).

(iv) Carbon dioxide is lost very easily from carboxymethyl groups (**423**) and readily from carboxyl groups (**424**).

(v) These effects are transferred through a vinyl group, and nucleophilic reagents will add to vinyl and ethynyl groups (**425**) (Michael reaction).

(vi) Electrons are withdrawn from aryl groups; thus electrophiles attack the *meta* position (**426**).



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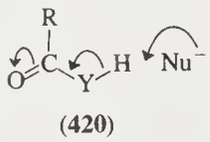

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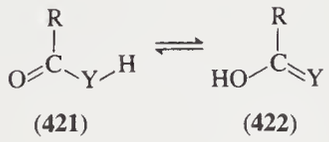
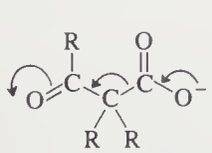


(**421**) (**422**)



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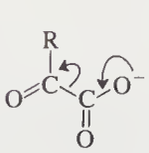
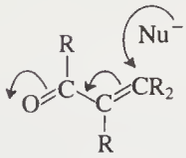
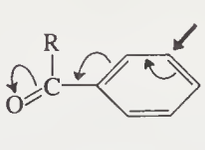


(**424**)



(**425**)



(**426**)

In Table 3 the consequences of effects (i)–(vi) are listed systematically for heterocycles, and compared with the similar effect found in the corresponding aliphatic carbonyl compound.

Table 3 The Carbonyl Analogy for Reactions of Azine Substituents

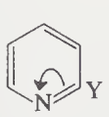
Reaction type	*Group*	*Tendency for substituent in azine*	*Discussed in Section*	*Compare with*
Nucleophilic displacement	Nitro	Ready displacement	3.2.3.6.1	—
	Halogen	Displacement	3.2.3.10.1	Acid chloride
	Alkoxy, Amino, Cyano	Displacement when additionally activated	3.2.3.8.1 3.2.3.5.4 3.2.3.4.2.iv	Ester Amide Acyl cyanide
Proton loss	Hydroxy	Acidity	3.2.3.7.1	Carboxylic acid
	Amino	Lower basicity	3.2.3.5.4	Amide
	Alkyl	'Activity'	3.2.3.3.2	Ketone
Tautomerism	Hydroxy	To exist in oxo form	3.2.3.7.1	Carboxylic acid (two equivalent structures)
	Amino	To exist as amine	3.2.3.5.5	Amide
	Mercapto	To exist in thione form	3.2.3.9.1	Thiocarboxylic acid
Decarboxylation	Carboxyl	To decarboxylate	3.2.3.4.2	α-Keto acids
	Carboxymethyl	To decarboxylate easily	3.2.3.4.2	β-Keto acids
Michael reactions	Vinyl	To undergo Michael additions	3.2.3.4.5	α,β-Unsaturated ketones
	β-Hydroxyethyl	To undergo reverse Michael reaction (loss of H_2O)	3.2.3.4.4	β-Hydroxy ketone
Electrophilic attack on phenyl groups	Phenyl	To undergo electrophilic substitution in the *meta* and *para* positions	3.2.3.4.1	Phenyl ketones

3.2.3.1.2 Effect of number, type and orientation of heteroatoms

(i) Pyridines and azines

An α-substituent in pyridine (**427**) is in an electronic environment approaching that of a substituent in the imino compound (**428**). Since the reactions of the carbonyl compounds (**429**) are better known than those of the imino compounds (**428**), the reactions of α-substituted pyridines are compared with those of the analogous carbonyl compounds (see preceding section). However, the electron pull is much greater in carbonyl compounds than in pyridine; α-substituents on pyridine accordingly show reactivities intermediate between those of substituents on benzene and substituents attached to carbonyl groups.

The electron-withdrawal to the cyclic nitrogen atom can be transmitted to the γ-position of pyridine (**430**) (illustrating the principle of vinylogy). Hence, γ-substituents have properties similar to those of α-substituents. β-Substituents in pyridine are not directly conjugated with the heteroatom; usually the reactivity is intermediate between that of the same substituent attached to a benzene ring, and that of an α- or γ-substituted pyridine.



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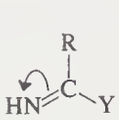

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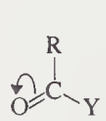

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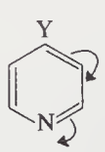


(430)

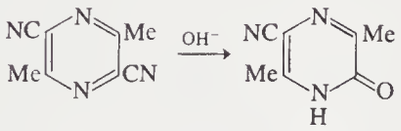
In the diazines, triazines and tetrazines, the effects of the additional nitrogen atom are roughly additive. In Table 4 the positions of substituents in the common azine ring systems are listed in order of increasing reactivity. The limit is reached in 2-, 4- or 6-substituted 1,3,5-triazines for which the reactivity approximates to that in the corresponding carbonyl compound (**429**).

Table 4 Substituent Environments in Azines Listed in Order of Increasing Reactivity

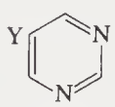
Position of substituent	*Ring system*	*Number of α- or γ-N*	*Number of β-N*
Any	Benzene	—	—
3 or 5	Pyridine	—	1
5	Pyrimidine	—	2
2, 4 or 6	Pyridine	1	—
3, 4, 5 or 6	Pyridazine	1	1
2, 3, 5 or 6	Pyrazine		
6	1,2,4-Triazine	1	2
2, 4 or 6	Pyrimidine	2	—
3 or 5	1,2,4-Triazine	2	
3 or 6	1,2,4,5-Tetrazine	2	2
2, 4 or 6	1,3,5-Triazine	3	—

The influence of additional nitrogen atoms in the azines sometimes allows new reactions. An example of this is that of nucleophilic displacement of a cyano group, as in (**431**)→(**432**); this does not normally occur in the pyridine series, but is analogous to a reaction of acyl cyanides (RCOCN).

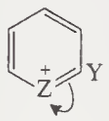
Substituents in the 5-position of pyrimidines (**433**) are the only substituents on diazines which are not α or γ to a ring nitrogen atom, and these behave similarly to the substituents in the 3-position of pyridines.



(**431**) (**432**)



(**433**)



(**434**)

The above considerations apply to the reactivity of *neutral* species. If a proton or other electrophile adds to a pyridine nitrogen atom, this is now transformed into a positive pole, with a far greater influence, as outlined in the next section.

(ii) Cationic rings

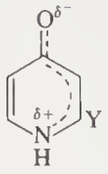
In cationic rings the electron pull of the positively charged heteroatom is much greater than that of an uncharged nitrogen atom. The effect of a single positively charged N, O or S atom at the α- or γ-position is somewhat stronger than *three* α,γ-nitrogen atoms and stronger than that of a carbonyl group. Hence substituents attached to the α- or γ-positions of pyridinium, pyrylium and thiinium ions (**434**) correspondingly show reactivity greater than that of the analogous carbonyl derivative (**429**). Additional nitrogen atoms, and especially a second positively charged atom, enhance the reactivity still further.

(iii) Rings with exocyclic conjugation

For pyridones, pyrones, azinones (*cf.* **435**) and also for *N*-oxides (*cf.* **436**) and β-oxidocationic rings (*cf.* **437**) the situation is more complex. The combined effect of the heteroatoms in such compounds is to act either as an electron source or as an electron sink depending on the

requirements of the reaction (see Section 3.2.1.1.4). In practice, in reactions involving neutral species, substituents α or γ to the heteroatom in 2- and 4-pyridones, 2- and 4-pyrones, and 2- and 4-thiinones (*e.g.* **435**) and pyridine *N*-oxides (**436**) are usually activated by electron withdrawal almost as much as they are in pyridine itself. Additional nitrogen atoms increase the reactivity as expected.

However, an important consideration again here is the species undergoing reaction. The reactivity of X in the cation (**439**) will be much more, and in the anion (**440**) much less, affected by electron withdrawal than that of X in (**438**).



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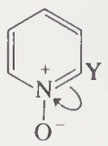

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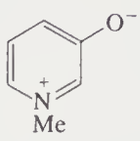

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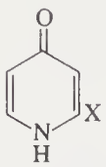

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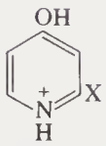

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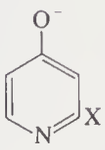

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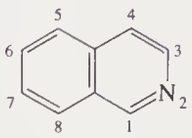


(441)

3.2.3.1.3 The effect of one substituent on the reactivity of another

This effect is generally similar to that observed in polysubstituted benzenes. Thus, groups such as NO_2 and CN reinforce the electron withdrawal from the substituent which is caused by the heteroatom(s).

As in naphthalene, a fused benzene ring induces bond fixation. Hence, whereas substituents in the 1-position of isoquinoline (**441**; note numbering) behave like substituents in the 2-position of the pyridine nucleus, substituents in the 3-position of isoquinoline show reactivity less than that of true α-substituents and about midway between those of 2- and 3-substituents on pyridine.

3.2.3.1.4 Reactions of substituents not directly attached to the heterocyclic ring

In general, substituents removed from the ring by two or more saturated carbon atoms undergo normal aliphatic reactions. A notable exception is the reverse Michael reaction which is undergone by β′-substituted ethyl compounds such as 2-(β-hydroxyethyl)pyridine (see Section 3.2.3.4.4).

Substituents directly attached to fused benzene rings or aryl groups mostly undergo the reactions of those on normal benzenoid rings. Naturally a substituent on the benzenoid ring in quinoline or isoquinoline should be compared with that on a naphthalene rather than with a benzene nucleus; *e.g.* such hydroxy derivatives undergo the Bucherer reaction, $ArOH + (NH_4)_2SO_3 \rightarrow ArNH_2$, typical for naphthols (see also Section 3.2.3.2.2).

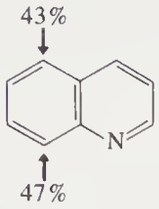
3.2.3.2 Benzenoid Rings

3.2.3.2.1 Fused benzene rings: unsubstituted

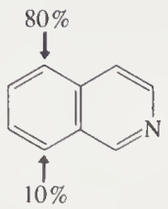
(i) Electrophilic substitution of benzazines

In azines with fused benzene rings, electrophilic substitution on carbon usually occurs in the benzenoid ring in preference to the heterocyclic ring. For quinoline and isoquinoline the only common exception is mercuration which in both occurs in the pyridine ring. However, a strong electron donor substituent such as NH_2 in the pyridine ring, or one or two strong electron acceptor substituents such as NO_2 in the benzenoid ring can also direct attack toward the pyridine ring.

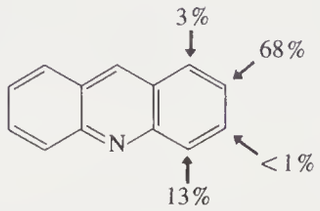
Frequently the orientation of substitution in benzazines parallels that of naphthalene. Nitration (H_2SO_4–HNO_3, 0 °C) of quinoline and isoquinoline proceeds in positions corresponding to α-substitution in naphthalene as shown in diagrams (**442**) and (**443**). Sulfonation of isoquinoline gives the 5- and 8-sulfonic acids, the former predominating below 180 °C. Sulfonation of quinoline (H_2SO_4–SO_3) is also temperature dependent (100–300 °C) yielding 5-, 7- and 8-quinolinesulfonic acids. Heating at 170 °C gives a mixture of the 8- and 5-isomers with the former predominating. At higher temperatures (300 °C) the main product is the thermodynamically favored 6-isomer and, as expected, both the 5- and 8-isomers undergo rearrangement to the 6-isomer under the appropriate conditions. Acridine (**444**), phenanthridine (**445**), cinnoline (**446**) and quinazoline (**447**) are nitrated as shown. Halogenation follows a somewhat similar pattern.



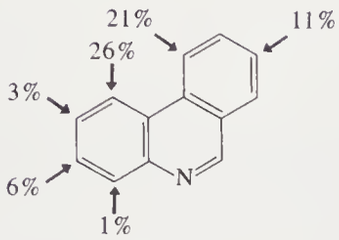
(**442**)



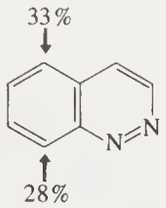
(**443**)



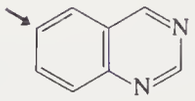
(**444**)



(**445**)



(**446**)



(**447**)

These substitution reactions probably all occur on the conjugate acid species as supported by the fact that the corresponding cations, such as *N*-methylquinolinium, undergo nitration at approximately the same rate.

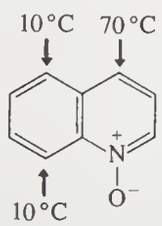
The relative reactivity of different positions toward electrophilic substitution is conveniently studied by acid-catalyzed deuterium exchange; reaction rates can be followed by NMR and introduction of deuterium hardly affects the reactivity of the remaining positions. In D_2SO_4 both quinoline and quinoline 1-oxide react as the conjugate acid at positions 8 > 5, 6 > 7 > 3.

(ii) Electrophilic substitution of benzopyridones and related compounds

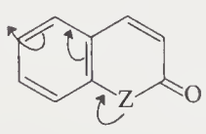
If the hetero ring is in the form of a pyridone, pyrone or *N*-oxide, or contains a strongly electron-donating substituent (OR or NR_2), electrophilic substitution into the hetero ring can compete with substitution into a fused benzene ring. In some such compounds, substitution occurs entirely in the heterocyclic ring; *e.g.* nitration of carbostyril (fuming HNO_3, no H_2SO_4) gives a 3-substituted product (see Section 3.2.1.4.4).

In other compounds, reaction can occur in both rings. Under such circumstances the orientation can depend on the conditions; frequently reaction in the benzene ring involves the cationic species, whereas that in the pyridine ring involves the free base. Thus the temperature dependent nitration of quinoline 1-oxide (**448**) reflects the decrease in intrinsic acidity as the temperature rises, which in turn increases the available amount of free base species.

Coumarins undergo nitration readily in the 6-position while bromination results in substitution at the 3-position as a consequence of addition–elimination.



(**448**)

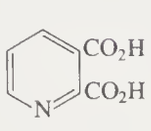


(**449**)

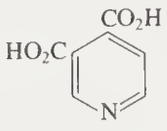
As outlined above, the orientation of substitution into bicyclic benzazines frequently occurs preferentially at the 5- and/or 8-positions. However, when the heterocyclic ring contains a carbonyl group, the orientation of substitution into a fused benzene ring frequently occurs in the 6-position. For carbostyril (**449**; Z = NH) (nitration, H_2SO_4–HNO_3, 20 °C) and for coumarin [nitration (H_2SO_4–HNO_3) and sulfonation (H_2SO_4)] this can be compared with the *para*-substitution of acetanilide and phenyl acetate.

(iii) Oxidation

Vigorous oxidation (*e.g.* $KMnO_4$) usually degrades fused benzene rings in preference to pyridine rings, especially under acid conditions. Quinoline and isoquinoline yield the dicarboxylic acids (**450**) and (**451**), respectively; phthalazine gives (**452**) and phenazine yields (**453**) and (**454**). Oxidation of such a fused benzene ring is facilitated when it carries electron-donating groups and is hindered by electron-withdrawing groups.



(450)



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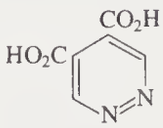

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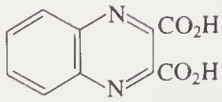

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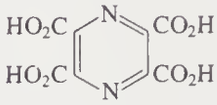


(454)

Ozonolysis of quinoline gives glyoxal and pyridine-2,3-dicarboxaldehyde.

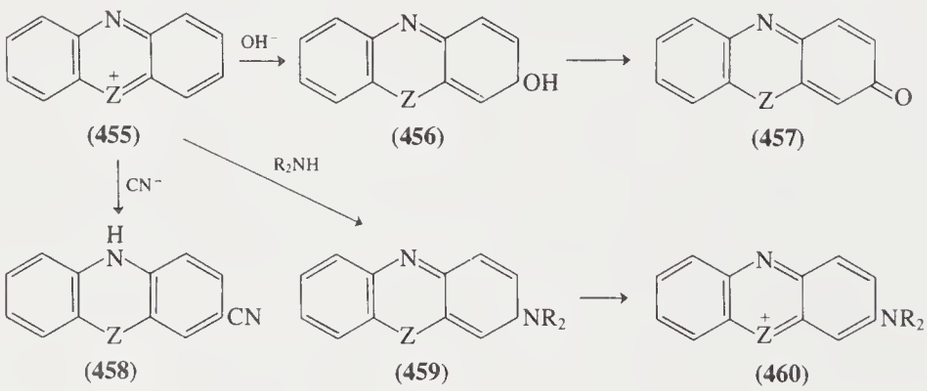
(iv) Radical reactions

Reactions with radicals are often unselective and form complex mixtures, Thus, phenylation of quinoline with benzoyl peroxide gives all seven phenylquinolines.

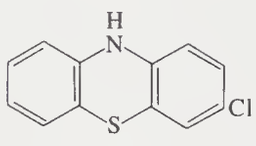
(v) Nucleophilic attack

Nucleophiles normally attack the heterocyclic ring (Section 3.2.1.6). However, if all positions on the heterocyclic ring are blocked, and if it is highly electron deficient, reactivity toward nucleophilic attack is found in a fused benzene ring. Such conditions apply in phenazinium, phenoxazinylium and phenothiazinylium ions (**455**; Z = NR, O, S). Hydroxide ions give pseudo-base intermediates (**456**) which are easily oxidized (with air, Br_2, *etc.*) to the pyridone analogues (**457**).

Similarly, ammonia and amines (*e.g.* $PhNH_2$, Me_2NH) give initial adducts of type (**459**), which are then oxidized (with air, Br_2, *etc.*) to new onium salts (**460**). The adduct with cyanide ion tautomerizes to (**458**); phenothiazonium chloride forms (**461**) *via* a similar addition and tautomerism (HCl–H_2O, 100 °C). Repeated reaction with amines gives products of type (**462**).



(455) (456) (457) (458) (459) (460)



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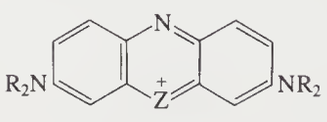
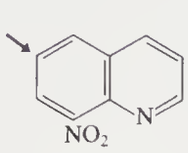


(462)

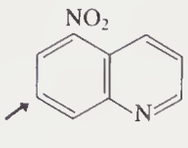
3.2.3.2.2 Fused benzene rings: substituted

(i) Electrophilic substitution

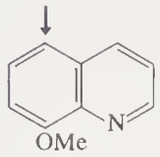
Substituents on the benzene rings exert their usual influence on the orientation and ease of electrophilic substitution reactions. For example, further nitration (HNO_3–H_2SO_4–SO_3) of nitroquinolines occurs *meta* to the nitro group as shown in diagrams (**463**) and (**464**). Friedel–Crafts acylation of 8-methoxyquinoline succeeds (*cf.* **465**) although this reaction fails with quinoline itself.



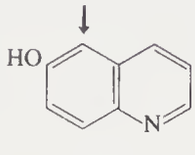
(**463**)



(**464**)



(**465**)



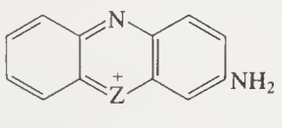
(**466**)

A heterocyclic ring induces partial double-bond fixation in a fused benzene ring. Hence diazo coupling occurs at the 5-position of 6-hydroxyquinoline (**466**), and not at the 7-position.

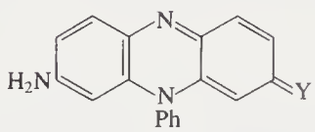
(ii) Amino groups

Amino groups on fused benzene rings in benzopyridines show basicity lower than aniline (initial proton addition occurs mainly on the hetero nitrogen atom) but are diazotized normally. Displacements of a diazonium group often occur under Gattermann but not under Sandmeyer conditions, probably because complexes are formed with Cu^{2+}.

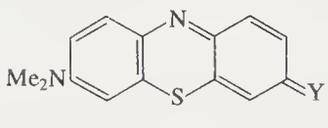
However, a strongly electron-deficient heterocyclic ring can induce unusual reactivity as occurs for the 3-amino groups in phenazonium, phenoxazonium and phenothiazonium salts (**467**; Z = NR, O or S) which are important in dye chemistry. Thus, phenosafranine (**462**; Z = NPh, R = H) is converted by alkali into the imine (**468**; Y = NH) or, on more vigorous treatment, into the phenazone (**468**; Y = O). Methylene blue (**462**; Z = S, R = Me) on oxidation ($K_2Cr_2O_7$ – HCl) gives the imine (**469**; Y = NMe) and on treatment with alkali the oxo derivative (**469**; Y = O).



(**467**)



(**468**)



(**469**)

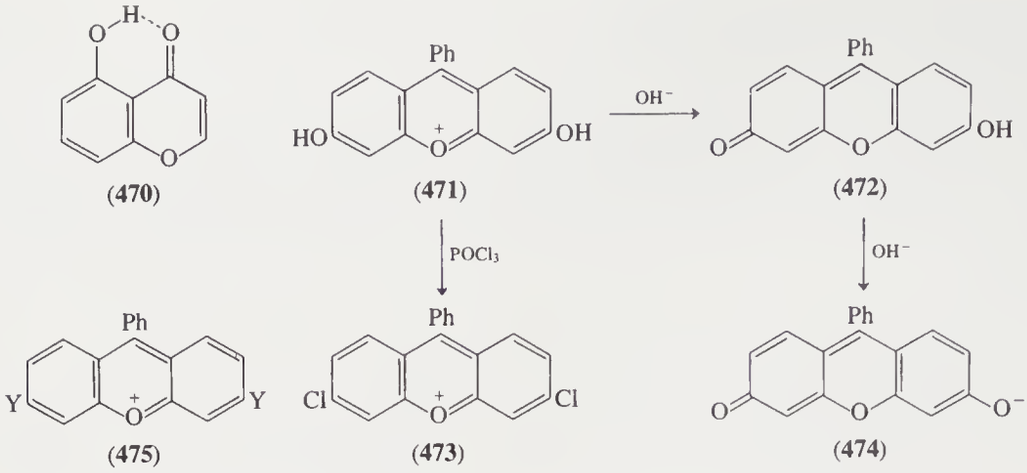
(iii) Hydroxy groups

In general, hydroxy groups on fused benzene rings undergo the expected reactions. *O*-Methylation is effected by diazomethane, methyl iodide or dimethyl sulfate. *O*-Alkylation is reversed by aluminum trichloride or tribromide in benzene or nitrobenzene.

However, the reactivity of phenolic hydroxy groups can be modified by a fused heterocyclic ring. Thus, hydroxy groups *peri* to a carbonyl group, *e.g.* (**470**), are hydrogen bonded, do not react with diazomethane, and are difficult to acylate. This allows selective reactions in polyhydroxychromones.

Hydroxy group acidity is increased, sometimes quite dramatically. Thus, hydroxy groups on benzene rings fused to pyrylium or pyridinium rings can lose a proton if the resulting anhydro-bases are stabilized by mesomerism with a non-charged *p*-quinonoid canonical form, *e.g.* (**471**)→(**472**); the corresponding *o*-quinonoid anhydro-bases are less stable. If two suitably oriented hydroxy groups are present, a further proton can be lost to give a mesomeric anion (*e.g.* **474**).

In favorable cases, a phenolic hydroxy group can show a reactivity usually associated only with substituents on the heterocyclic ring and be converted into a chloro group (**471**→**473**).



(iv) Halogen atoms

In extreme cases, halogen atoms on fused benzene rings are labile, *e.g.* (**475**; Y = Cl) + $PhNH_2$ →(**475**; Y = NHPh).

3.2.3.3 Alkyl Groups

3.2.3.3.1 Reactions similar to those of toluene

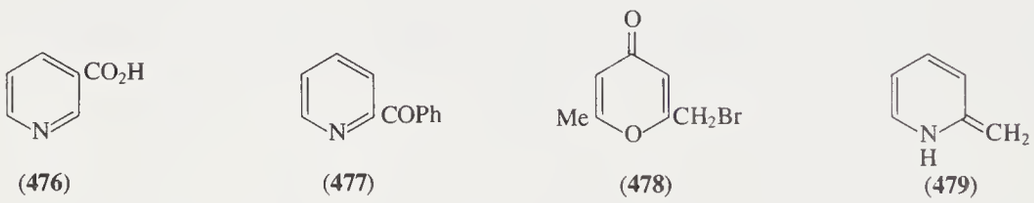
The typical reactions of alkyl groups attached to benzenoid rings involve benzyl-type radical intermediates. An azine ring can stabilize a methyl radical just as a phenyl ring can, and thus most alkylpyridines and azines show these reactions.

(i) Oxidation in solution ($KMnO_4$, CrO_3, *etc.*) gives the carboxylic acid, *e.g.* 3-picoline→nicotinic acid (**476**), or ketone, *e.g.* 2-benzylpyridine→2-benzoylpyridine (**477**).

(ii) Controlled catalytic vapor phase oxidation converts, for example, 2-, 3- and 4-picolines into 2-, 3- and 4-pyridinecarboxaldehydes.

(iii) Free radical bromination with *N*-bromosuccinimide succeeds, *e.g.* 2,6-dimethyl-4-pyrone→(**478**).

(iv) So-called am–ox vapor phase conversion by O_2–NH_3 of CH_3 into CN.



3.2.3.3.2 Alkyl groups: reactions via *proton loss*

Alkyl groups α or γ to a pyridine nitrogen show additional reactions because of the possibility of losing a proton from the carbon atom of the alkyl group which is adjacent to the ring. The ease of proton loss depends on the number, orientation and nature of the heteroatoms in the ring carrying the alkyl groups as discussed in Section 3.2.3.1. Reactions of this type consist of two essential steps: loss of the proton and then subsequent reaction with an electrophile. For the neutral alkylazines, we distinguish between:

(i) use of a strong base which removes the proton completely before addition of electrophile;

(ii) use of a weaker base which sets up a pre-equilibrium giving traces of reactive anion which reacts with the electrophile and is then replenished by the equilibrium; and

(iii) use of an *acid* catalyst which affords small amounts of the tautomeric methylene form (*e.g.* **479**) which reacts.

A similar distinction between these three mechanisms of reaction with electrophiles can be made in the chemistry of ketones.

3.2.3.3.3 Alkylazines: reactions involving essentially complete anion formation

The strongest bases such as sodamide ($NaNH_2$–NH_3, −40 °C) or organometallic compounds (PhLi–Et_2O, 40 °C) convert 2- and 4-alkylpyridines, 2- and 4-methylpyrimidines and 3- and 4-methylpyridazines, *etc.*, essentially completely into the corresponding anions (*e.g.* **480**). These anions react readily (as **481**) with even mild electrophilic reagents, thus the original alkyl groups can be substituted in the following ways.

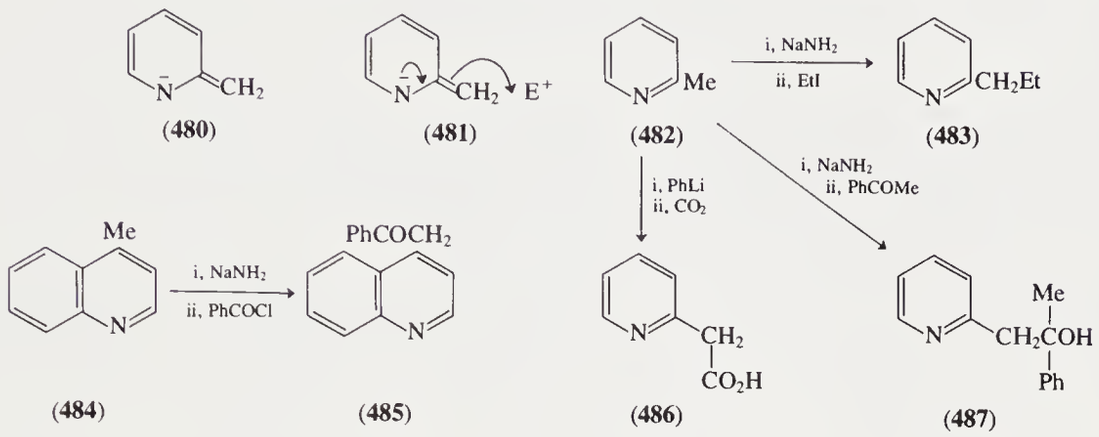
(i) Alkylation, *e.g.* 2-picoline (**482**)→2-*n*-propylpyridine (**483**).

(ii) Acylation, *e.g.* lepidine (**484**)→4-phenacylquinoline (**485**).

(iii) Carboxylation, *e.g.* 2-picoline (**482**)→2-pyridylacetic acid (**486**) which is esterified before isolation (see Section 3.2.3.4.2).

(iv) Reaction with carbonyl compounds to form alcohols, *e.g.* 2-picoline (**482**)→the tertiary alcohol (**487**).

(v) An alkyl nitrite and sodamide in liquid ammonia give an oxime (Scheme 48).



Scheme 48

The methyl group of 3-picoline is sufficiently reactive to be alkylated and acylated in this way, although the yields are poor.

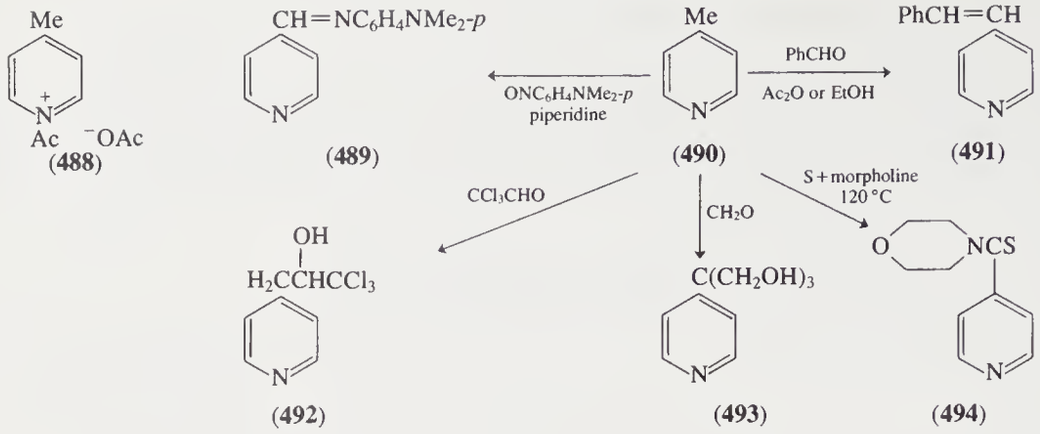
With 2,4-dimethyl-pyridine and -quinoline, selective alkylation or acylation may be achieved at either position. *n*-Butyllithium promotes ionization at the 2-methyl groups, whereas lithium diisopropylamide reacts at the 4-methyl group.

3.2.3.3.4 Alkylazines: reactions involving traces of reactive anions or traces of methylene bases

In aqueous or alcoholic solution, activated alkyl groups in heterocyclic rings react with bases to give traces of anions of type (**480**). In such reactions, alkoxide or hydroxide ions, aliphatic amines (*e.g.* NEt_3, piperidine) or the alkylpyridine itself can act as the base. With suitable electrophilic reagents the anions (*cf.* **480**) undergo reasonably rapid and essentially non-reversible reaction, gradually converting the whole of the heterocyclic compound. An obvious prerequisite for reaction under these conditions is that the base used does not react irreversibly with the electrophile.

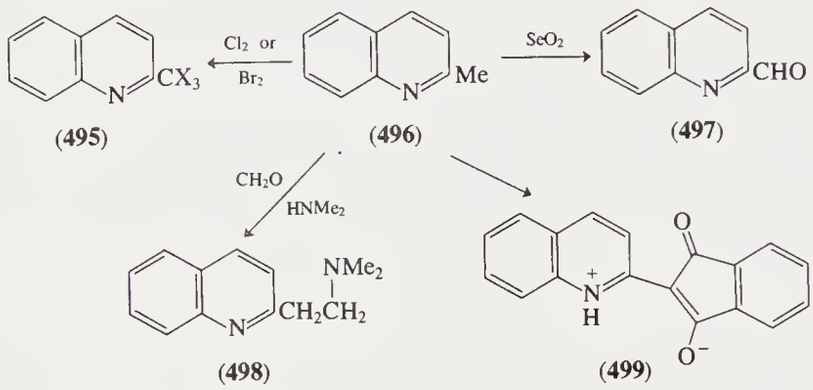
In acidic media, loss of a proton can give traces of methylene forms of type (**479**). Alternatively, a Lewis acid catalyst such as acetic anhydride may be used which involves formation of complexes of type (**488**) from which proton loss is facile. Such methylene bases can also react with electrophiles, gradually causing complete conversion of the heterocycle.

Reactions of these types will be illustrated using 4-picoline (**490**) and quinaldine (**496**) as typical substrates.



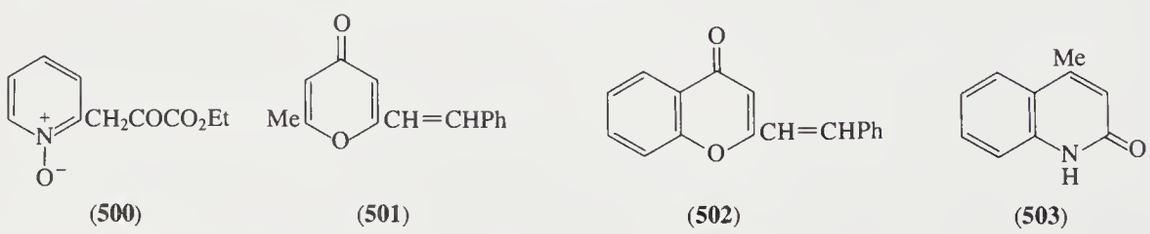
(i) Formaldehyde gives poly-alcohols (**490**→**493**).
(ii) Other aliphatic aldehydes form mono-alcohols (**490**→**492**).
(iii) Aromatic aldehydes give styryl derivatives (**490**→**491**) by spontaneous dehydration of the intermediate alcohol (*cf.* Section 3.2.3.4.4).
(iv) Nitroso compounds form Schiff's bases (**490**→**489**).
(v) Halogens substitute all adjacent hydrogen atoms (**496**→**495**).
(vi) Formaldehyde plus amines yield Mannich bases (**496**→**498**).
(vii) Phthalic anhydride gives indane-1,3-dione derivatives (**496**→**499**).
(viii) Selenium dioxide oxidizes CH_3 to CHO (**496**→**497**).
(ix) Willgerodt conversion of $CH_3 \rightarrow CSNR_2$ with S/R_2NH (**490**→**494**).

Although the last two examples have radical intermediates, they probably involve electron transfer from the type (**480**) anion to the reagent in the rate-limiting step.



The above reactions have been illustrated for 2- and 4-alkylpyridines. They generally fail if no heteroatom is α or γ, as in 3-alkylpyridines and 5-alkylpyrimidines. α- and γ-Alkyl groups in pyridine *N*-oxides are somewhat more reactive than those on the corresponding pyridines. In addition to the reactions already mentioned, 2-picoline 1-oxide undergoes Claisen condensation with ethyl oxalate to yield the pyruvic ester (**500**) (for the conversion of alkyl substituents in *N*-oxides into CH_2OAc groups see Section 3.2.3.12.5.iv).

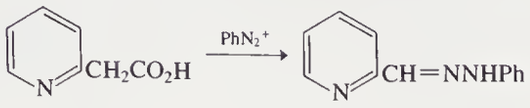
Methyl groups in the 2-, 4- or 6-position of pyrimidine are also more reactive. In addition to typical reactions such as condensation with benzaldehyde, selenium dioxide oxidation and halogenation, they can be converted into oximino groups by nitrous acid, and undergo Claisen condensation with $(CO_2Et)_2$. In quinazolines partial double bond fixation makes a methyl group in the 4-position more reactive than that in the 2-position.



α- and γ-Alkyl groups in pyrones and pyridones also undergo many reactions of these types. For example, with benzaldehyde, 2,6-dimethylpyrone gives the styryl derivative (**501**). 2-

Methylchromone yields (**502**) and 1,4- and 1,6-dimethylpyrid-2-ones condense with ethyl oxalate. 2-Methyl groups in pyran-4-ones and chromones condense with benzaldehyde and can be halogenated. However, reactions sometimes fail; (**503**) will not condense with benzaldehyde.

If an α- or γ-alkyl group itself carries an electron-withdrawing substituent, proton loss is facilitated, and additional reactions can occur (*e.g.* **504**→**505** + CO_2) (*cf.* the Japp–Klingemann reaction: $MeCOCH_2CO_2H + PhN_2^+ \rightarrow MeCOCH{=}NNHPh$).

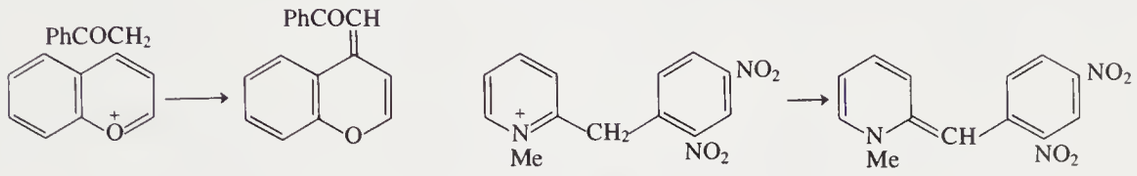


(**504**) (**505**)

3.2.3.3.5 *Alkyl-azonium and -pyrylium compounds*

(i) Formation of stable anhydro-bases

Compounds containing methylene groups activated by both a cationic ring and another electron-withdrawing group easily form stable anhydro-bases, *e.g.* (**506**)→(**507**), (**508**)→(**509**). Stabilization is also achieved by utilization of the aromatic character of the cyclopentadiene anion or the pyrrole anion; compounds of type (**510**; Z = NR, O, S) and (**513**) readily lose protons to give the mesomeric anhydro-bases (as **511** ↔ **512**).



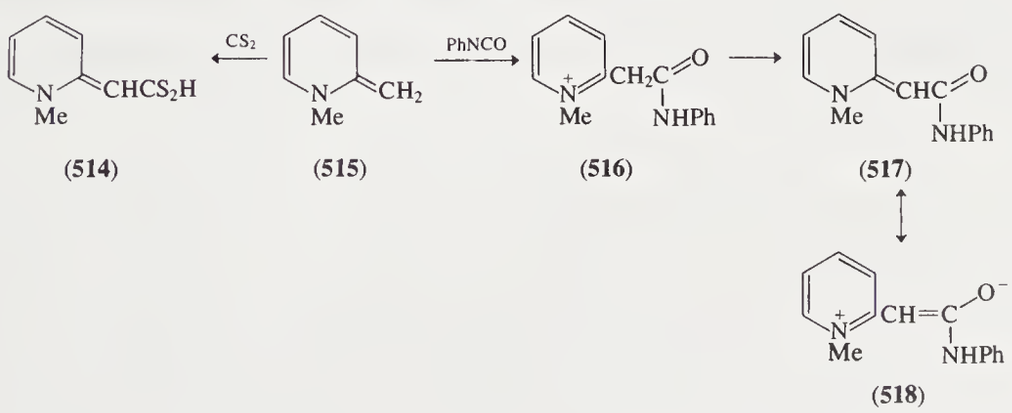
(**506**) (**507**) (**508**) (**509**)

(**510**) (**511**) (**512**) (**513**)

(ii) Anhydro-bases as intermediates

Proton loss from α- and γ-alkyl groups on a cationic (pyridinium, pyrylium or thiinium) ring is comparatively easy. The resulting unstable and highly reactive neutral anhydro-bases or 'pyridone methides' (*cf.* **515**) can be isolated by using 10M sodium hydroxide, but are generally used directly.

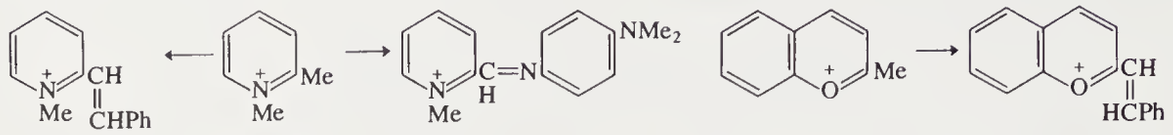
These anhydro-bases are heterocyclic equivalents of enamines and enol ethers and react readily with electrophilic reagents to give products which can often lose a proton to give a new resonance-stabilized anhydro-base. Thus anhydro-1,2-dimethylpyridinium hydroxide (**515**) reacts with phenyl isocyanate to give an adduct (**516**) which is converted to the stabilized product (**517**↔**518**). A similar sequence with carbon disulfide yields the dithio acid (**514**).



(**514**) (**515**) (**516**) (**517**)

(**518**)

α- and γ-Alkyl cationic heterocycles, analogous to the 2- and 4-alkylpyridines, can also react with electrophilic reagents without initial complete deprotonation. They undergo the same types of reaction as the alkylpyridines under milder conditions; such reactions are often catalyzed by piperidine. For example, 1,3-dimethylpyridinium cation (**520**) with PhCHO and with *p*-$NMe_2C_6H_4NO$ yields (**519**) and (**521**), respectively, and 2-methylchromylium (**522**) gives (**523**).

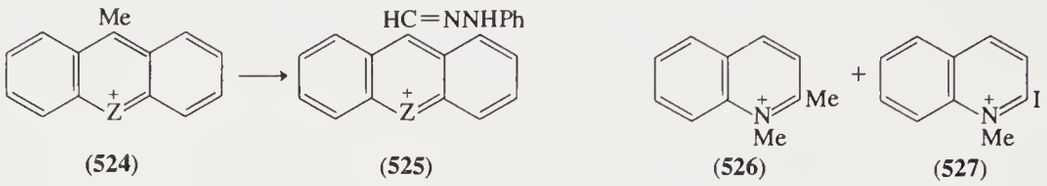


(**519**) (**520**) (**521**) (**522**) (**523**)

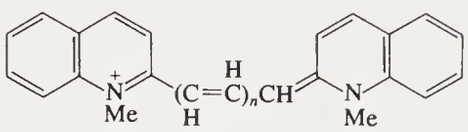
Some weak electrophilic reagents, which are usually inert toward neutral pyridines and azines, also react.

(a) Diazonium salts yield phenylhydrazones (*e.g.* **524**→**525**; Z = NMe, O) in a reaction analogous to the Japp–Klingemann transformation of β-keto esters to phenylhydrazones.

(b) Monomethine cyanines are formed by reaction with an iodoquaternary salt (*e.g.* **526** + **527**→**528**; $n = 0$).



(**524**) (**525**) (**526**) (**527**)



(**528**)

$EtO(CH{=}CH)_nCH(OEt)_2$

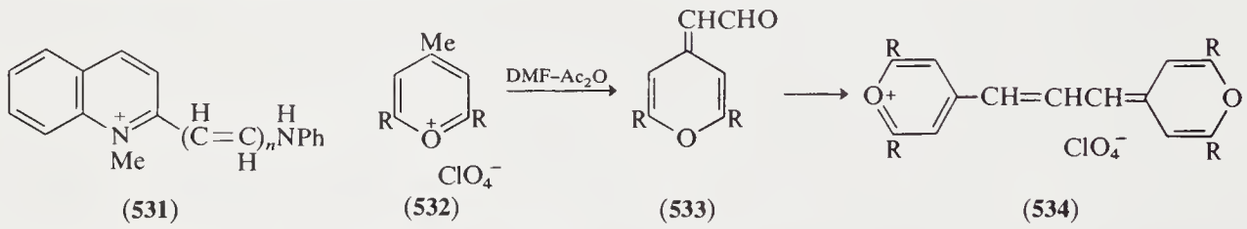
(**529**)

$PhNH(CH{=}CH)_nCH{=}NPh$

(**530**)

(c) Tri-, penta- and hepta-carbocyanines (*e.g.* **528**; $n = 1$, 2 and 3, respectively) are obtained by the reaction of two molecules of a quaternary salt with one molecule of ethyl orthoformate (**529**; $n = 0$), β-ethoxyacrolein acetal (**529**; $n = 1$) or glutacondialdehyde dianil (**530**; $n = 2$), respectively.

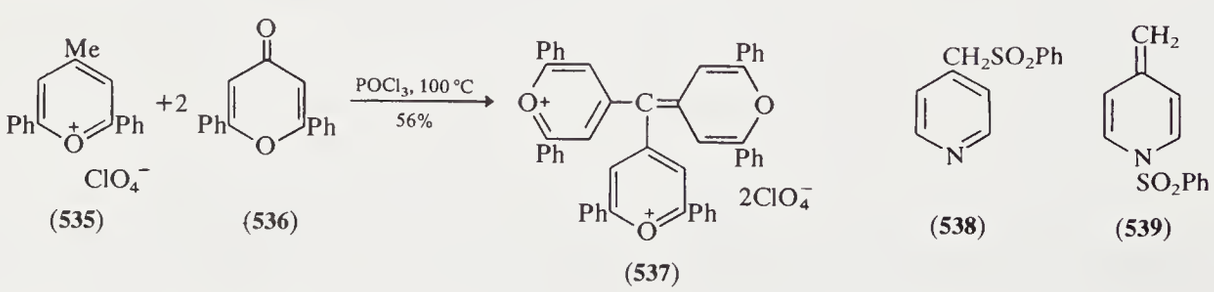
(d) With the anils (**530**; $n = 0$, 1 or 2), it is possible to isolate intermediates of type (**531**; $n = 1$, 2 or 3) which react with another molecule of the same or a different quaternary base to give symmetrical or unsymmetrical tri-, penta- and hepta-carbocyanines. A similar reaction sequence in the pyrylium series is shown by (**532**)→(**533**)→(**534**).



(**531**) (**532**) (**533**) (**534**)

(e) α- and γ-Alkyl groups of pyrylium salts condense with pyrones to yield trinuclear cyanine dyes, *e.g.* (**535**) + (**536**)→(**537**).

(f) γ-Alkylpyridines with benzenesulfonyl chloride yield products of type (**538**), probably *via* intermediates such as (**539**).



(**535**) (**536**) (**537**) (**538**) (**539**)

3.2.3.3.6 Tautomerism of alkyl derivatives

Analogous to the tautomerism of the hydroxy- and amino-pyridines (Sections 3.2.3.7.1 and 3.2.3.5.5), there are alternative tautomeric alkylidene forms of the 2- and 4-alkylpyridines (*e.g.* **479** for 2-picoline). Although the proportion of alkylidene form at equilibrium is very small (as is discussed in Section 2.2.5.1), it can be important as a reactive intermediate (see above).

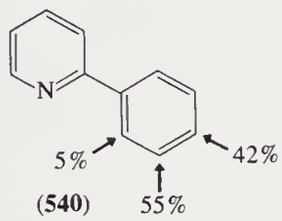
3.2.3.4 Further Carbon Functional Groups

3.2.3.4.1 Aryl groups

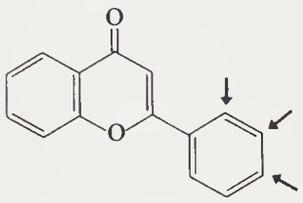
(i) Electrophilic substitution

Electrophilic substitution usually occurs preferentially in the aryl group. In compounds containing both an aryl group and a fused benzene ring, electrophiles usually attack the aryl group exclusively. α- and γ-Phenylpyridines are nitrated to form mixtures of the α- and γ-(*o*-, *m*- and *p*-nitrophenyl)pyridines (*cf.* **540**); the proportion of the isomers formed does not greatly vary with the acidity of the reaction mixture. Likewise, nitration (H_2SO_4–MeOH–HNO_3, 0 °C) of flavone also gives a mixture of the 2′-, 3′- and 4′-nitro derivatives (**541**). This represents reactivity midway between the corresponding carbonyl and benzenoid derivatives: acetophenone is nitrated exclusively *meta*; biphenyl, exclusively *ortho* and *para*.

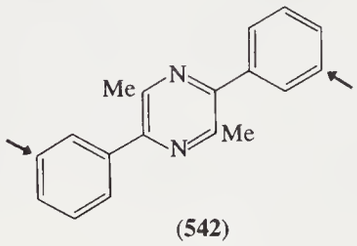
The tendency to be nitrated *meta* increases with the electron deficiency of the parent ring, and presumably depends on the species that reacts. 4-Phenylpyrimidine is nitrated in the phenyl group at all positions in proportions depending on the conditions, whereas the pyrazine derivative (**542**) reacts at the *meta*-positions as shown. Positively charged heterocyclic rings direct the substitution to the *m*-position of α- or γ-phenyl groups but to the *o,p*-positions of β-phenyl groups as exemplified by the orientation for nitration in (**543**)–(**545**). The activating and *para*-directing influence of an *N*-oxide group toward electrophilic substitution (*cf.* Section 3.2.1.4.4.v) does not extend to phenyl substituents, *e.g.* 2-phenylpyridine 1-oxide is nitrated as shown (**546**).



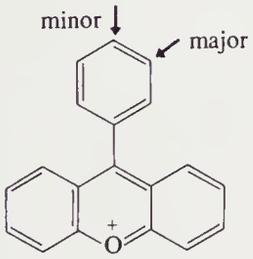
(**540**)



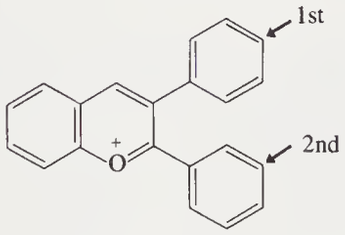
(**541**)



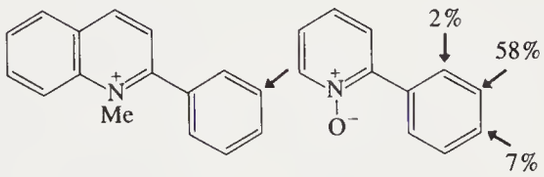
(**542**)



(**543**)



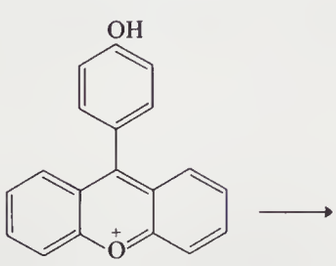
(**544**)



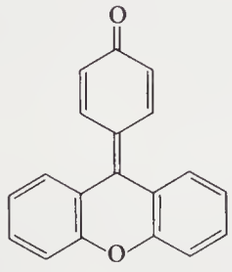
(**545**) (**546**)

(ii) Reactions of substituents

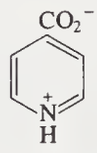
An example of a significant effect on the reactivity of a substituent on a phenyl ring is found in the easy proton loss in (**547**)→(**548**).



(**547**)



(**548**)



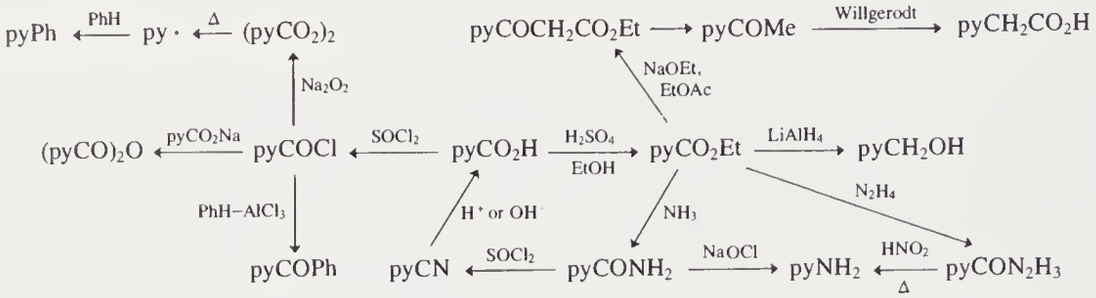
(**549**)

3.2.3.4.2 Carboxylic acids and derivatives

(i) General

Pyridine- and azine-carboxylic acids, as amino acids, exist partly as betaines (*e.g.* **549**) in aqueous solution, but as neutral molecules in ethanol which has a lower dielectric constant.

In most of their reactions, the pyridine- and azine-carboxylic acids and their derivatives behave as expected (*cf.* Scheme 49). However, some acid chlorides can be obtained only as hydrochlorides, and we must also consider decarboxylation.



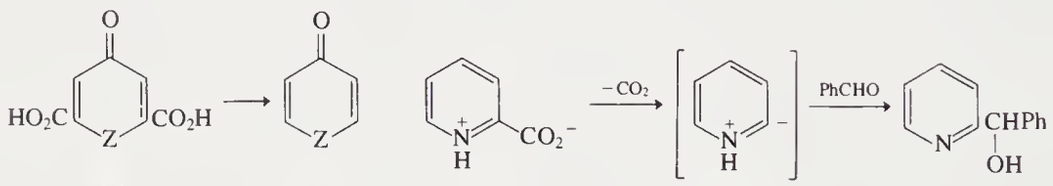
(py represents 2-, 3- or 4-pyridyl)

Scheme 49

(ii) Decarboxylation of carboxy groups directly attached to ring

Azinecarboxylic acids lose CO_2 significantly more easily than benzoic acid. Pyridinecarboxylic acids decarboxylate on heating with increasing ease in the order $\beta \ll \gamma < \alpha$. 2-Pyridazinecarboxylic acid gives pyrazine at 200 °C, and 4,5-pyrimidinedicarboxylic acid forms the 5-mono-acid on vacuum distillation. Pyrone and pyridone acids also decarboxylate relatively easily; thus, chelidonic acid (**550**; Z = O) at 160 °C over copper powder and chelidamic acid (**550**; Z = NH) at 260 °C give (**551**; Z = O, NH).

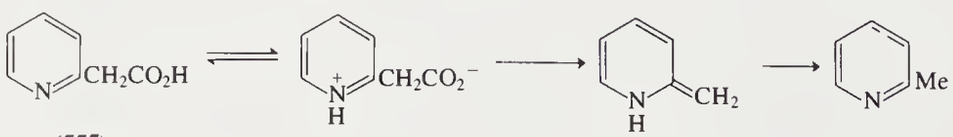
The relatively easy decarboxylation of α- (**552**) and γ-carboxylic acids is a result of inductive stabilization of intermediate ylides of type (**553**) (*cf.* Section 3.2.1.7). By carrying out the decarboxylation in the presence of aldehydes or ketones, products of type (**554**) are formed (Hammick Reaction).



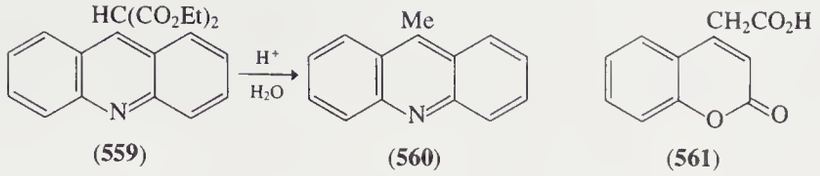
(**550**) (**551**) (**552**) (**553**) (**554**)

(iii) Decarboxylation of carboxymethyl groups

Pyridines with an α- or γ-carboxymethyl group (*e.g.* **555**) undergo facile decarboxylation by a zwitterion mechanism (**555**→**558**) somewhat similar to that for the decarboxylation of β-keto acids (*cf.* Section 3.2.3.1.1). Carboxymethylpyridines often decarboxylate spontaneously on formation; thus, hydrolysis of (**559**) gives (**560**). The corresponding 2- and 4-pyridone and 2- and 4-pyrone acids are somewhat more stable, *e.g.* (**561**) decarboxylates at 170 °C. 3-Pyridineacetic acid shows no pronounced tendency to decarboxylate.



(**555**) (**556**) (**557**) (**558**)

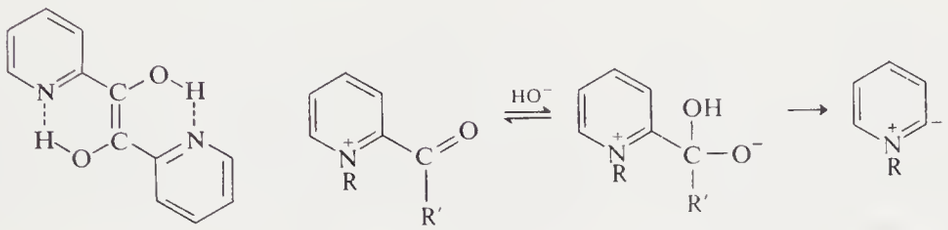


(iv) Nucleophilic displacement of cyano groups

Pyridinenitriles show normal reactions. However, with rather more electron-deficient rings, such as those in pyrimidine nitriles or pyridinium nitriles, nucleophilic displacement of the CN becomes possible (*cf.* **431**→**432**, Section 3.2.3.1.2.i).

3.2.3.4.3 Aldehydes and ketones

In general, the properties of these compounds and those of their benzenoid analogues are similar: thus, pyrimidinecarbaldehydes show the usual reactions, as do aldehyde groups attached to chromone and pyrone rings. Aldehyde groups α to the hetero atom undergo the benzoin condensation very readily because the end products are stabilized as hydrogen-bonded ene-diols (*e.g.* **562**).

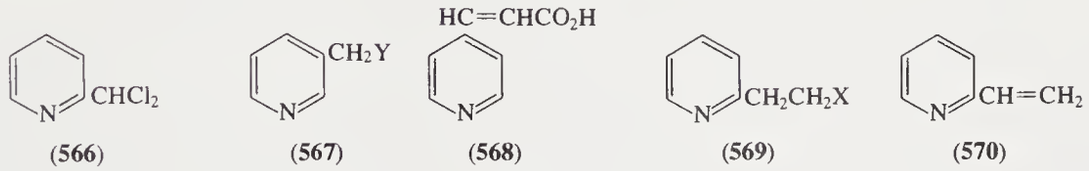


Acyl groups adjacent to a quaternized pyridinium nitrogen atom (*e.g.* **563**) are susceptible to removal by nucleophilic attack *via* (**564**) and the ylide (**565**).

3.2.3.4.4 Other substituted alkyl groups

(i) Examples of normal reactivity

These include halogen atoms in side chains: (**566**) + H_2SO_4 + H_2O→pyridine-2-carboxaldehyde; (**567**; Y = Cl)+KCN→(**567**; Y = CN); (**492**)+KOH→(**568**).

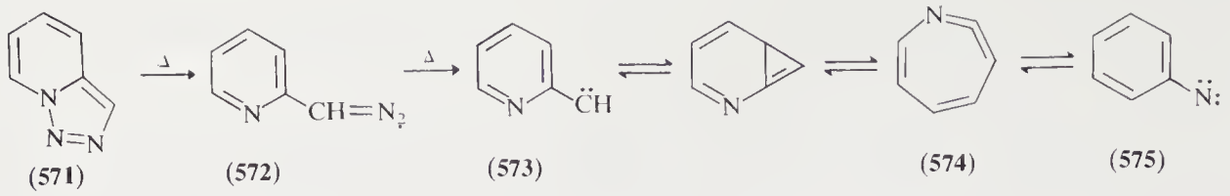


(ii) Reverse Michael reactions

Compounds of type Het—CH_2CH_2X where X is a leaving group (*e.g.* halogen, OR, NR_2, SR, *etc.*) undergo reverse Michael reaction *via* Het—$\bar{C}HCH_2X$→Het—$CH{=}CH_2 + X^-$. In this way we find ready dehydration of α- or γ-(2-hydroxyethyl) groups, *e.g.* (**569**; X = OH)→(**570**).

(iii) Diazoalkyl groups and related carbenes

2-(Diazomethyl)pyridine (**572**) which normally exists in the ring-closed form (**571**) thermolyzes to 2-pyridylcarbene (**573**) which interconverts in the gas phase with phenylnitrene (**575**). Photolysis of 2-(diazomethyl)pyridine in an argon matrix allows identification of 1-aza-1,2,4,6-cycloheptatetraene (**574**). 3- and 4-Pyridylcarbenes also interconvert with phenylnitrene ⟨81AHC(28)279⟩.



(571) (572) (573) (574) (575)

(iv) Nucleophilic displacements

Trihalomethyl groups can be replaced in nucleophilic substitution reactions in sufficiently activated systems, as for example in *s*-triazines. 2,4,6-Tris(trichloromethyl)-*s*-triazine is converted into the 2,4,6-triamino-*s*-triazine by ammonia.

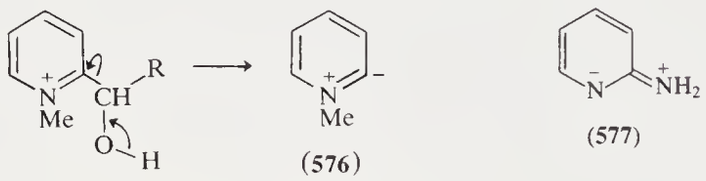
(v) Formation of zwitterion intermediate

2-(α-Hydroxyalkyl) groups are removed by nucleophiles in 'retro-aldol' type reactions. The heterocycle is eliminated as the zwitterion species, or 'nucleophilic carbene' (**576**).

3.2.3.4.5 Vinyl groups

Vinyl groups α or γ to the pyridine nitrogen atom readily undergo Michael additions. Water, alcohols, ammonia, amines and hydrogen cyanide are among the nucleophiles which may be added. For example, 2-vinylpyridine and dimethylamine give the adduct (**569**; $X = NMe_2$).

The usual alkenic reactions are also shown by *C*-vinyl heterocycles, including ready free radical or nucleophilic polymerization.



(576) (577)

3.2.3.5 Amino and Imino Groups

3.2.3.5.1 Orientation of reactions of amino-pyridines and -azines with electrophiles

These compounds contain three types of site for electrophilic attack: ring nitrogen, amino nitrogen and ring carbon. In 2- and 4-aminopyridines, canonical forms of type (**577**) increase the nucleophilicity of the hetero nitrogen atom and the α- and γ- carbon atoms but decrease that of the amino group. Consequently, all electrophiles would be expected to attack the ring nitrogen preferentially. Indeed, as is discussed in Section 3.2.1.3, protons, alkylating agents, metal ions and percarboxylic acids do react at the hetero nitrogen atom.

However, certain other electrophilic reagents form products derived by reaction at the amino group or at a ring carbon atom. There are four different sets of circumstances under which this behavior is found.

(i) The initial reversible reaction at the pyridine nitrogen forms an unstable product which dissociates to regenerate the reactants, or undergoes inter- or intra-molecular rearrangement [see examples (i), (iv)–(vi) and (viii) in Section 3.2.3.5.2].

(ii) In acid media the pyridine nitrogen is protonated, and reaction on this species now occurs on the amino nitrogen [see examples (ii), (iii) and (vii) in Section 3.2.3.5.2].

(iii) Reaction at the ring nitrogen can be sterically hindered. Whereas 4-dimethylaminopyridine undergoes methylation and *N*-oxide formation at the ring nitrogen as expected, in 2-dimethylaminopyridine it is the dimethylamino nitrogen which is both quaternized and *N*-oxidized, because the ring nitrogen is shielded.

(iv) If the reaction of the electrophile at the amino nitrogen is also reversible, then subsequent slower but irreversible reaction at the ring carbon can slowly go to completion. In this way, the electrophiles responsible for nitration, sulfonation and halogenation react at the ring carbon atoms, as discussed in Section 3.2.1.4.

3.2.3.5.2 Reaction of aminoazines with electrophiles at the amino group

These reactions are illustrated (**578–589**) for 2-aminopyridine.

(i) Carboxylic and sulfonic acid chlorides and anhydrides give acylamino- and sulfonamido-pyridines (**580**, **581**).

(ii) Nitric acid–sulfuric acid gives nitramino compounds (**579**) which are easily rearranged to *C*-nitro derivatives (**578**) (*cf.* Section 3.2.1.4.4).

(iii) Oxidation by permonosulfuric acid yields nitropyridines (**587**).

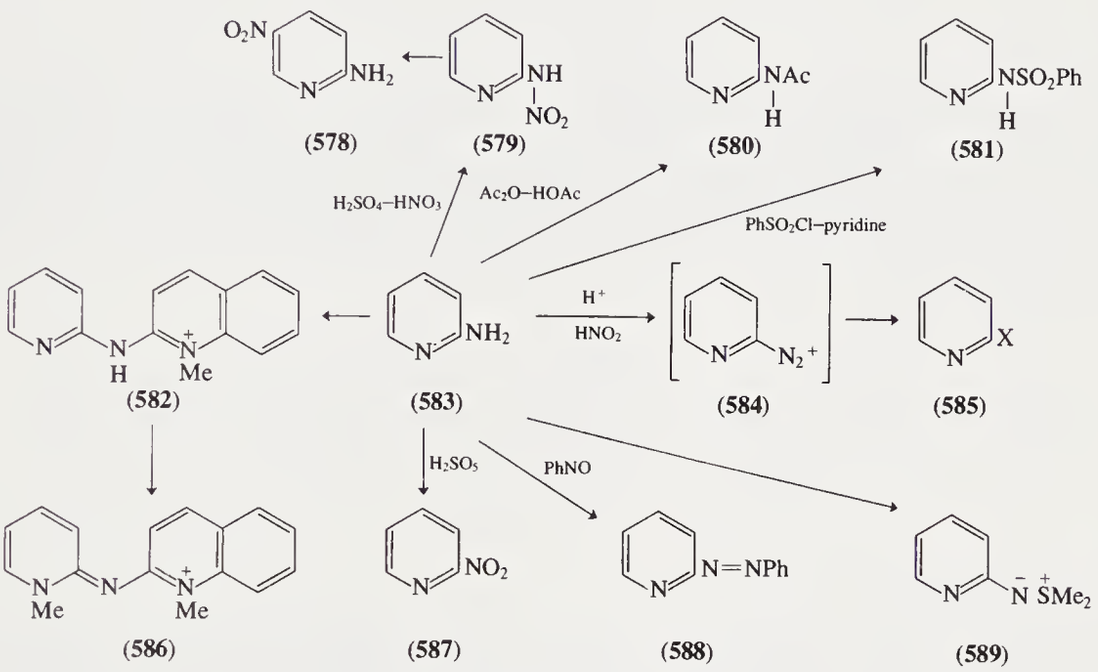
(iv) Nitrosobenzene yields phenylazopyridines (**588**).

(v) Sodium hypochlorite gives symmetrical azopyridines.

(vi) With dimethyl sulfide and *N*-chlorosuccinimide the sulfilimine (**589**) is formed, which can be oxidized to the corresponding nitroso heterocycle.

(vii) Nitrous acid gives highly unstable diazonium salts (**584**) (*cf.* next section).

(viii) Quaternary heterocyclic iodides give products (*e.g.* **582** from 1-methylquinolinium iodide) which can be converted into azacyanine dyes (*e.g.* **586**).



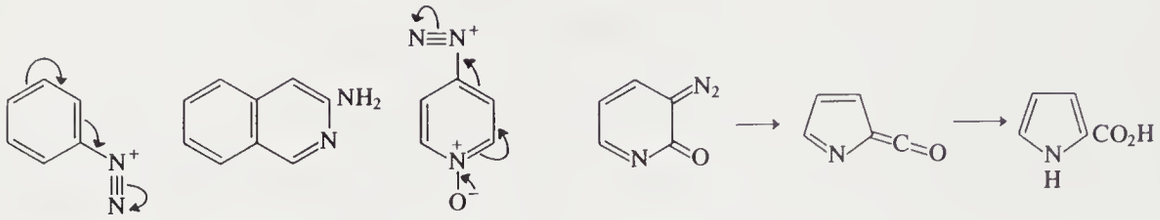
3.2.3.5.3 Diazotization of amino compounds

The stabilities of pyridine-2- and -4-diazonium ions resemble those of aliphatic rather than benzenoid diazonium ions. Benzenediazonium ions are stabilized by mesomerism (**590**) which involves electron donation from the ring and such electron donation is unfavorable in 2- and 4-substituted pyridines. On formation they normally immediately react with the aqueous solvent to form pyridones. However, by carrying out the diazotization in concentrated HCl or HBr, useful yields of chloro- and bromo-pyridines may be obtained. Amino-pyridazines and -pyrazines and 2- and 4-aminopyrimidines behave similarly.

The reactions of 3-amino groups in pyridines and 5-amino groups in pyrimidines, by contrast, are close to those of the amino group in aniline. The diazonium salts are reasonably stable and undergo coupling and replacement reactions and can be reduced to hydrazines. Amino groups in the 3-position of isoquinolines (**591**) are subject to bond fixation and react in a manner intermediate between that of α- and β-amino groups; they can be diazotized under the conditions normally employed.

Aminopyridine *N*-oxides can be diazotized, and the diazonium salts undergo coupling, *etc.* These diazonium salts are stabilized by mesomerism (**592**), *cf.* (**590**). Amino groups in pyridazine *N*-oxides can also be diazotized and the diazonium group further replaced by other functionality.

β-Aminopyridones form diazo anhydrides (*e.g.* **593**) (*cf.* aminophenols) which on irradiation give pyrrolecarboxylic acids (**595**) *via* (**594**).



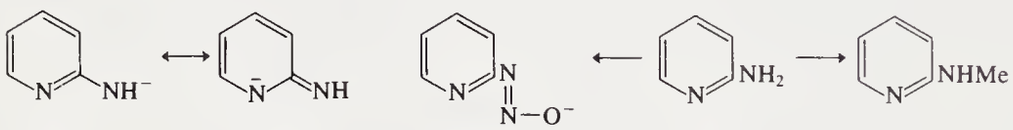
(**590**) (**591**) (**592**) (**593**) (**594**) (**595**)

3.2.3.5.4 Reactions of amino compounds with nucleophiles

Three modes of reaction are possible: proton loss, nucleophilic displacement and Dimroth rearrangement.

(i) Proton loss

Just as they decrease the susceptibility of 2- and 4-amino groups to electrophilic attack, canonical forms of type (**577**) facilitate proton loss from amino groups. Aminoazines are thus weak acids; their anions, *e.g.* (**596**)↔(**597**), react with electrophilic reagents preferentially at the amino nitrogen. 2-Aminopyridine (**599**) is thus converted by $NaNH_2$–MeI to the 2-methylamino derivative (**600**). With EtONO–NaOEt, the reaction (**599**)→(**598**) gives a sodium diazotate which couples with phenols.

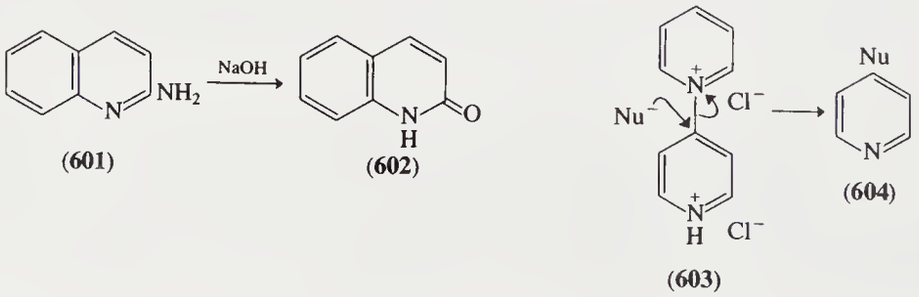


(**596**) (**597**) (**598**) (**599**) (**600**)

(ii) Nucleophilic displacement

Nucleophilic reagents can also react with 2- and 4-aminopyridines at the carbon atom which carries the amino group in a replacement reaction (*e.g.* **601**→**602**) similar to, but far less facile than, that undergone by chloro and alkoxy compounds, *etc.* In this way aminopyrimidines can be converted into pyrimidinones by direct acidic or alkaline hydrolysis under rather vigorous conditions.

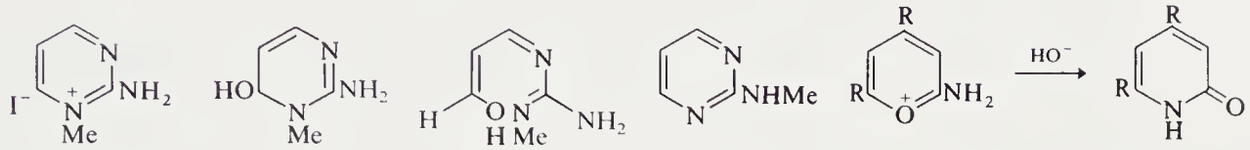
Reactions of this type are easy if the amino group is quaternized as in, for example, 1-(4′-pyridyl)pyridinium chloride (**603**), which gives pyridine and 4-substituted pyridines [**604**; Y = Cl, Br (with PX_5), Y = SH, SR (with SH^-, SR^-), Y = NH_2, NHR (with NH_3, NH_2R).] Similarly, NMe_3^+ groups in pyrimidines undergo nucleophilic displacement.



(**601**) (**602**) (**603**) (**604**)

(iii) Dimroth rearrangement

Cationic α-amino derivatives with base undergo a rearrangement in which the two nitrogen atoms change places. Thus, 1-methyl-2-aminopyrimidinium ion (**605**) yields 2-methylaminopyrimidine. This, the Dimroth rearrangement, involves nucleophilic (usually OH^-) addition at the 6-position, followed by electrocyclic ring opening to (**607**) and reclosure to (**608**).



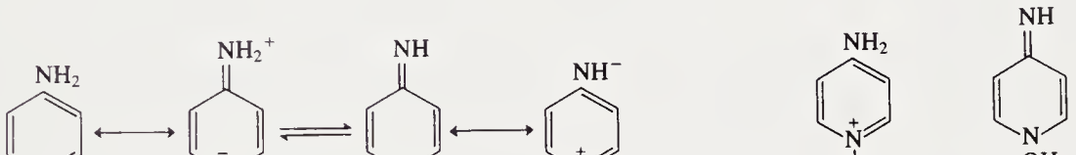
(**605**) (**606**) (**607**) (**608**) (**609**) (**610**)

2-Amino-pyrones and -pyrylium salts similarly rearrange readily into substituted pyridones (**609**→**610**).

3.2.3.5.5 Amino–imino tautomerism

2- and 4-Aminopyridines (*e.g.* **611**) can also exist in tautomeric pyridonimine forms (*e.g.* **613**). However, the pyridonimine forms are unimportant (Section 2.2.5.1) in direct contrast to the 2- and 4-hydroxypyridines which exist largely as pyridones. This difference can be rationalized by consideration of the mesomerism of the alternative forms. Resonance stabilization of aminopyridines (**611**↔**612**) is greater than that of hydroxypyridines, while resonance stabilization of pyridonimines (**613**↔**614**) is less than that of pyridones.

α- and γ-Amino *N*-oxides also exist predominantly in the amino form, *e.g.* as (**615**) rather than (**616**).

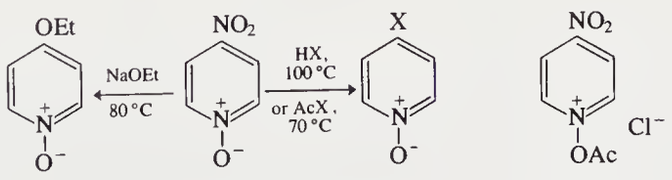


(**611**) (**612**) (**613**) (**614**) (**615**) (**616**)

3.2.3.6 Other *N*-Linked Substituents

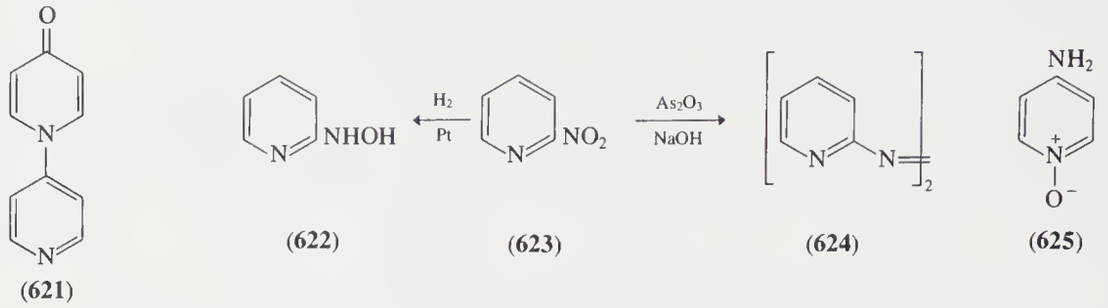
3.2.3.6.1 Nitro groups

2- and 4-Nitro groups on pyridines and pyridine *N*-oxides are smoothly displaced by nucleophilic reagents, indeed, more readily than the corresponding halogen compounds. Thus, 4-nitropyridine is converted by sodium ethoxide at 80 °C into 4-ethoxypyridine. Such reactions are of particular importance in *N*-oxides where the nitro derivatives are readily available by direct nitration and are exemplified by the transformations (**618**)→(**617**), and (**618**)→(**619**; X = Cl, Br). The reactions involving hydrogen bromide and chloride are acid catalyzed, while those with acetyl chloride probably proceed *via* intermediates of type (**620**). 4-Nitropyridine gives (**621**) and other products on keeping; *cf.* polymerization of 4-halopyridines (Section 3.2.3.10.6). Nitro groups at all the positions of pyridazine 1-oxide are easily substituted by halogen or other nucleophiles.



(**617**) (**618**) (**619**) (**620**)

Nitro compounds are easily reduced, catalytically or chemically, to amino compounds. Incomplete reduction can lead to a hydroxylamino derivative or to binuclear azo, azoxy and hydrazo compouds, *e.g.* (**623**)→(**622**), (**624**). A nitro group can be reduced in the presence of an *N*-oxide group, *e.g.* (**618**)→(**625**).



(**621**) (**622**) (**623**) (**624**) (**625**)

3.2.3.6.2 Nitramino compounds

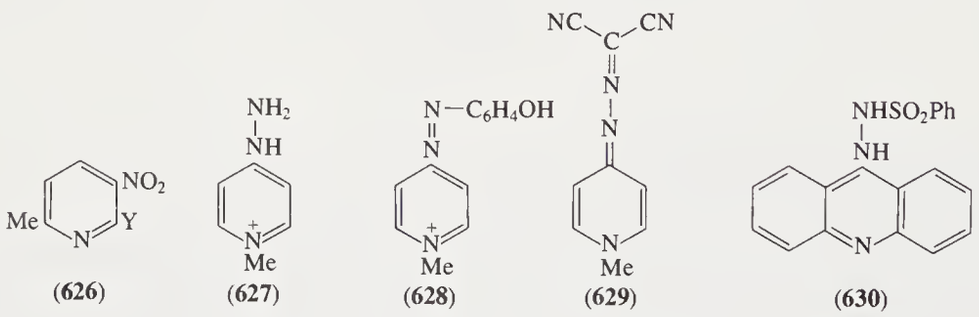
These compounds can be rearranged (*cf.* Section 3.2.3.5.1.iv), reduced to hydrazino derivatives or hydrolyzed to pyridones.

3.2.3.6.3 Hydrazino groups

These form derivatives with carbonyl compounds and can be acylated, sulfonylated, eliminated by mild oxidation [*e.g.* (**626**; Y = $NHNH_2$) + $CuSO_4$ + AcOH→(**626**; Y = H)], and converted by nitrous acid into azides as in benzenoid chemistry.

Hydrazino groups attached to cationic rings (as **627**) undergo oxidative coupling reactions with amines, phenols (to give *e.g.* **628**) and reactive methylene compounds, *e.g.* (**627**) + $CH_2(CN)_2$ →(**629**).

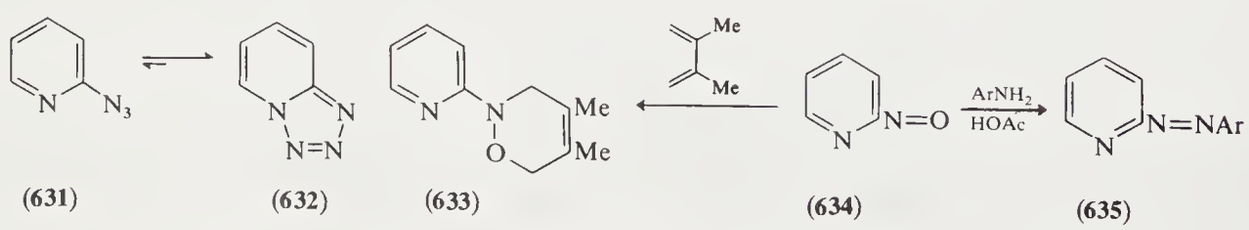
α- or γ-Phenylsulfonylhydrazino groups are eliminated by alkali (*e.g.* **630**→acridine + N_2 + $PhSO_2H$); *cf.* the McFadyen and Stevens reaction ($RCONHNHSO_2Ph$→RCHO + N_2 + $PhSO_2H$).



(**626**) (**627**) (**628**) (**629**) (**630**)

3.2.3.6.4 Azides

2-Azidopyridines exist largely, and 3-azidopyridazines completely, in the bicyclic form (**631**⇌**632**).



(**631**) (**632**) (**633**) (**634**) (**635**)

3.2.3.6.5 Nitroso groups

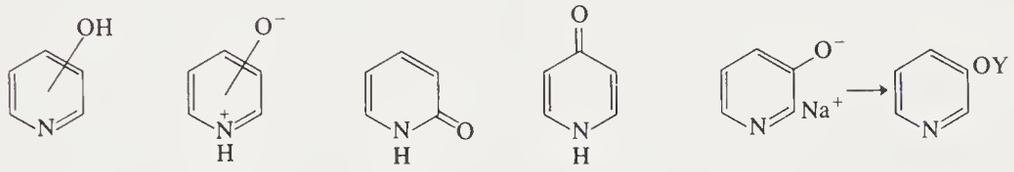
Ready addition to 1,3-dienes gives 3,6-dihydro-1,2-oxazines, *e.g.* (**634**)→(**633**), and condensation with aromatic amines gives azo compounds, *e.g.* (**634**)→(**635**). Nitroso compounds are oxidized by ozone or sodium hypochlorite to the corresponding nitro compounds. 5-Nitrosopyrimidines can be reduced to the 5-amino derivatives or condensed with activated methylene groups.

3.2.3.7 Hydroxy and Oxo Groups

3.2.3.7.1 Hydroxy groups and hydroxy–oxo tautomeric equilibria

Hydroxypyridines (**636**) are both weak acids and bases and can therefore exist as zwitterions (**637**) (see Section 2.2.5.1). The zwitterions of 2- and 4-hydroxypyridines are known as 2- and 4-pyridones because of their uncharged canonical forms, *e.g.* (**638**) and (**639**). α- and γ-Hydroxypyridines exist in aqueous solution very predominantly as the oxo or pyridone form. For α- and γ-hydroxy-benzopyridines and -benzazines, the equilibrium favors the benzopyridone form still more, with the exception of 3-hydroxyisoquinoline. The reactivity of the pyridones and azinones is considered in Sections 3.2.3.7.2–4.

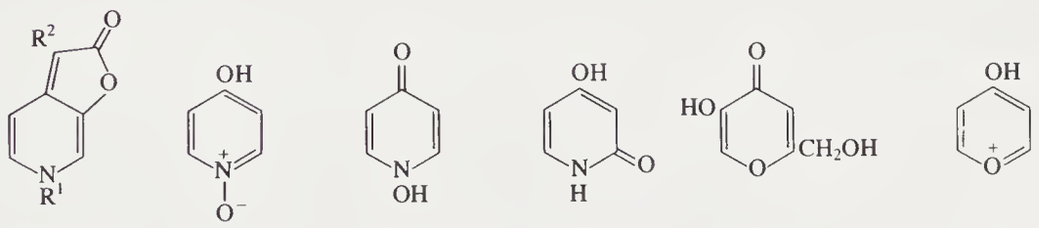
In aqueous solutions the hydroxy and zwitterionic forms of β-hydroxypyridines coexist in comparable amounts. 3-Hydroxypyridine behaves as a typical phenol. It gives an intense violet color with ferric chloride and forms a salt (**640**) with sodium hydroxide which can be alkylated by alkyl halides (to give **641**; Y = alkyl) and acylated by acid chlorides (to give **641**; Y = acyl). 5-Hydroxypyrimidines also exist as such, behave as phenols and are easily acylated.



(**636**) (**637**) (**638**) (**639**) (**640**) (**641**)

Cycloaddition reactions of 3-oxidopyridinium betaines involving addition at two of the ring atoms have been discussed in Section 3.2.1.9. However, with chloroketenes reaction occurs across the exocyclic oxygen atom and either the 4- or the 2-position giving compounds of type (**642**).

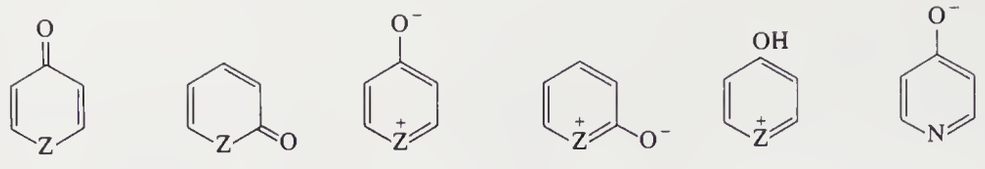
Hydroxypyridine 1-oxides are also tautomeric; the 4-isomer exists in about equal amounts of forms (**643**) and (**644**). 4-Hydroxy-pyrones and -pyridones exhibit a different type of tautomerism: the α-one (*e.g.* **645**) structure is favored relative to the γ-one structure. β-Hydroxy-4-pyrones such as kojic acid (**646**) show phenolic properties (CHEC 3.28, Scheme 30). α- and γ-Hydroxy cations (*e.g.* **647**) are the conjugate acids of pyridones and pyrones and are considered in the next section.



(**642**) (**643**) (**644**) (**645**) (**646**) (**647**)

3.2.3.7.2 Pyridones, pyrones, thiinones, azinones, etc.*: general pattern of reactivity*

These compounds are usually written in the uncharged form (**648**, **649**; Z = NH, NR, O, S), but canonical forms of types (**650**) or (**651**) are of comparable importance, *i.e.* the compounds can also be considered as betaines derived from pyridinium, pyrylium and thiinium cations. They possess considerable stability and aromaticity in that in many of their reactions they 'revert to type'.



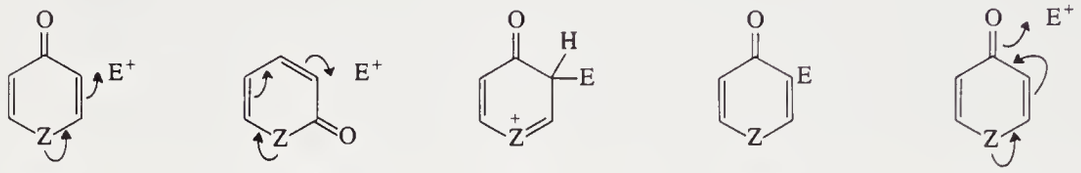
(**648**) (**649**) (**650**) (**651**) (**652**) (**653**)

The reactivity pattern of these compounds considered briefly in Section 3.2.1.1.4 will now be summarized. The system of heteroatoms in these molecules can act either as an electron source or an electron sink. This, together with the possibility of readily forming cationic (**652**) and anionic (**653**) species, increases considerably the possibilities for reaction in these compounds.

(i) Reactions with electrophiles

These can attack ring carbon atoms β to the cyclic heteroatom as shown in (**654**) and (**655**); the intermediates (*e.g.* **656**) usually revert to type by proton loss (**656**→**657**). These electrophilic substitution reactions are considered in Section 3.2.1.4.

Electrophilic reagents can also attack the carbonyl oxygen atom (*e.g.* **658**); reactions of this type are considered in Section 3.2.3.7.3.



(**654**) (**655**) (**656**) (**657**) (**658**)

(ii) Reactions with nucleophiles

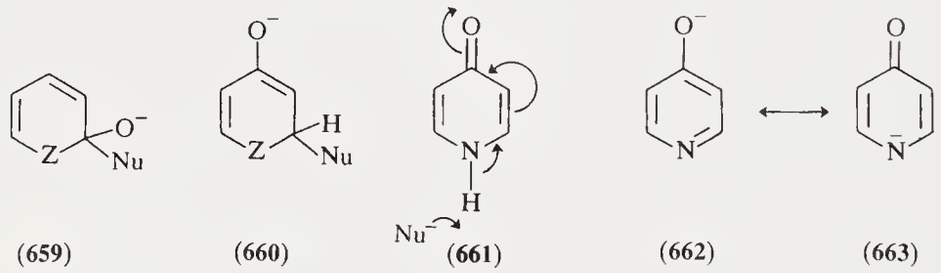
Four modes of reaction exist.

(a) Attack at a ring carbon atom, other than that of the carbonyl group, can be followed by proton addition, *i.e.* overall Michael-type reaction. An example of this rather rare reaction type, which involves loss of aromaticity, is given in Section 3.2.1.6.8.

(b) Nucleophilic reagents can attack the carbon atom of the carbonyl group (as in **659**). The reaction sequence proceeds by complete loss of the carbonyl oxygen and subsequent re-aromatization. These reactions are considered in Section 3.2.3.7.4.

(c) Nucleophiles can attack α- and γ-pyrones and oxazinones, *etc.*, at a carbon α or γ to the ring oxygen to give initial adducts (**659**, **660**) which undergo ring opening (*e.g.* with OH^-) which can be followed by reclosure in suitable cases (*e.g.* with NH_3, RNH_2). These reactions are considered in Section 3.2.1.6.

(d) A hydrogen atom on the heterocyclic nitrogen atom of pyridones can be removed as a proton by nucleophilic reagents, *e.g.* (**661**)→(**662**). The resulting mesomeric anion, *e.g.* (**662**)↔(**663**), reacts readily with electrophilic reagents at the nitrogen, β-carbon or oxygen atoms as discussed in Section 3.2.1.7.4.



(**659**) (**660**) (**661**) (**662**) (**663**)

(iii) Reactions with radicals and electron-deficient species

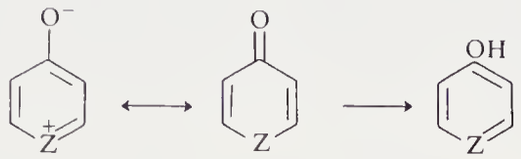
These reactions are discussed in Section 3.2.1.9. Pyridones and pyrones are easily reduced catalytically.

(iv) Intra- and inter-molecular reactions with cyclic transition states

Reactions of these types are discussed in Sections 3.2.1.2 and 3.2.1.9 respectively; due to the reduced aromaticity and polarizability, reactions of these types are of considerable importance.

3.2.3.7.3 Pyridones, pyrones and azinones: electrophilic attack at carbonyl oxygen

Pyridines and pyrones are weak bases: 4- and 2-pyridone have pK_a values of 3.3 and 0.8, respectively, for proton addition to the carbonyl oxygen atom, *e.g.* (**664**)↔(**665**)→(**666**).



(664) (665) (666)

O-Alkylation of pyridones can be effected with diazomethane: 2-pyridone forms 2-methoxypyridine. Frequently *O*- and *N*-alkylation occur together: 4-pyridone with CH_2N_2 yields 4-methoxypyridine and 1-methyl-4-pyridone. Et_3O^+ and similar active alkylating agents also alkylate the carbonyl oxygen of pyridones and pyrones.

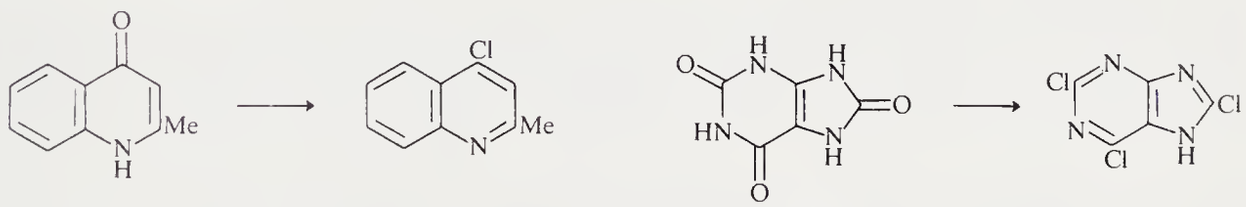
Alkylation of pyridones *via* the anion is discussed in Section 3.2.1.7.4.

3.2.3.7.4 Pyridones, pyrones and azinones: nucleophilic displacement of carbonyl oxygen

Nucleophilic attack on the carbon atom of the carbonyl group, in reactions which lead to substitution rather than to ring opening, is discussed in this section.

Pyridones and pyrones behave as cyclic amides and esters and, predictably, do not normally react with nucleophilic 'ketonic reagents' such as HCN, RNH_2, $NaHSO_3$, NH_2OH, N_2H_4, PhN_2H_3 and $NH_2CON_2H_3$. Strong nucleophiles of the type that attack amides generally do react with pyridones and pyrones, as described in (i)–(v) below. However, in all these reactions, the nucleophilic attack is preceded by electrophilic attack at the carbonyl oxygen and it is this that allows the nucleophilic attack that is being discussed.

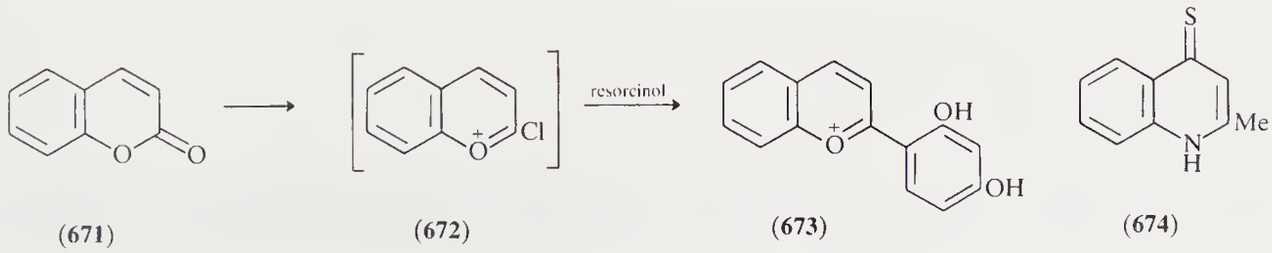
(i) Pyridones are converted into chloropyridines with $POCl_3$ or PCl_5, *e.g.* 2-methyl-4-quinolinone (**667**) gives (**668**). Bromopyridines may be prepared using PBr_5. Azinones react similarly; thus, pyrimidinones yield chloropyrimidines, and uric acid (**669**) yields 2,6,8-trichloropurine (**670**).



(667) (668) (669) (670)

Alkyl substituents on the pyridone nitrogen atom are usually lost in reactions of this type, but the quaternary salts from *N*-substituted acridones can be isolated. Pyrones (with PCl_5 or $POCl_3$) form highly reactive (*cf.* Section 3.2.3.10.3) chloropyrylium ions which are used *in situ* as reaction intermediates, *e.g.* (**671**)→(**672**)→(**673**).

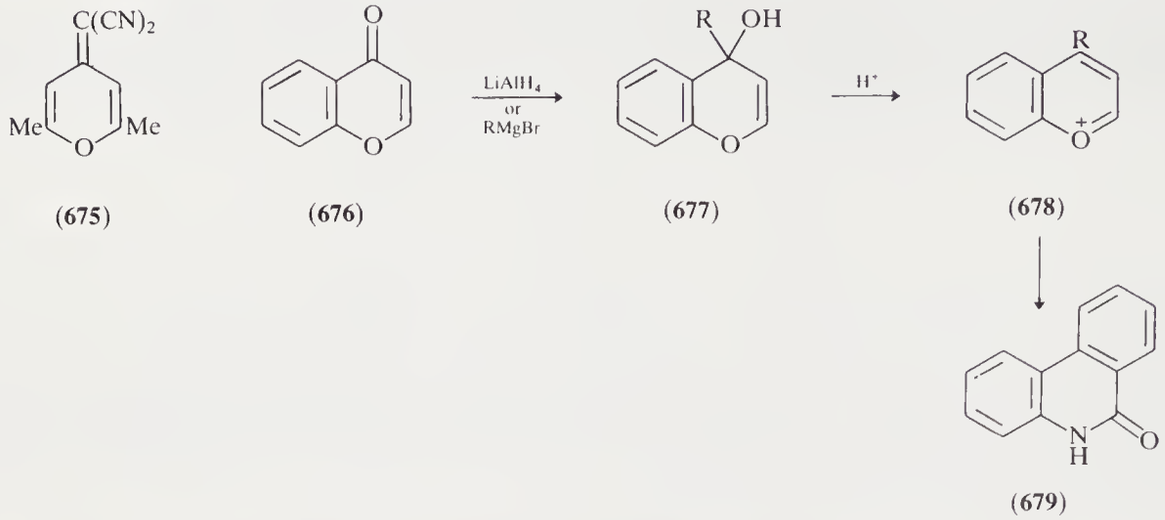
(ii) Phosphorus pentasulfide converts carbonyl groups into thiocarbonyl groups, *e.g.* (**667**)→(**674**). Pyridazinethiones and pyrimidinethiones are similarly prepared.



(671) (672) (673) (674)

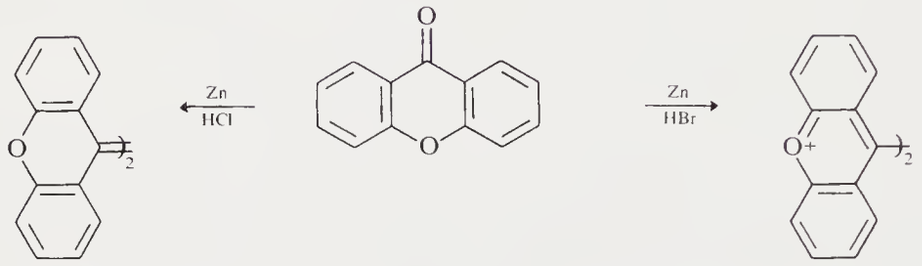
(iii) Pyrones react with active methylene compounds with Ac_2O as a catalyst, *e.g.* 2,6-dimethyl-4-pyrone and malononitrile give (**675**).

(iv) Lithium aluminum hydride and Grignard reagents react with chromones, coumarins and xanthones to give the pseudo-bases, *e.g.* (**676**)→(**677**; R = alkyl, H) of pyrylium salts (*e.g.* **678**). Some pyridones react analogously (*e.g.* **679** + $LiAlH_4$→phenanthridine).



(675) (676) (677) (678) (679)

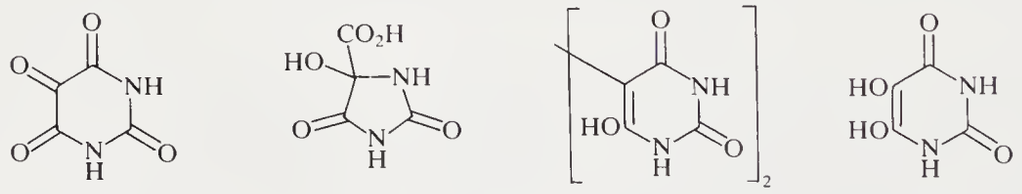
(v) Reduction of xanthones (**681**) in acid solution gives bimolecular reduction products (**680**, **682**).



(680) (681) (682)

3.2.3.7.5 Heterocyclic quinones

Pyridine quinones are little known, but the diazine analogues of benzoquinones include alloxan (**683**) in which the carbonyl group in the 5-position shows ketonic properties. Alloxan undergoes the benzilic acid rearrangement (Na_2CO_3→alloxanic acid **684**) and can be reduced to a dimeric product (H_2S→alloxantoin **685**), or to the hydroquinone analogue ($SnCl_2$→dialuric acid **686**).



(683) (684) (685) (686)

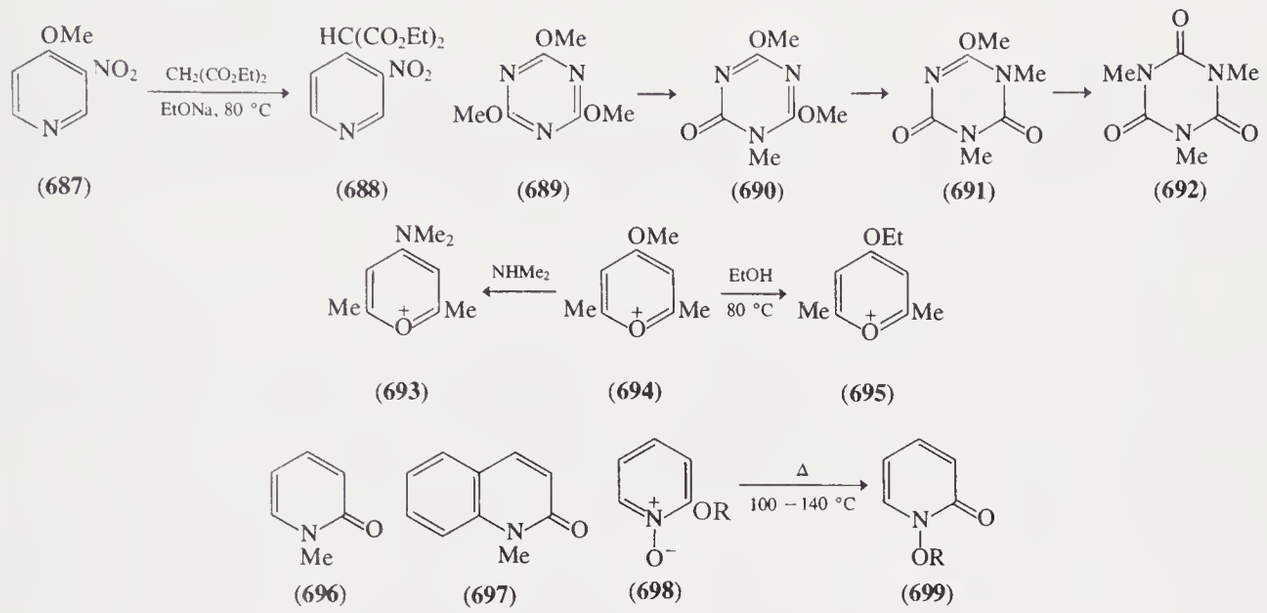
3.2.3.8 Other *O*-Linked Substituents

3.2.3.8.1 Alkoxy and aryloxy groups

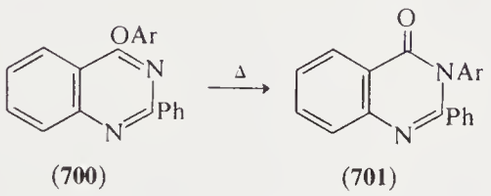
2- and 4-Alkoxy groups in pyridines undergo nucleophilic replacement when some additional activation is present as is the case for 3-nitro-4-methoxypyridine (**687**→**688**). Such reactions are

facilitated in the pyrimidine series for 2-, 4- and 6-alkoxy groups which are α and γ to *two* nitrogen atoms; they are often used to prepare aminopyrimidines. Alkyl cyanurates (**689**) behave as esters being hydrolyzed to cyanuric acid and the alcohol and readily undergoing transesterification. Nucleophilic displacement of alkoxy groups on cationic rings occurs exceedingly readily as is illustrated for 4-methoxy-2,6-dimethylpyrylium cation (**694**→**693**, **695**).

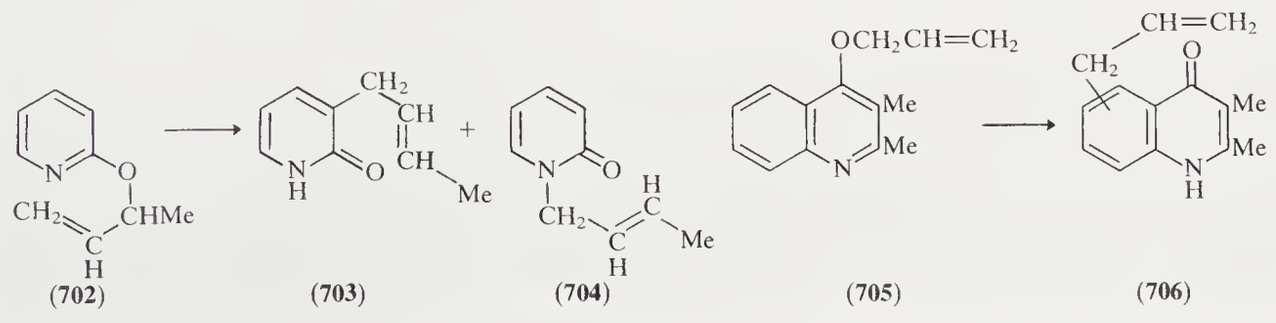
Pyridines and benzopyridines with alkoxy groups in the α- or γ-position rearrange to *N*-alkyl-2- and -4-pyridones on heating. 2-Methoxypyridine gives (**696**) at 300 °C whereas 2-methoxyquinoline forms (**697**) at 100 °C. One molecule of alkoxy compound acts as an alkylating agent for another in these intermolecular reactions. Similarly, 2-alkoxypyridine *N*-oxides rearrange thermally to *N*-alkoxy-2-pyridones (**698**→**699**). The thermal rearrangement of alkoxypyrimidines to *N*-alkylpyrimidinones is known as the Hilbert–Johnson reaction. Alkyl cyanurates (**689**) on heating isomerize to isocyanurates (**692**), in a step-wise manner *via* (**690**) and (**691**).



Aryloxy groups are more resistant to rearrangement (unless nitroactivation of the aryl group is present); however, under forcing conditions the reaction (**700**→**701**) forms the basis for a synthetic technique for converting a phenol into an amine.



Allyl ethers undergo true intramolecular rearrangement from oxygen to nitrogen. Thus, 2-(1-methylallyloxy)pyridine (**702**) gives approximately equal amounts of 1- (**704**) and 3-crotyloxy-2-pyridone (**703**). 4-Allyloxyquinolines rearrange to 3-allyl-4-quinolones. If the 3-position is occupied by a methyl group (*cf.* **705**) the allyl group rearranges to the benzene ring to give (**706**) of uncertain orientation ⟨67AHC(8)147⟩.



3.2.3.8.2 *Acyloxy groups*

2- and 4-Acyloxypyridines are so easily hydrolyzed that they are difficult to isolate; the reactions of 3-acyloxypyridines parallel those of phenyl acetate.

3.2.3.9 *S*-Linked Substituents

3.2.3.9.1 *Mercapto–thione tautomerism*

Pyridines and azines with α- or γ-mercapto groups exist predominantly in the pyridinethione *etc.* forms, *e.g.* as (**709**) rather than in the mercapto form (**708**). This behavior is analogous to that of the corresponding hydroxypyridines (Section 3.2.3.8.1); see also Section 2.2.5.1.

3.2.3.9.2 *Thiones*

Pyridine-, pyran- and azine-thiones behave as cyclic thioamides or thioesters and show their typical reactions. Thus they react with electrophiles at the sulfur atom [as exemplified in (i)–(iv)], and with nucleophiles including the typical 'ketonic' reagents at the thione carbon atom [as exemplified in (v)–(vii)].

(i) Alkyl halides give alkylthiopyridines, *e.g.* (**709**→**710**), azines, or in the absence of an NH group, alkylthio cationic rings.

(ii) Iodine oxidation forms disulfides (**709**→**707**).

(iii) Oxidation with H_2O_2 forms the sulfinic acid which usually spontaneously loses SO_2 to give the CH derivative. Mercapto groups in any position of the pyrimidine ring can be replaced by hydrogen in this way.

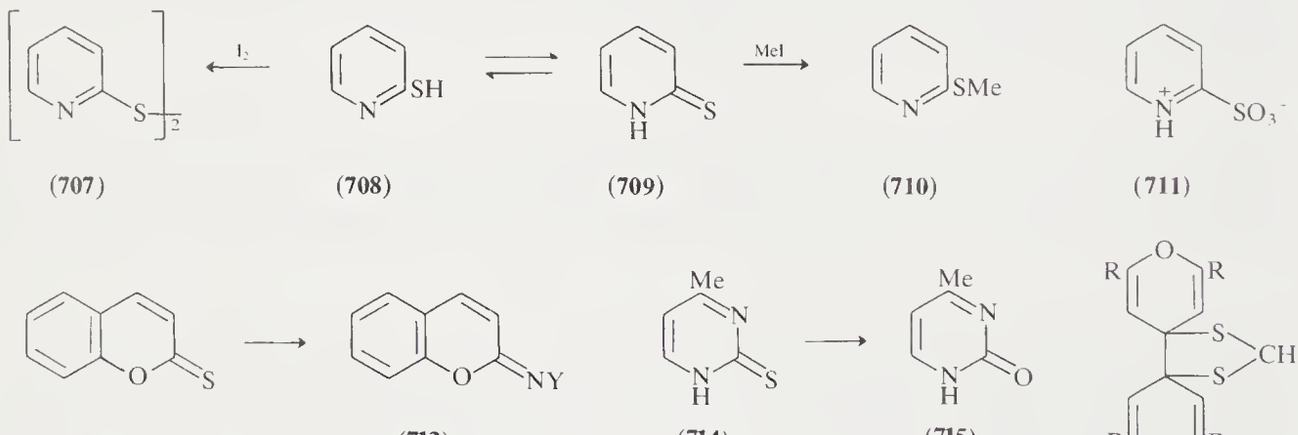
(iv) Strong oxidation forms a sulfonic acid (**709**→**711**).

(v) Phenylhydrazine forms (**713**; Y = NHPh) from thiocoumarin (**712**).

(vi) PCl_5 gives chloro compounds, *e.g.* chloropyrimidines from pyrimidinethiones (*e.g.* **714**).

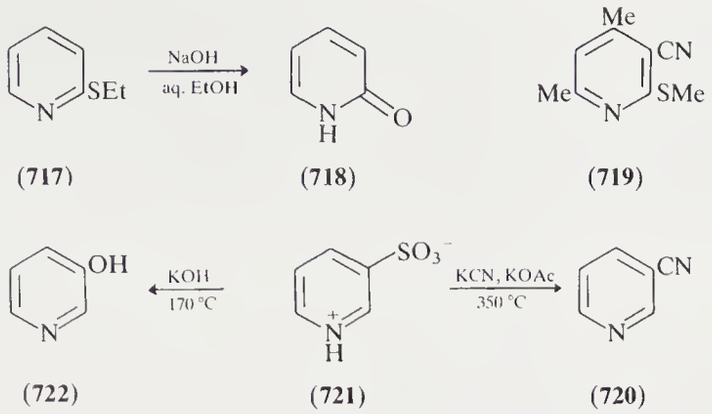
(vii) Hydrolysis with HCl–H_2O converts compounds such as pyrimidinethiones into pyrimidinones (**714**→**715**).

(viii) Pyran-4-thiones and diazomethane are converted into unusual dimeric products (**716**).



3.2.3.9.3 *Alkylthio, alkylsulfinyl and alkylsulfonyl groups*

The SR substituent can be nucleophilically displaced by amines and hydroxide (**717**→**718**) and removed reductively by dissolving metals, *e.g.* from (**719**) with Zn/H^+. Oxidation gives the corresponding sulfoxide and sulfone, in which nucleophilic displacement is easier. Thus, 2- and 4-(phenylsulfonyl)pyrimidines give the corresponding replacement products with various nitrogen and oxygen nucleophiles.



(717) (718) (719)

(722) (721) (720)

3.2.3.9.4 Sulfonic acid groups

Pyridinesulfonic acids exist as zwitterions (*e.g.* **721**). As in benzenesulfonic acid, the sulfonic acid group can be replaced by hydroxy or cyano groups under vigorous conditions, *e.g.* (**721**)→(**720**), (**722**).

3.2.3.10 Halogen Atoms

3.2.3.10.1 Pattern of reactivity

Halogen atoms attached to ring carbon of heteroaromatic six-membered rings show both reactions typical of aryl halides and their own characteristic reactions.

Just as in phenyl halides, the halogen can be replaced by hydrogen, by a metal, or coupled. Two of the four mechanisms of nucleophilic substitution are also familiar from benzene chemistry: *via* arynes, and by the $S_{RN}1$ mechanism. However, of the two further mechanisms of nucleophilic replacement, the ANRORC is unique to heterocycles, and S_{AE} reactions occur only with strongly activated benzenoid systems.

3.2.3.10.2 Replacement of halogen by hydrogen or a metal, or by coupling

Heterocyclic nuclear halogen atoms undergo the following reactions which are typical of aryl halogens.

(i) They can be replaced with hydrogen atoms by catalytic (Pd, Ni, *etc.*) or chemical reduction (HI or Zn/H_2SO_4). Reductive removal of halogen atoms is accompanied by reduction of the ring in compounds of relatively low aromaticity (*e.g.* quinazolines).

(ii) They can be converted into Grignard reagents which show the normal reactions. However, in the preparation of such Grignard reagents ethyl bromide usually has to be added to activate the magnesium ('entrainment method').

(iii) Pyridyllithium reagents can be formed by halogen–metal exchange using *n*-butyllithium at −60 °C. The products react with electrophiles in the manner typical of aryllithiums: CO_2→acids, RCHO→alcohols, esters→ketones, *etc.*

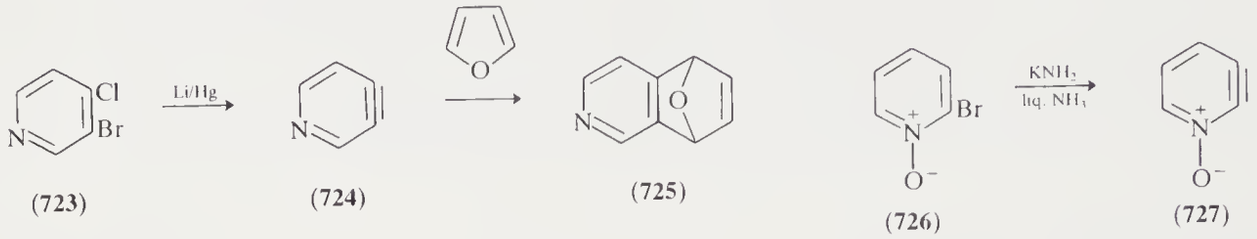
(iv) Ullmann reactions succeed; *e.g.* 2-bromopyridine yields 2,2′-bipyridyl (with Cu).

3.2.3.10.3 Reactions via *hetarynes* ⟨65AHC(4)127⟩

Very strong bases such as $NaNH_2$ convert unactivated aryl halides into benzyne intermediates which react rapidly with nucleophiles to form the products of an apparent simple nucleophilic substitution. It is now clear that hetarynes are frequent intermediates in reactions of not too highly activated heteroaromatic halides.

Thus, reaction of 3-chloro-, 3-bromo- and 3-iodo-pyridine with potassamide in liquid ammonia gave in each case the same mixture of 3- and 4-aminopyridine, showing the intermediacy of 3,4-pyridyne. Under these conditions the corresponding 4-halopyridines also give reaction entirely through 3,4-pyridyne (**724**).

Pyridynes are also formed from α-dihalides and alkali metals. Thus, reaction of 3-bromo-4-chloropyridine (**723**) with lithium amalgam and furan gives product (**725**) by trapping of the 3,4-pyridyne (**724**). Although 2,3-pyridyne is not formed from 3-halopyridines, becuase of the weaker acidity of the 2- as compared to the 4-hydrogen atom (see Section 3.2.1.7.2), it can be trapped from the reaction of 3-bromo-2-chloropyridine with lithium amalgam by furan in small yield; water is eliminated from the resulting addition product to give quinoline.

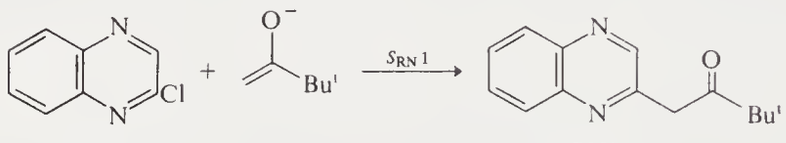


(**723**) (**724**) (**725**) (**726**) (**727**)

2,3-Pyridyne 1-oxide (**727**) is obtained by the action of potassamide on 2-bromopyridine 1-oxide (**726**), as shown by the formation of a mixture of the 2- and 3-aminopyridine oxides. Reaction of 5-bromopyrimidine with sodamide in liquid ammonia involves 4,5-pyrimidyne as an intermediate.

3.2.3.10.4 The S_{RN} mechanistic pathway

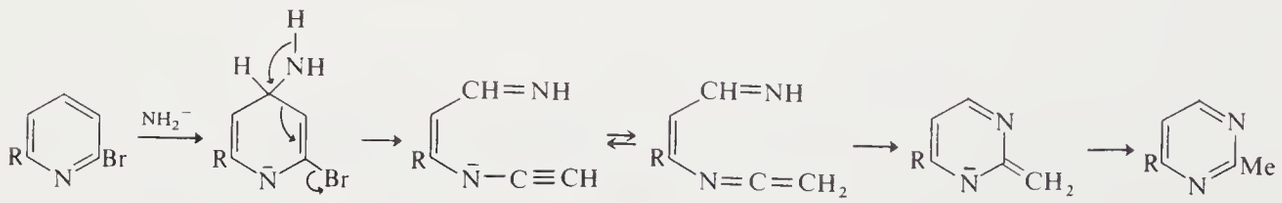
Unactivated aryl halides also undergo nucleophilic displacement *via* electron transfer in the initial step: the so-called $S_{RN}1$ mechanism. It is now clear that in the case of heteroaromatic compounds, nucleophilic substitution by the S_{RN} process often competes with the addition–elimination pathway. The S_{RN} reactions are radical chain processes, and are usually photochemically promoted. For example, ketone (**729**) is formed by the $S_{RN}1$ pathway from 2-chloroquinoxaline (**728**) ⟨82JOC1036⟩.



(**728**) 70% (**729**)

3.2.3.10.5 ANRORC reactions

The ANRORC (*A*ddition of *N*ucleophile, *R*ing *O*pening, *R*ing *C*losure) reaction involves the initial addition of a nucleophile to a ring carbon atom *not* carrying the halogen followed by electrocyclic ring opening. The sequence, exemplified by Scheme 50, is similar to that of the Dimroth rearrangement (Section 3.2.3.5.4.iii) but in the ANRORC reaction the initial ring opening involves elimination of the halogen atom. The ring formed can be the same or different to that started with.



Scheme 50

Further examples of ANRORC reactions are the conversions of quinoline (**730**) into quinazoline (**731**) and of pyrimidine (**732**) into triazine (**733**).

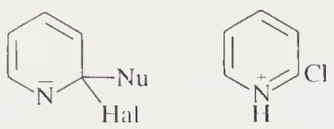
(730) (731) (732) (733)

3.2.3.10.6 Nucleophilic displacement by classical S_{AE} mechanism

(i) Dichotomy of mechanisms

Nucleophilic displacement of an α- or γ-halogen atom by the classical S_{AE} mechanism of nucleophilic displacement *via* a Meisenheimer intermediate (*e.g.* **734**) is facilitated by mesomeric stabilization of the transition state. However, the mechanistic balance is fine: whereas 4-bromopyridine 1-oxide reacts with potassamide by the A–E mechanism, the 2-bromo analogue prefers the E–A route. Again, nucleophilic displacement of chloropyrazines can involve the ANRORC mechanism.

Some of the reactions of α- and γ-halopyridines are acid catalyzed, *i.e.* ions of type (**735**) are formed and react with nucleophilic reagents (*e.g.* 2-chloro-5-nitropyridine + $PhNH_2$ → 2-anilino-5-nitropyridine, catalyzed by H_2O– HCl).



(734) (735)

(ii) Reactivity dependence on halogen and nucleophile

The relative reactivities with respect to nucleophilic S_{AE} displacement increase in the order $Cl \leqslant Br \leqslant I \leqslant F$.

The relative reactivities of nucleophiles are illustrated by the reactions of 2-bromopyridine: replacement by the following groups occurs under the conditions indicated:

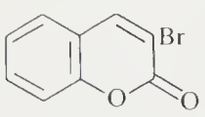
(a) Hydroxy*, by $NaOH–H_2O$, 150 °C.
(b) Alkoxy, *e.g.* methoxy by NaOMe–MeOH, 65 °C.
(c) Phenoxy, PhONa–EtOH.
(d) Mercapto*, KSH–propylene glycol.
(e) Methylmercapto, NaSMe–MeOH, 65 °C.
(f) Amino ($NH_3–H_2O$, 200 °C), dimethylamino ($NHMe_2$, 150°C) or hydrazino (N_2H_4, 100 °C).
(g) Cyano, by distillation with CuCN.
(h) Di(ethoxycarbonyl)methyl by the sodio derivative of malonic ester.
(i) Isothiouronium, $(NH_2)_2CS$–EtOH, reflux; the product is converted by alkali into urea and pyridine-2-thione.
(j) Sulfonic acid ($NaHSO_3$).

(iii) Reactivity dependence on nature of heterocyclic rings

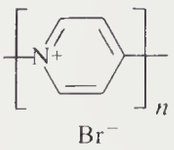
The reactivity of halogen atoms in azines toward S_{AE} displacement is in line with the sequence discussed in Section 3.2.3.1.1.

β-Halogen atoms in pyrones and pyridones (*e.g.* **736**) are unreactive toward S_{AE} nucleophilic displacement. β-Halopyridines are less reactive than the α- and γ-isomers but distinctly more reactive than unactivated phenyl halides. Thus, a bromine atom in the 3-position of pyridine or quinoline can be replaced by methoxy (NaOMe–MeOH, 150 °C), amino ($NH_3–H_2O–CuSO_4$, 160 °C) or cyano (CuCN, 165 °C). 5-Halogens in pyrimidines are also relatively unreactive.

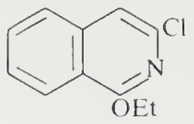
*The products tautomerize to an alternative form; see Sections 3.2.3.7.1 and 3.2.3.9.1.



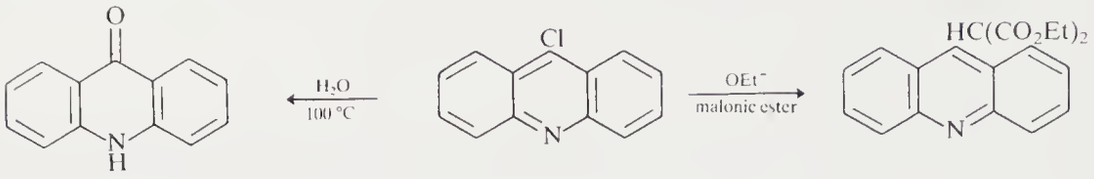
(736)



(737)



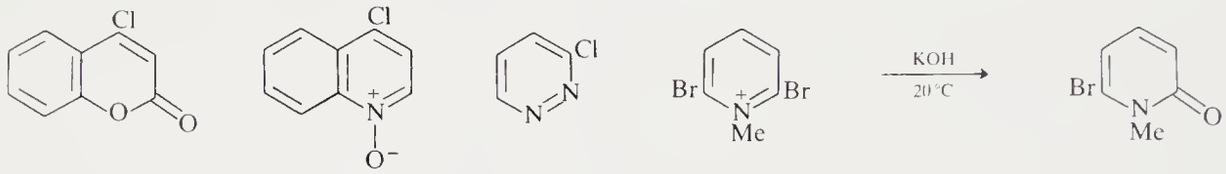
(738)



(739) (740) (741)

The reactions of the 4-halopyridines parallel those of the corresponding 2-isomers, with the exception that 4-halopyridines polymerize much more readily (*e.g.* to **737**) because the pyridine nitrogen atom is not sterically hindered and is more basic (*cf.* Section 3.2.1.3.4). As expected, the chlorine atom in the 1-position of 1,3-dichloroisoquinoline is more reactive than that in the 3-position, thus mild treatment with sodium ethoxide gives (**738**). Halogens in the 9-position of acridine are more reactive, *e.g.* (**740**)→(**739**), (**741**).

α- and γ-Halogen atoms on benzo-pyridines, -pyridones, -pyrones (*e.g.* **742**) and *N*-oxides (*e.g.* **743**) are about as reactive as those in the corresponding monocyclic compounds. A 2-chlorine atom in chromone is readily displaced by nucleophiles; a 3-halogen atom is less reactive, but can still undergo nucleophilic displacement.



(742) (743) (744) (745) (746)

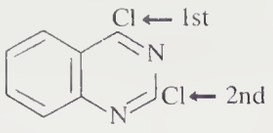
Reactivity increases in the diazines as compared with pyridines. 3-Chloropyridazine (**744**) and 2-chloropyrazine, for example, undergo the usual nucleophilic replacements (*cf.* Section 3.2.3.10.6.ii) rather more readily than does 2-chloropyridine. 2-, 4- and 6-Halogen atoms in pyrimidines are easily displaced. The reactivity of halogens in pyridazine 1-oxides toward nucleophilic substitution is in the sequence 5 > 3 > 6 > 4.

Halogen atoms in the α- and γ-positions of cationic nuclei are very reactive, as illustrated by the hydrolysis to 2,6-dibromo-1-methylpyridinium ion at 20 °C (**745**→**746**). Halogen groups in the α- or γ-positions of thiinium cations are also highly reactive.

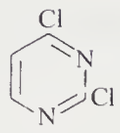
(iv) Reactivity in polyhalo compounds

In polyhalo compounds such as 2,4,6-trichloropyrimidine, each successive chlorine atom is replaced more slowly than the last because the groups introduced (*e.g.* NH_2) partially cancel the activating effect of the annular nitrogen atoms. Similarly, the chlorine atoms in cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) are replaced sequentially: the reactivity of the first chlorine is very high. Cyanuric fluoride behaves similarly to the chloride.

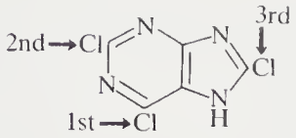
A halogen atom in the 4-position of quinazoline is more reactive than one in the 2-position because of partial double bond fixation. Thus, in 2,4-dichloroquinazoline (**747**), replacement occurs almost exclusively in the 4-position, whereas 2,4-dichloropyrimidine (**748**) yields approximately equal amounts of the 2- and 4-monoreplacement products. Similarly, in 2,6,8-trichloropurine (**749**) the order of replacement of the halogen atoms is 6, 2 and 8, successively. Only the 4-chlorine atom in 3,4-dichlorocinnoline is readily replaced. In tetrachloropteridine, the 6- and 7-chlorine atoms are the most reactive followed by the 2-chlorine.



(747)



(748)



(749)

(750) (751)

Just as in benzene chemistry, all types of halogen atom are activated toward nucleophilic displacement by the presence of other electron-withdrawing substituents. This is illustrated by the conversion of 5-nitro-2-chloropyridine (**750**) to the 2-hydrazine derivative (N_2H_4, 20 °C) and the 2-thione (**751**) under relatively mild conditions.

3.2.3.11 Metals and Metalloid Derivatives

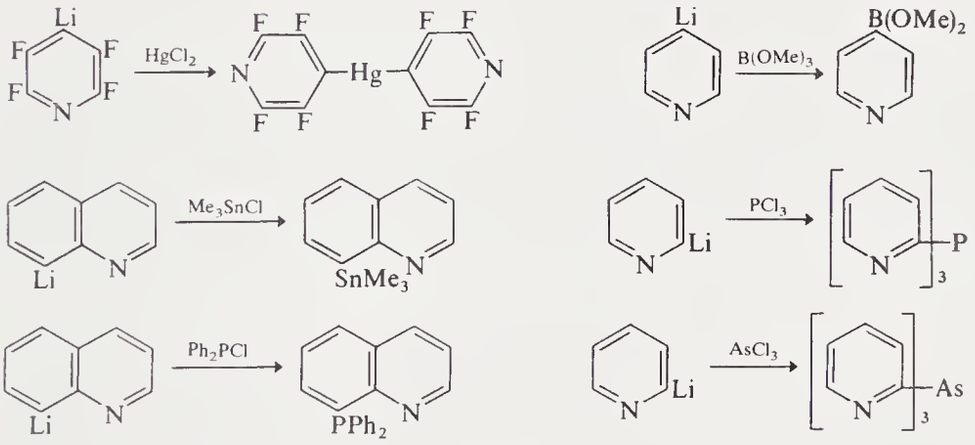
Azine Grignard reagents and sodium and lithium compounds in which the metal atom is attached directly to the ring are considered under the corresponding halogen compounds (Section 3.2.3.10) because they are generally prepared from their halogen derivatives by metal–halogen exchange, and are seldom isolated.

Lithium derivatives of azine *N*-oxides are likewise considered in Section 3.2.1.7.1 because they are generally prepared by direct lithiation of the *N*-oxide, and again are seldom isolated.

Finally, those organometallic derivatives of azines in which the metal is separated from the ring by one carbon atom are considered under the corresponding alkyl compound (Section 3.2.3.3).

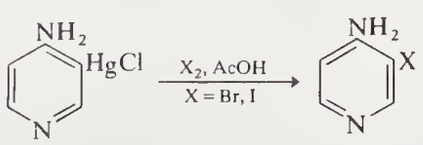
As exemplified in the sections indicated, these compounds show most of the typical reactions of Grignard reagents and alkyllithiums.

Thus, pyridyllithiums and their benzo analogues allow the introduction of other metals, and non-metals, on to the ring, such as mercury, boron, phosphorus, tin and arsenic (Scheme 51).



Scheme 51

Organomercury derivatives can be converted into bromides and iodides by standard methods, *e.g.* Scheme 52.



Scheme 52

3.2.3.12 Substituents Attached to Ring Nitrogen Atoms

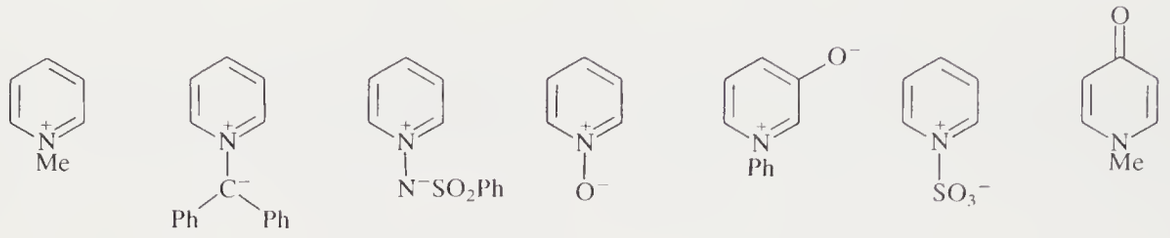
3.2.3.12.1 Introduction

(i) Types

Substituents attached to a nitrogen atom in a six-membered heteroaromatic ring are to be found in compounds of the following types:

(a) cations, *e.g.* (**752**);
(b) ylides, including *C*-ylides (**753**), *N*-ylides (**754**) and *N*-oxides (**755**);
(c) zwitterions, *e.g.* (**756**), (**757**);
(d) compounds with exocyclic conjugation, *e.g.* (**758**).

Significantly, types (b), (c) and (d) can all be derived from a compound of type (a) by deprotonation.



(**752**) (**753**) (**754**) (**755**) (**756**) (**757**) (**758**)

(ii) Overall survey of reactivity

We will survey the reactions of *N*-linked substituents classified by the atom attached to the cyclic nitrogen. Unlike heterocyclic *C*-substituents where the benzene prototype and the carbonyl analogy link much of the typical chemical behavior to familiar compounds, no simple model exists for *N*-substituents. However, certain trends are clear. The existence of the positive pole in cations of type (**752**) ensures that nucleophilic attacks (a)–(d) are the most important of the following reaction classes, many of which occur for several of the different classes of *N*-substituents.

(a) The *N*-substituent can be completely removed (**759**). This is the reverse of the reaction of an electrophile at the pyridine nitrogen atom (Section 3.2.1.3).

(b) An α-proton in the substituent can be removed (**760**→**761**); this gives an ylide (*cf.* **753**, **754** above). Such ylides can revert to their precursors by protonation or react with other electrophiles (**761**→**762**).

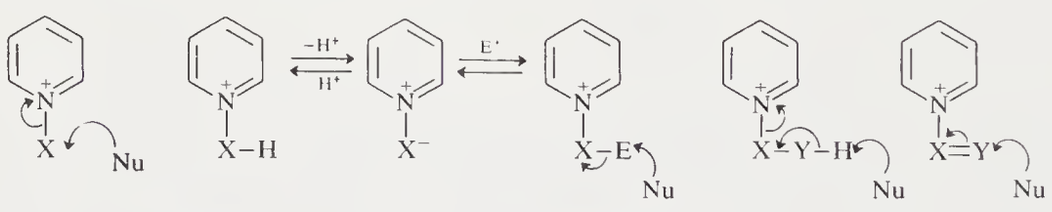
(c) An $\alpha\beta$ bond can cleave in a substituent by nucleophilic attack or spontaneously, in the reverse (**762**→**761**) of the reaction just mentioned.

(d) An elimination reaction (**763**) can occur.

(e) A nucleophile can add to an $\alpha\beta$-multiple bond in the substituent (**764**) to give an ylide.

(f) Rearrangements of *N*-substituent into the ring. A variety of thermal and photochemical rearrangements are known for *C*-, *N*- and *O*-linked substituents.

(g) Electrocyclic addition involving *N*-linked substituent and an α-position of the ring.



(**759**) (**760**) (**761**) (**762**) (**763**) (**764**)

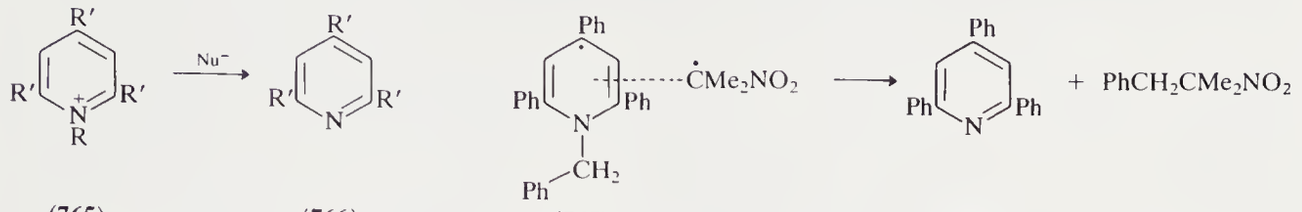
3.2.3.12.2 Alkyl groups

(i) Loss of alkyl groups

1-Alkylpyridinium halides dissociate reversibly into the alkyl halide and pyridine on vacuum distillation. Reactions of type (**765**→**766**) + RNu are accelerated by bulky α-substituents R′ and

also by electron-withdrawing groups in the ring. Reactions occur with a wide range of halogen, oxygen, sulfur, nitrogen, phosphorus and carbon nucleophiles. If R can form a stabilized carbon cation (*p*-methoxybenzyl, *s*-alkyl, *etc.*), the N—C cleavage can occur by the S_N1 as well as the S_N2 mechanism.

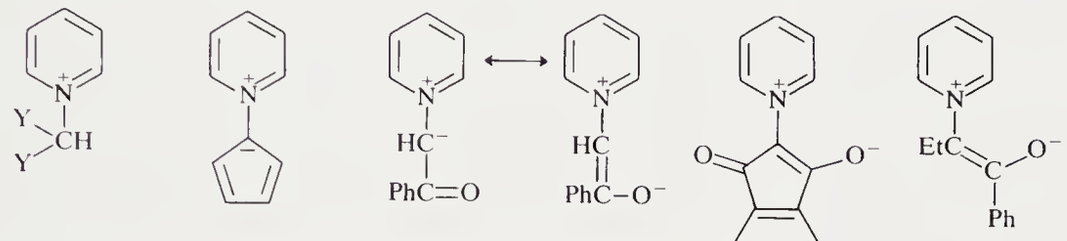
Transfer of an *N*-alkyl group to certain nucleophiles can also occur by a radicaloid non-chain mechanism, *e.g.* (**765**; R = CH_2Ph, R′ = Ph) + $\bar{C}Me_2NO_2$ → (**767**) → (**768**) + (**769**).



(765) (766) (767) (768) (769)

(ii) Proton loss from a carbon atom

The ease with which this occurs is determined by the other groups attached to the carbon (*cf.* **770**). The resulting ylide can be isolated only in special cases (*e.g.* **771**; **772** ↔ **773**; **774**); ylide stability increases with increasing possibility for spreading the negative charge (*cf.* **772** ↔ **773**; **774**).



(770) (771) (772) (773) (774) (775)

Stabilized ylides show the following properties:

(a) they form salts (**770**) with proton acids;

(b) they can be alkylated, *e.g.* (**772**) + EtBr + OH^- → (**775**);

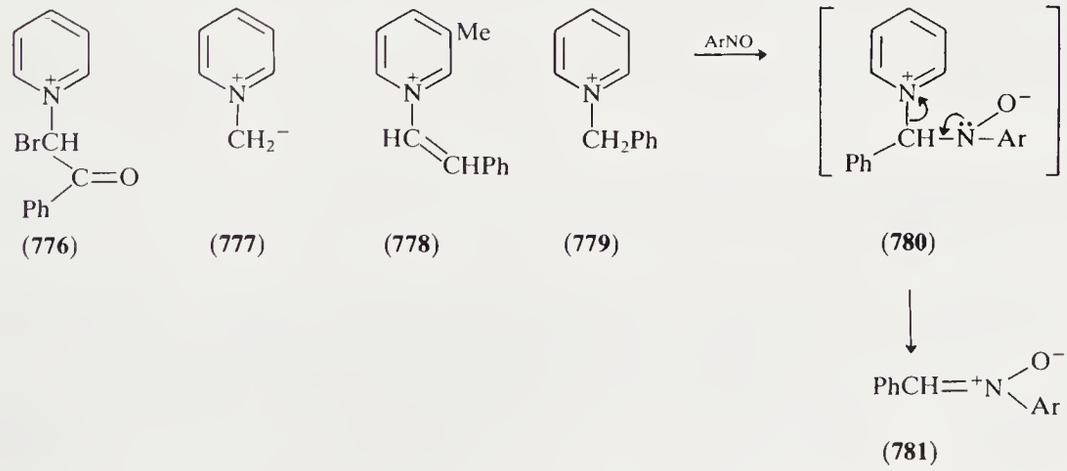
(c) they can be halogenated: (**772**) + Br_2 + H_2O → PhCOCHO + C_5H_5N at 20 °C probably *via* (**776**).

Ylides of type (**777**) are important as intermediates in the following reactions:

(a) the formation of β-hydroxyalkyl derivatives with aldehydes, *e.g.* 1,3-dimethylpyridinium + PhCHO + NaOH → (**778**);

(b) the Kröhnke reaction of benzylpyridines (**779**) with nitroso compounds to give nitrones (**781**) *via* (**780**).

Ylide thermolysis and photolysis can cause N—C cleavage to give carbene intermediates, *e.g.* (**782**) → (**783**) + pyridine.



(776) (777) (778) (779) (780)

(781)

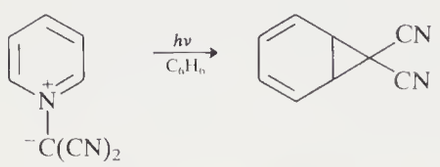
(iii) Cleavage of an αβ-substituted bond

Nucleophilic reagents can remove a part of the *N*-substituent because of the relative stability of the resulting zwitterions. Examples include:

(a) (**784**)→1-methylpyridinium ion + $PhCO_2^-$;

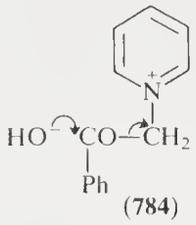
(b) (**785**) + OH^- → 1-methylpyridinium ion + 1-methyl-2-pyridone;

(c) decarboxylation of 1-carboxymethoxypyridiniums (**786**).

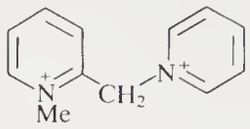


(**782**)

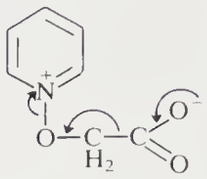
(**783**)



(**784**)



(**785**)



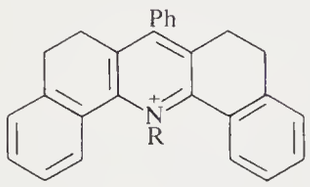
(**786**)

(iv) Elimination reactions (*cf.* **763**, Section 3.2.3.12.1.iii)

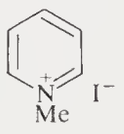
If compounds of type (**787**) are heated in the absence of nucleophile, E1 elimination occurs: thus, the pentacyclic triflates (**787**; R = primary alkyl) decompose at 150 °C. The *s*-alkyl analogues form alkenes already at 20 °C.

(v) Rearrangements

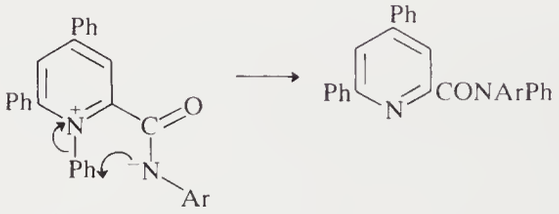
1-Alkylpyridinium halides give mixtures of alkylpyridines on heating, *e.g.* (**788**) gives 2- and 4-picoline, with other minor products. This reaction is known as the Ladenburg rearrangement, and involves *N*-alkyl bond homolysis.



(**787**)



(**788**)



(**789**) (**790**)

3.2.3.12.3 Other C-linked substituents

(i) N-*Aryl groups*

Typical reactions include:

(a) Electrophilic substitution. Nitration and sulfonation of the 1-phenylpyridinium cation occurs at the *meta* position of the 1-substituent.

(b) C—N Bond cleavage. Normally this is very difficult, but it can be achieved intramolecularly, *e.g.* (**789**)→(**790**).

(ii) N-*Acyl and related groups*

1-Acylpyridinium ions are very susceptible to attack by nucleophilic reagents and are good acylating agents. They are generally encountered only as intermediates (Section 3.2.1.3.7). *N*-Cyano and *N*-imidoyl groups are also easily transferred to nucleophiles; the former render the α ring position particularly susceptible to nucleophilic attack (see Section 3.2.1.6).

Derivatives of this type formed from 4-dimethylaminopyridine possess considerably more stability and can be isolated readily.

(iii) N-*Vinyl groups*

The typical reaction is Michael addition of nucleophiles: thus 1-vinylpyridinium ion (**791**) adds N-, S- and C-nucleophiles to give products of type (**792**). *N*-Vinyl groups can also undergo polymerization.

(iv) Other substituted alkyl groups

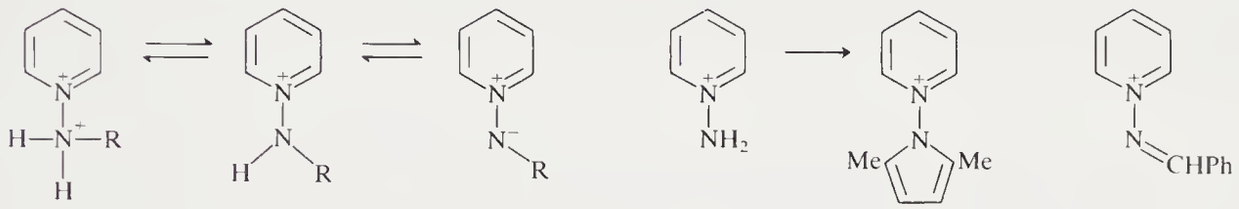
N-Allyl compounds can be rearranged to *N*-propenyl derivatives. Similarly, *N*-propargyl compounds (**793**) give *N*-allenyl derivatives (**794**).

(**791**) (**792**) (**793**) (**794**)

3.2.3.12.4 N-*Linked substituents*

(i) Prototropic equilibria

N-(Monosubstituted amino)pyridiniums (**796**) are in prototropic equilibrium with *N*-imides (**797**) and dications (**795**). For R = H or allyl, the *N*-imides (**797**) are very strong bases and cannot usually be isolated; if R is an electron-withdrawing group (*e.g.* acyl, sulfonyl, nitro), then the imide (**797**) is less basic and more stable. The cations (**795**) are only obtained in very strongly acid media.



(**795**) (**796**) (**797**) (**798**) (**799**) (**800**)

(ii) Reactions of N-*amino compounds with electrophiles*

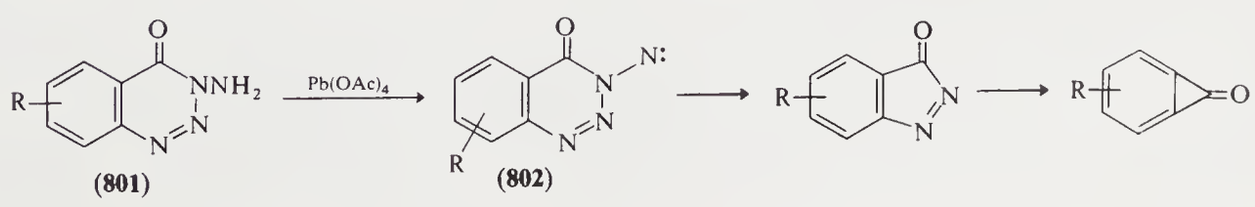
N-Aminopyridinium cations can be acylated or sulfonylated (with acid halides) and nitrated (H_2SO_4–HNO_3) to give the corresponding *N*-(substituted amino)pyridines (**796**), often isolated as the imides (**797**; R = COR′, SO_2R' or NO_2).

Both the NH_2 protons in (**798**) can be replaced by electrophiles in this way; *e.g.* with hexane-2,5-dione the *N*-(pyrrol-1-yl)pyridinium (**798**) is formed.

Aldehydes readily yield imines, *cf.* (**800**), and aryldiazonium salts form aryl azides and pyridine, presumably *via* $ArN{=}N{-}\bar{N}{-}py^+$. Nitrous acid and *N*-aminopyridinium cations yield pyridine and N_2O.

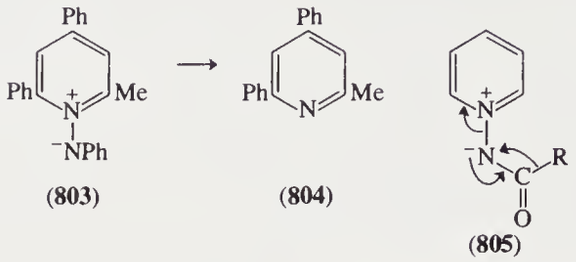
(iii) Other reactions of N-*amino compounds*

N-Aminopyridones can be oxidized to nitrenes. Thus, 3-amino-1,2,3-benzotriazin-4-ones (**801**) with lead tetraacetate lead to an intermediate nitrene (**802**), which can lose one or two molecules of nitrogen.



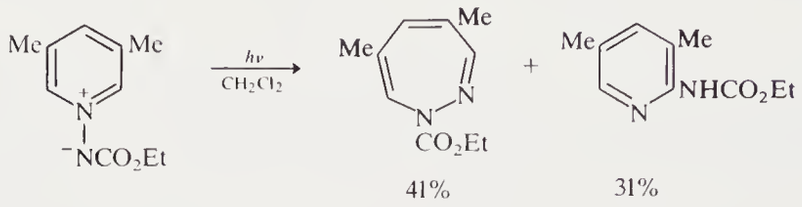
(**801**) (**802**)

N-Aminopyridiniums and *N*-imines yield pyridines and amines upon reduction, *e.g.* **(803)**→**(804)**+$PhNH_2$ (H_2/Pt or Zn/NaOH).



(803) **(804)** **(805)**

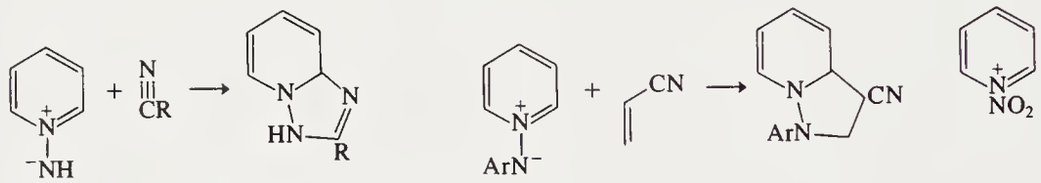
Thermolysis of pyridine *N*-acylimides (**805**) gives isocyanates RNCO and pyridine. Photochemical rearrangements of *N*-imides can be complex (Scheme 53).



41% 31%

Scheme 53

Heteroaromatic *N*-imines undergo 1,3-dipolar cycloaddition reactions across the *N*-imine nitrogen atom and the α-position of the ring. With nitriles, triazolopyridines are formed by dehydrogenation of intermediate adducts (**806**). The more stable the *N*-imine, the more reactive the dipolarophile has to be. *N*-Arylimines react with acrylonitrile to give similar adducts (**807**) ⟨74AHC(17)246⟩.



(806) **(807)** **(808)**

(iv) Other N*-linked substituents*

N-Nitropyridiniums (**808**) are mild nitrating agents.

3.2.3.12.5 O*-Linked substituents*

(i) Reactivity pattern of N*-oxides*

1-Hydroxypyridinium ions (**809**) readily lose a proton to give *N*-oxides; *N*-oxides are themselves weak bases which form 1-hydroxypyridinium ions by proton addition.

Pyridine 1-oxides possess a unique pattern of reactivity:

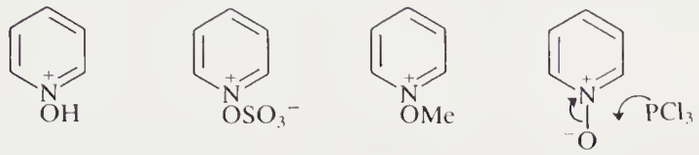
(a) Electrophiles can attack *either* at ring carbon (usually γ to the *N*-oxide on the free base, β-position on the conjugate acid) in electrophilic substitution reactions (see Section 3.2.1.4), *or* at the oxygen atom as discussed below.

(b) Nucleophiles can attack at *either* α *or* γ ring carbon atoms (strong nucleophiles on free bases, weaker nucleophiles on intermediates first formed by electrophile addition to the *N*-oxide oxygen—see Section 3.2.1.6). Certain nucleophiles also lead to *N*-oxygen removal as discussed below.

(c) *N*-Oxides undergo a variety of electrocyclic additions and rearrangements as discussed below.

(ii) Reactions of N*-oxides with electrophiles at the* N*-oxide oxygen*

These include the following:
(a) Proton acids give 1-hydroxypyridinium salts (**809**).
(b) Lewis acids give complexes, *e.g.* $SO_3 \rightarrow$(**810**).
(c) Alkyl halides form 1-alkoxypyridinium salts (**811**).
(d) Pyridine 1-oxides with arenediazonium salts yield *N*-aryloxypyridinium salts.
(e) Metal ions give coordination compounds.



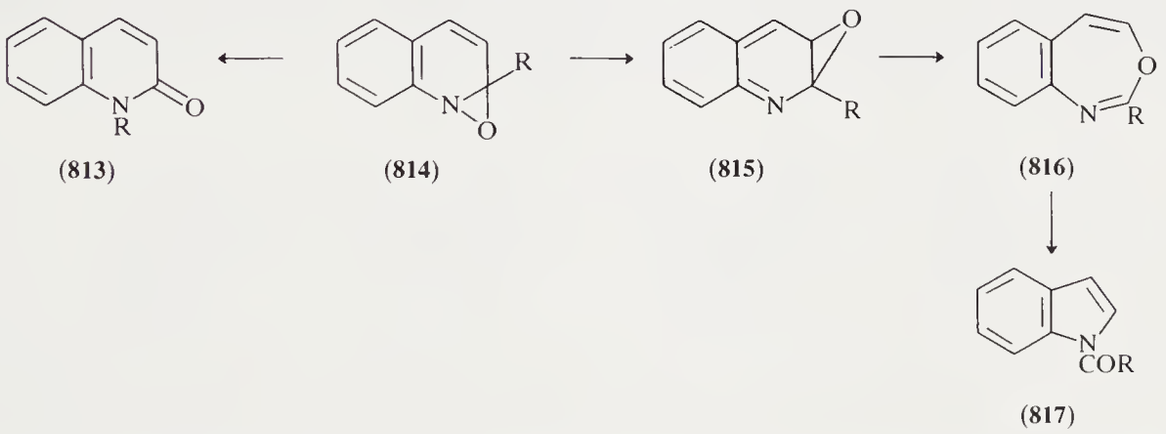
(**809**) (**810**) (**811**) (**812**)

(iii) Loss of the N*-oxide group*

Reduction of *N*-oxides affords the parent heterocycle and can be achieved by:
(a) Catalytic hydrogenation, *e.g.* over Pd.
(b) Chemical reduction, *e.g.* with Fe–HOAc.
(c) Electrochemical means.
(d) Deoxygenation with a trivalent phosphorus compound, *e.g.* PCl_3, PPh_3, $P(OEt)_3$. This can be formulated as nucleophilic attack on oxygen (**812**), but probably initial electron donation of the *N*-oxide lone pair into the vacant phosphorus *d*-orbital is involved. In this way, for example, pyrimidine *N*-oxides are converted to pyrimidines by phosphorus trichloride in chloroform (*cf.* **812**).

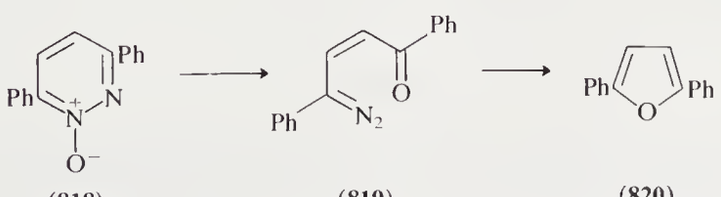
(iv) Rearrangement reactions

The most important rearrangements include:
(a) Photochemical. Photolysis of pyridine 1-oxide in benzene solution yields, *via* the excited triplet state, phenol and pyridine. Photolysis to the excited triplet state in a polar solvent like water takes a different course *via* the oxaziridine (**814**) to 2-quinolinone (**813**; R = H). Methyl migration can occur in such reactions: (**814**)→(**813**), R = Me. The primary oxaziridine can isomerize and undergo valence bond tautomerism to an oxepin, *e.g.* (**814**)→(**815**)→(**816**). Hydrolytic ring opening of the oxepin followed by ring closure can give a pyrrole or indole (**816**→**817**).



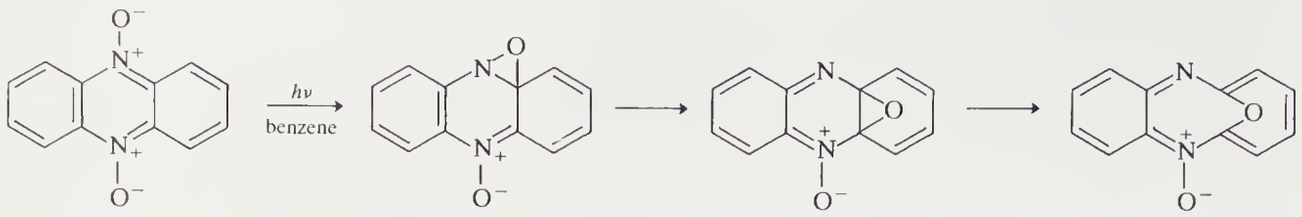
(**813**) (**814**) (**815**) (**816**) (**817**)

Certain pyridazine *N*-oxides are isomerized into the corresponding diazoketones, *e.g.* (**818**)→(**819**); ring contraction to the corresponding furan (**820**) can then occur.



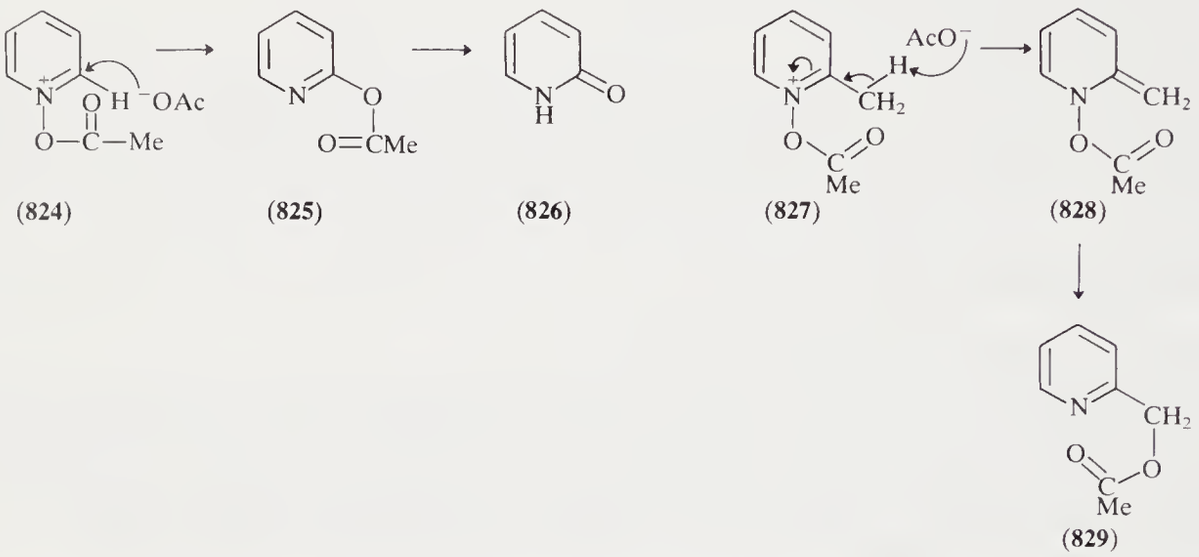
(**818**) (**819**) (**820**)

Phenazine 9,10-dioxide (**821**) is converted by irradiation in benzene to the 1,6-oxidoannulene (**823**) *via* (**822**) and an oxygen walk ⟨82AHC(30)253⟩.



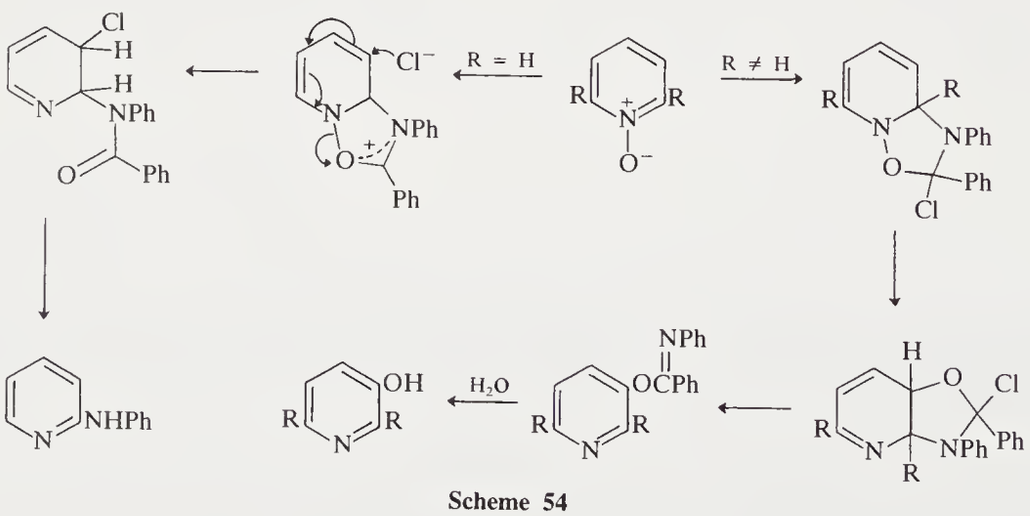
(**821**) (**822**) (**823**)

(b) Acid anhydrides. Pyridine 1-oxides heated with acid anhydrides are converted in good yield into pyridones (**824**→**826**) (see Section 3.2.1.6.3) unless the *N*-oxide contains an α- or γ-alkyl group. In the latter case an alternative reaction occurs with acetic anhydride to form an α- or γ-acetoxy alkylpyridine (*e.g.* **829**). For attack on α- (**827**→**829**) and γ-alkyl groups these reactions appear to be similar to the *ortho*- and *para*-Claisen rearrangement, respectively, of allyl phenol ethers; however, the formation of (**829**) proceeds *via* a radical cage. In these reactions, β-acetoxy compounds are formed as by-products, *e.g.* 3-acetoxy-2-methylpyridine from (**827**).



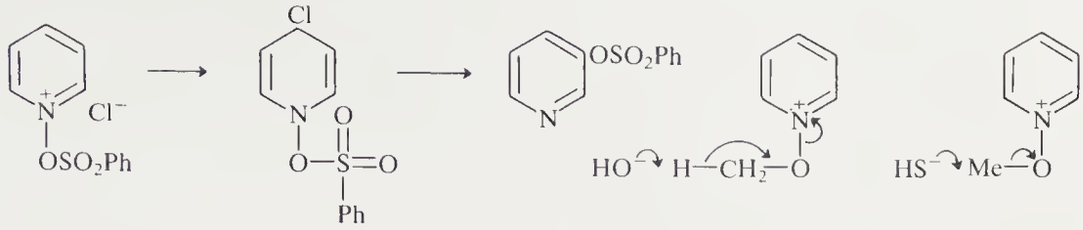
(**824**) (**825**) (**826**) (**827**) (**828**) (**829**)

(c) Imidoyl chlorides. The treatment of *N*-oxides with imidoyl chlorides leads to intramolecular amination *via* the intermediates as shown. When the 2- and 6-positions are both substituted, reaction goes further to give a 3-hydroxypyridine (Scheme 54).



Scheme 54

(d) Benzenesulfonyl chlorides. The reaction with *N*-oxides gives β-benzenesulfonyloxy compounds, *e.g.* (**832**) *via* (**830**) and (**831**).



(830) (831) (832) (833) (834)

(v) Reactions of N*-alkoxy-pyridines and -azines*

Two distinct types of reaction are common.

(a) 1-Alkoxypyridinium compounds react with hydroxide ions to give aldehydes and pyridines in an elimination reaction (*cf.* **833**).

(b) Soft nucleophiles can remove the alkyl group, *e.g.* (**834**)→pyridine 1-oxide + MeSH.

3.2.3.12.6 Other substituents

(i) S*-Linked*

Pyridine *N*-sulfides are known only in the form of derivatives. Thus 1-arylthiopyridinium cations (from pyridine and sulfenyl chloride) react with KCN to form ArSCN and pyridine ⟨81CC703⟩.

Pyridine–sulfur trioxide is a mild sulfonating reagent, used for sulfonation of furan and pyrrole.

(ii) Halogens

Pyridine–halogen complexes (**60**) dissociate on heating; halogen is lost so readily that these compounds act as mild halogenating agents toward phenol or aniline for example.

(iii) Metalloids

The complexes formed with boron trihalides are decomposed to pyridine by boiling water. Complexes with other Lewis acids behave similarly.

3.3

Reactivity of Five-membered Rings with One Heteroatom*

3.3.1 REACTIONS AT HETEROAROMATIC RINGS

3.3.1.1 General Survey of Reactivity

We first consider the different types of reactivity of which five-membered heteroaromatic rings with one heteroatom are capable. We compare and contrast the effects of the different heteroatoms and compare these compounds with analogous aliphatic and benzenoid derivatives. All these reactions are considered later in this chapter in more detail.

Electrophilic attack at ring heteroatoms is rare for the neutral compounds, although examples are known for thiophenes and selenophenes. However, pyrrole anions undergo easy reaction with electrophiles at both C and N atoms.

The most important reactions involve electrophilic attack on ring carbon atoms, a wide variety of which are known for pyrroles, furans and thiophenes. Most frequently, such electrophilic attack is followed by proton loss, resulting in overall substitution.

Nucleophilic attack on neutral pyrroles, furans and thiophenes is restricted to deprotonation at N or C atoms. However, the cations formed by electrophilic attack on pyrrole, furan and thiophene rings react readily with weak nucleophiles, resulting in overall addition or ring-opening reactions.

The neutral rings react readily with radicals and other electron-deficient species, and a variety of reactions at surfaces are known.

Several types of reaction involving cyclic transition states are known.

The five-membered ring heterocycles possess Diels–Alder reactivity of varying degree. This is most pronounced in the case of furan and benzo[*c*]-fused heterocycles such as isoindole. In this capacity they are functioning as heterocyclic analogues of cyclopentadiene, and high Diels–Alder reactivity can be correlated with low aromaticity.

3.3.1.1.1 Comparison with aliphatic series

Many common reactions of aliphatic amines, ethers and sulfides (**1**) involve initial attack by an electrophilic reagent at a lone pair of electrons on the heteroatom; salts, quaternary salts, coordination compounds, amine oxides, sulfoxides and sulfones are formed in this way. Corresponding reactions are very rare (*cf.* Section 3.3.1.3) with pyrroles, furans and thiophenes. These heterocycles react with electrophilic reagents at the carbon atoms (**2**–**3**) rather than at the heteroatom. Vinyl ethers and amines (**4**) show intermediate behavior reacting frequently at the β-carbon but sometimes at the heteroatom.

(1) (2) (3) (4)

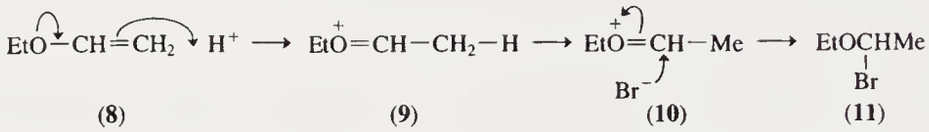
*Based on Chapter 3.02 of 'Comprehensive Heterocyclic Chemistry', by C. W. Bird and G. W. H. Cheeseman, Queen Elizabeth College, University of London.

(5) (6) (7)

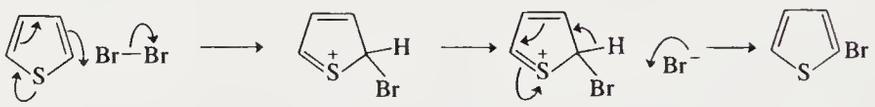
The heteroatoms of pyrrole, furan and thiophene carry partial positive charges in the ground state which hinder reaction with electrophilic reagents. Conversely, the carbon atoms of these compounds are partially negatively charged, which aids reaction with electrophilic reagents at the ring carbons. This charge distribution follows from the valence bond theory as a consequence of contributions to the resonance hybrids of canonical forms (**5**)↔(**6**). Molecular orbital theory leads to similar predictions, the heteroatom contributing two electrons to the π-molecular orbitals and the carbon atoms only one each (**7**).

3.3.1.1.2 Effect of aromaticity

Vinyl ethers and amines disclose little tendency to 'revert to type'; thus, the intermediate formed by reaction with an electrophilic reagent reacts further by adding a nucleophilic species to yield an addition compound; *cf.* the sequence (**8**)→(**11**). Thiophene and pyrrole have a high degree of aromatic character; consequently the initial product formed by reaction of thiophene or pyrrole with an electrophilic species subsequently loses a proton to give a substituted compound; *cf.* the reaction sequence (**12**)→(**15**). Furan has less aromatic character and often reacts by overall addition as well as by substitution. In electrophilic addition, the first step is the same as for substitution, *i.e.* the formation of a σ-complex (*e.g.* **13**), but instead of losing a proton this now adds a nucleophile.



(8) (9) (10) (11)



(12) (13) (14) (15)

(16) (17)

The Kekulé resonance of the benzene ring is impaired in the 3,4-benzo derivatives (**16**), and these compounds are unstable and usually react by overall addition. 2,3-Benzo derivatives (**17**) have appreciable resonance energies and usually 'revert to type'.

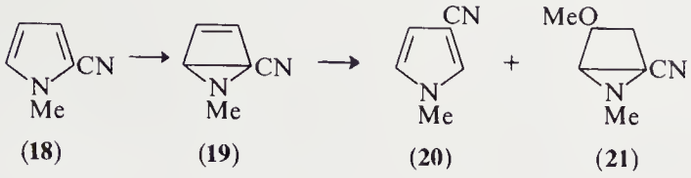
3.3.1.2 Thermal and Photochemical Reactions Involving No Other Species

Photochemical scrambling of ring atoms can involve a 'ring-walk' or a cyclopropene mechanism.

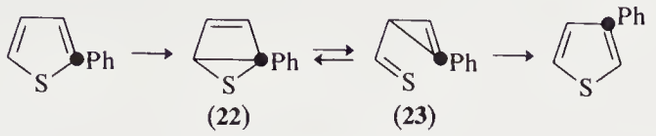
2-Cyanopyrrole undergoes photochemical rearrangement to 3-cyanopyrrole. Analogous rearrangement of *N*-methyl-2-cyanopyrrole (**18**) in methanol gives in addition to the 3-cyanopyrrole (**20**) the bicyclic intermediate (**19**) trapped as the methanol adduct (**21**) ⟨78CC131⟩.

The light-induced rearrangement of 2-phenyl- to 3-phenyl-thiophene may involve an equilibrium between the bicyclic intermediate (**22**) and the cyclopropenylthioaldehyde (**23**) (Scheme 1). The formation of *N*-substituted pyrroles on irradiation of either furans or thiophenes in the presence of a primary amine supports this suggestion (Scheme 2).

Pyrrole, furan and thiophene rings are thermally very stable.

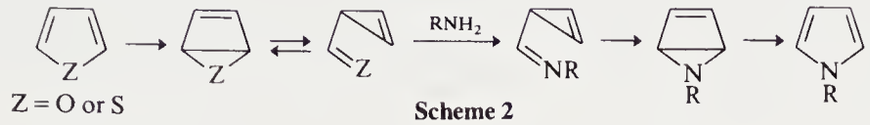


(18) (19) (20) (21)



(22) (23)

Scheme 1



Z = O or S

Scheme 2

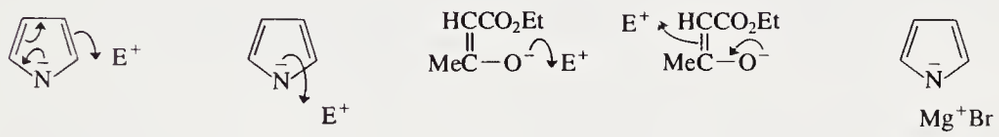
3.3.1.3. Electrophilic Attack on Ring Heteroatoms

Reactions of this type are rare for reasons discussed in Section 3.3.1.4. No examples are known of electrophilic attack at the furan oxygen atom.

Neutral pyrroles also are not susceptible to attack at the cyclic nitrogen, but pyrrole anions undergo easy reaction. Increasing tendency to electrophilic attack at the ring heteroatom is shown in thiophenes, selenophenes and tellurophenes.

3.3.1.3.1 Pyrrole anions

As discussed in Section 3.3.1.6.1, pyrroles are weak acids. The resulting ion reacts exceedingly readily, even with weak electrophilic reagents at either carbon (**24**) or nitrogen (**25**); this behavior is similar to that of the ambident anion from acetoacetic ester which shows alternative reactions (**26**, **27**).



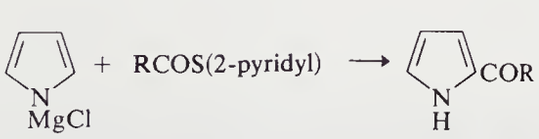
(24) (25) (26) (27) (28)

(i) Pyrrole Grignard reagents

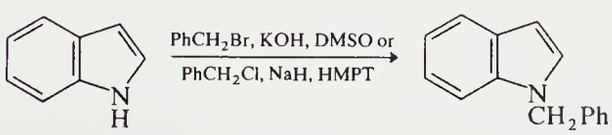
Pyrroles and indoles with Grignard reagents give hydrocarbons and new, largely ionic Grignard reagents derived from the pyrrole or indole (*e.g.* **28**). Pyrrolyl- and indolyl-magnesium halides undergo many of the normal Grignard reactions to give 1- or 2-substituted pyrroles (*cf.* **24**, **25**) or 1- or 3-substituted indoles (*cf.* the discussion in Section 3.3.1.4.2). Mixtures of the *N*- and *C*-substituted products are often formed, the proportions of which are frequently altered by changing the solvent, temperature or reagent.

A classical method for preparing *C*-acylated pyrroles involves the acylation of pyrrylmagnesium bromide. In general, tightly coordinated *N*-pyrryl and indolyl salts, exemplified by their Grignard derivatives, undergo preferential *C*-acylation and *C*-alkylation (Scheme 3) ⟨81TL4647⟩.

Ketones and esters usually react further with Grignard reagents; however, both ketones and esters of type (**29**) and pyrrolyl Grignard reagents are stabilized by mesomerism, and are therefore less reactive.



Scheme 3 (**29**)



Scheme 4

(ii) Further pyrrole anion intermediates

Pyrroles can be converted into alkali metal salts (with $NaNH_2/NH_3$ or K/toluene). The use of pyrrolyl or indolyl sodium or potassium salts under ionizing conditions favors the formation of *N*- acyl or *N*-alkyl derivatives (Scheme 4) ⟨74OS(54)58, 74OS(54)60⟩.

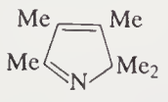
In addition to Grignard reactions and those occurring through complete transformation into alkali metal salts, there are reactions which take place under conditions of only partial conversion into anions. In some cases, 1-substituted compounds are formed, *e.g.* pyrrole is benzoylated in the presence of $NaOH–H_2O$ to yield 1-benzoylpyrrole.

More often, 2-substituted pyrroles and 3-substituted indoles result; the following exemplify reactions of this type:

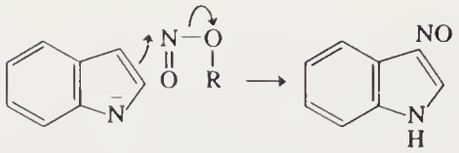
(a) Boiling aqueous potassium carbonate converts pyrrole into its 2-carboxylic acid; the anion reacts with carbon dioxide as in (**24**).

(b) 1,2,3,4-Tetramethylpyrrole with MgO–MeI gives pentamethylpyrrolenine (**30**).

(c) Alkyl nitrites or nitrates with sodium ethoxide convert indole into 3-nitroso- (*e.g.* **31**→**32**) or 3-nitro-indoles, respectively.



(**30**)



(**31**) (**32**)

A mild and effective method for obtaining *N*-acyl- and *N*-alkyl-pyrroles and -indoles is to carry out these reactions under phase-transfer conditions ⟨80JOC3172⟩. For example, *N*-benzenesulfonylpyrrole is best prepared from pyrrole under phase-transfer conditions rather than by intermediate generation of the potassium salt ⟨81TL4901⟩. In this case the softer nature of the tetraalkylammonium cation facilitates reaction on nitrogen. The thallium salts of indoles prepared by reaction with thallium(I) ethoxide, a benzene-soluble liquid, also undergo *N*-alkylation and *N*-acylation ⟨81S389⟩.

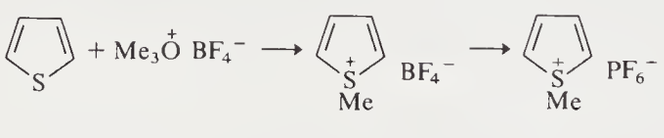
N-Chlorination of pyrrole occurs when a solution of pyrrole in carbon tetrachloride is stirred at 0 °C with an aqueous solution of sodium hypochlorite.

Pyrrolenines are formed by the alkylation of the Grignard derivatives of polyalkylated pyrroles. Alkylation occurs at positions 2 and 3, although the former predominates.

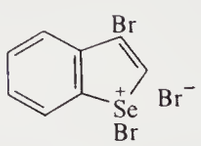
3.3.1.3.2 Thiophenes, selenophenes and tellurophenes

(i) Alkylation and halogenation

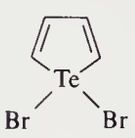
Alkylating agents capable of forming thiophenium salts include trimethyloxonium tetrafluoroborate ($Me_3O^+BF_4^-$) and alkyl fluorosulfonates ($ROSO_2F$). The salts (*e.g.* **33**) are conveniently isolated as hexafluorophosphates (**34**).



(**33**) (**34**)



(**35**)



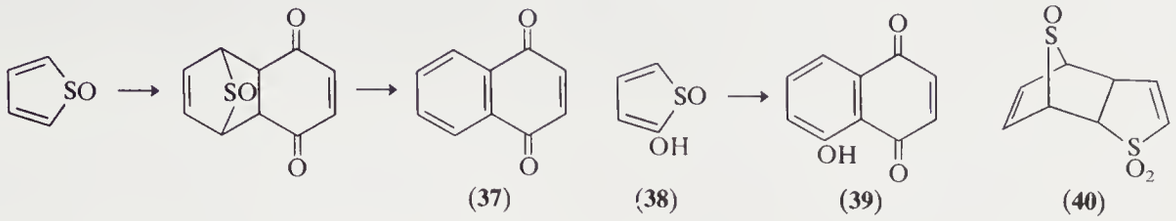
(**36**)

Halogens attack the ring heteroatom in selenophene and tellurophene. Thus the selenienyl bromide (**35**) is among the bromination products of benzo[*b*]selenophene. Tellurophene reacts with halogens to give 1,1-dihalo derivatives (*e.g.* **36**).

(ii) Oxidation

Oxidation of thiophene with peracid under carefully controlled conditions gives a mixture of thiophene sulfoxide and 2-hydroxythiophene sulfoxide (**38**). These compounds are trapped by

addition to benzoquinone to give ultimately naphthoquinone (**37**) and its 5-hydroxy derivative (**39**) ⟨76ACS(B)353⟩. Diels–Alder reaction also gives (**40**).



(**37**) (**38**) (**39**) (**40**)

Stable sulfones have been obtained from oxidation of 2,5-dimethylthiophene and benzo-[*b*]thiophene. Singlet oxygen oxidation of 2,5-dimethylthiophene results in the formation of a cyclic peroxide which subsequently ring opens. Very vigorous oxidation of the thiophene ring results in breakdown to maleic and oxalic acids and ring sulfur is oxidized to sulfuric acid.

3.3.1.4 Electrophilic Attack on Carbon: General Considerations

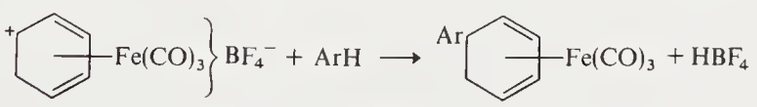
3.3.1.4.1 Relative reactivities of heterocycles

Electrophilic substitution is much easier than in benzene, and thiophene reacts about as readily as mesitylene; pyrrole and furan react as readily as phenol or even resorcinol.

The reactivity of five-membered rings with one heteroatom to electrophilic reagents has been quantitatively compared. Table 1 shows that the rates of substitution for (a) formylation by phosgene and *N,N*-dimethylformamide, (b) acetylation by acetic anhydride and tin(IV) chloride, and (c) trifluoroacetylation with trifluoroacetic anhydride ⟨71AHC(13)235⟩ are all in the sequence furan > tellurophene > selenophene > thiophene. Pyrrole is still more reactive as shown by the rate for trifluoroacetylation, by the relative rates of bromination of the 2-methoxycarbonyl derivatives (pyrrole > furan > selenophene > thiophene), and by the rate data on the reaction of the iron tricarbonyl-complexed carbocation $[C_6H_7Fe(CO)_3]^+$ (Scheme 5) (2-methylindole ≃ *N*-methylindole > indole > pyrrole > furan > thiophene ⟨73CC540⟩).

Table 1 Relative Rates of Reaction of Thiophene, Selenophene, Tellurophene and Furan in Selected Electrophilic Substitution Reactions

	Acetylation (25 °C)	*Trifluoroacetylation (75 °C)*	*Formylation (30 °C)*
Thiophene	1	1	1
Selenophene	2.28	7.33	3.64
Tellurophene	7.75	46.4	36.8
Furan	11.9	140.0	107.0



(**41**) **Scheme 5**

The electrophilic substitution of thiophene is much easier than that of benzene; thus, thiophene is protonated in aqueous sulfuric acid about 10^3 times more rapidly than benzene, and it is brominated by molecular bromine in acetic acid about 10^9 times more rapidly than benzene. Benzene in turn is between 10^3 and 10^7 times more reactive than an uncharged pyridine ring to electrophilic substitution.

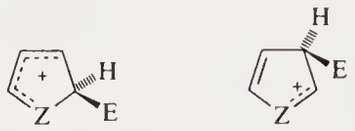
The effect of substituents on the reactivity of heterocyclic nuclei is broadly similar to that on benzene. Thus *meta*-directing groups such as methoxycarbonyl and nitro are deactivating. The effects of strongly activating groups such as amino and hydroxy are difficult to assess since simple amino compounds are unstable and hydroxy compounds exist in an alternative tautomeric form. Comparison of the rates of formylation and trifluoroacetylation of the parent heterocycle and its 2-

methyl derivative indicates the following order of sensitivity to substituent effects: furan > tellurophene > selenophene ≈ thiophene ⟨77AHC(21)119⟩.

The effect on electrophilic substitution reactions of the fusion of a benzene ring to the '*b*' face of a furan or thiophene ring is to decrease reactivity; this decrease is much more pronounced in the case of fusion to a furan than to a thiophene ring. As a consequence the overall reactivities of benzo[*b*]furan and benzo[*b*]thiophene are approximately equal ⟨71AHC(13)235⟩.

3.3.1.4.2 Directing effects of the ring heteroatom

Monocyclic five-membered heteroaromatics with one heteroatom all undergo preferential α rather than β electrophilic substitution. This is rationalized in terms of the more effective delocalization of charge in the intermediate (**42**) leading to α substitution than in the intermediate (**43**) leading to β substitution.



(**42**) (**43**)

Z = NH, O, S, Se or Te

However, these considerations apply to reactions in solution. In the dilute gas phase, where the intrinsic orientating properties of pyrrole can be examined without the complication of variable phenomena such as solvation, ion-pairing and catalyst attendant on electrophilic substitution reactions in solution, preferential β-attack on pyrrole occurs. In gas phase *t*-butylation, the relative order of reactivity at β-carbon, α-carbon and nitrogen is 10.3:3.0:1.0 ⟨81CC1177⟩.

The α directing effect of the heteroatom in furan ≫ thiophene ≈ selenophene ≫ pyrrole. The α-directing effect in tellurophene is also pronounced ⟨77AHC(21)119⟩.

Possible reasons for the high regioselectivity of furan in electrophilic substitution reactions include complex formation between substrates and reagents and the ability of heteroatoms to assist in the stabilization of cationic intermediates ⟨80CHE1195⟩.

The observed ratio of α- to β-substitution products may also be influenced by reaction temperature. For example, in the acylation of thiophene a higher proportion of β-substituted product is obtained by reaction at higher temperatures ⟨71AHC(13)235⟩. The isolated product ratios may reflect thermodynamic rather than kinetic control because of acid-catalyzed rearrangements. 2- or 3-Substituted pyrroles undergo acid-mediated rearrangement, in some cases under extremely mild conditions. Migration of bromo, chloro, acyl, sulfinyl, sulfonyl and sulfenyl groups have all been observed ⟨82JOC3668⟩. Acid-mediated rearrangements have also been documented in the thiophene series.

3.3.1.4.3 Directing effects of substituents in monocyclic compounds

Large 1-alkyl substituents increase β-substitution in the Vilsmeier formylation of pyrroles ⟨70JCS(C)2573⟩. A similar trend occurs in trifluoroacetylation of *N*-alkylpyrroles ⟨80JCR(S)42⟩. The trifluoroacetylation, formylation and bromination of 1-tritylpyrrole occur regioselectively at the 3-position in high yield ⟨83JCS(P1)93⟩.

Electron donor 2-substituents orient substitution in furan, thiophene and selenophene into the 5-position. In pyrrole, although the ratio of α to β reactivity is much smaller than in the other five-membered rings, 5-substituted 2-alkylpyrroles still appear to be the major products.

Electron donor 3-substituents supplement the α-directing effect of the heteroatom and direct the incoming substituent into the 2-position. However, steric effects can result in an increased proportion of 5-substitution.

For pyrroles with electron acceptor substituents in the 1-position electrophilic substitution with soft electrophiles can be frontier orbital controlled and occur at the 2-position, whereas electrophilic substitution with hard electrophiles can be charge controlled and occur at the 3-position.

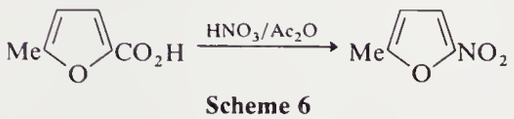
Nitration and Friedel–Crafts acylation of 1-benzenesulfonylpyrrole occur at the 3-position, whereas the softer electrophiles generated in the Mannich reaction ($R_2\overset{+}{N}=CH_2$), in formylation under Vilsmeier conditions ($R_2\overset{+}{N}=CHCl$), or in formylation with dichloromethyl methyl ether and aluminum chloride ($MeO\overset{+}{=}CHCl$) effect substitution mainly in the 2-position ⟨81TL4899. 81TL4901⟩.

For electron acceptor substituents such as NO_2, CN and COR in the 2-position, position 4 is least deactivated by the substituent, but position 5 is most activated by the ring heteroatoms. In fact, such 2-substituted furans give exclusively 5-substitution, whereas for analogous thiophenes and especially pyrroles increasing amounts of 4-substitution occur. The harder the electrophile, the greater the tendency to 4-substitution.

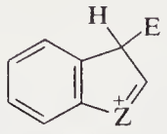
Formylation of 2-methoxycarbonyl-1-methylpyrrole with dichloromethyl methyl ether and aluminum chloride occurs in the 4-position, while under Vilsmeier conditions the main product is the 5-formyl derivative ⟨78JOC4849⟩.

With electron-withdrawing substituents in the 3-position mutually reinforcing directing effects combine to direct substitution into the 5-position.

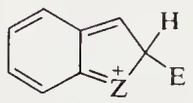
Electrophilic substitution of 2,5-disubstituted compounds normally occurs at that β-position expected from normal rules, but in some cases displacement of an α substituent such as carboxyl, acyl or halogen takes place (Scheme 6)



Scheme 6



(44)



(45)

3.3.1.4.4 Directing effects of fused benzene rings

A [*b*]-fused benzene ring would be expected to favor β-substitution in the heterocyclic ring (**44**) over α-substitution (**45**) based on the expected σ-complex stability.

In fact, benzo[*b*]furan undergoes mainly α-substitution, benzo[*b*]thiophene undergoes mainly β-substitution and indole undergoes almost exclusive β-substitution. This again illustrates the very strong directing effect of the oxygen atom to the α-position.

3.3.1.4.5 Range of substitution reactions

The range of preparatively useful electrophilic substitution reactions is often limited by the acid sensitivity of the substrates. Whereas thiophene can be successfully sulfonated in 95% sulfuric acid at room temperature, such strongly acidic conditions cannot be used for the sulfonation of furan or pyrrole. Attempts to nitrate thiophene, furan or pyrrole under conditions used to nitrate benzene and its derivatives invariably result in failure. In the case of sulfonation and nitration milder reagents can be employed, *i.e.* the pyridine–sulfur trioxide complex and acetyl nitrate, respectively. Attempts to carry out the Friedel–Crafts alkylation of furan are often unsuccessful because the catalysts required cause polymerization.

The higher relative rate of reaction of pyrrole with electophilic reagents, compared with the other five-membered rings with one heteroatom, is paralleled by the greater range of reactions it undergoes. Thus pyrrole, unlike furan and thiophene, can be *C*-nitrosated and can undergo diazo coupling reactions. In a similar fashion, *N,N*-dimethylaniline and enamines show enhanced reactivity over anisole and enol ethers, respectively.

The benzo[*b*] heterocycles are generally less reactive than their monocyclic counterparts. Thus benzo[*b*]thiophene unlike thiophene does not undergo Vilsmeier formylation or the Mannich reaction.

3.3.1.5 Electrophilic Attack on Carbon: Specific Reactions

3.3.1.5.1 Proton acids

The σ-complexes formed by proton addition to a carbon atom can sometimes be isolated to give, for example, pyrrole salts. Reversal by proton loss leads to acid-catalyzed hydrogen exchange of

the ring hydrogen atoms. The σ-complex can undergo rearrangement before proton loss. The σ-complex can itself react as an electrophile, with other molecules of heterocycle, leading to oligomerization or polymerization, or with other nucleophiles; such reactions are discussed in Section 3.3.1.6.3.

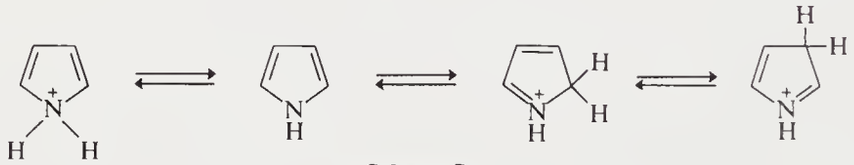
(i) Base strengths

The pK_a values of pyrroles and benzopyrroles are given in Table 2. These basicities are lower than those of enamines in consequence of the loss of aromaticity which accompanies protonation on the ring nitrogen or on carbon 2 or carbon 3 of the ring.

Table 2 pK_a Values of Some Pyrroles and Benzopyrroles

Compound	pK_a	*Position of protonation*	*Ref.*
Pyrrole	−3.8	2	63JA2763
1-methyl	−2.9	2	63JA2763
2-methyl	−0.2	2	63JA2763
3-methyl	−1.0	2	63JA2763
Indole	−3.6	3	64JA3796
1-methyl	−2.3	3	64JA3796
2-methyl	−0.3	3	64JA3796
3-methyl	−4.6	3	64JA3796
Isoindole		1	
2,5-dimethyl-1,3-diphenyl	+2.05	1 or 3	76T1767
Indolizine	+3.9	3	76T1767
Carbazole	−6.0	9	76T1767

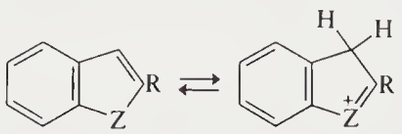
The pK_a for protonation of pyrrole at C-2 to thermodynamically stable 2*H*-pyrrolium ion is − 3.8; the corresponding pK_a values for protonation at C-3 and at nitrogen are − 5.9 and *ca.* − 10 (Scheme 7).



Scheme 7

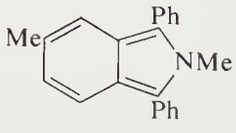
For pyrrole, furan and thiophene the pK_a values of their 2,5-di-*t*-butyl derivatives are − 1.01 − 10.01 and − 10.16, respectively. In each case protonation occurs at position 2. The base-strengthening effect of alkyl substitution is clearly apparent by comparison of pyrrole and its alkyl derivatives, *e.g.* *N*-methylpyrrole has a pK_a for α-protonation of − 2.9 and 2,3,4,5-tetramethylpyrrole has a pK_a of +3.7. In general, protonation of α-alkylpyrroles occurs at the α′-position whereas β-alkylpyrroles are protonated at the adjacent α-position. As expected, electron-withdrawing groups are base-weakening; thus *N*-phenylpyrrole is reported to have a pK_a of − 5.8.

The pK_a for the protonation of indole at position 3 is − 3.6 and the pK_a values of 2-methylindole, 2-methylbenzo[*b*]furan and 2-methylbenzo[*b*]thiophene for β-protonation are −0.3, − 13.3 and − 10.4, respectively (Scheme 8).



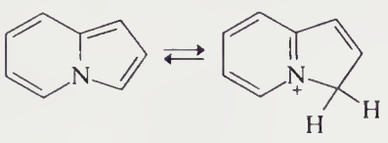
Z = NH, O or S

Scheme 8

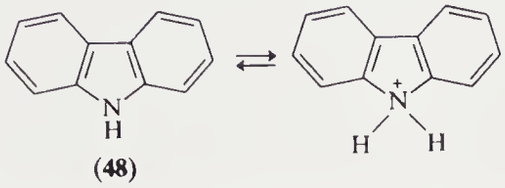


(46)

Isoindoles are more basic than indoles or pyrroles. For example, 2,5-dimethyl-1,3-diphenylisoindole (**46**) has a pK_a of +2.05; protonation of isoindoles occurs at positions 1 or 3. The pK_a for protonation of indolizine (**47**) at position 3 is +3.94 and that for carbazole (**48**) for protonation on nitrogen is estimated as −6.0.



(**47**)



(**48**)

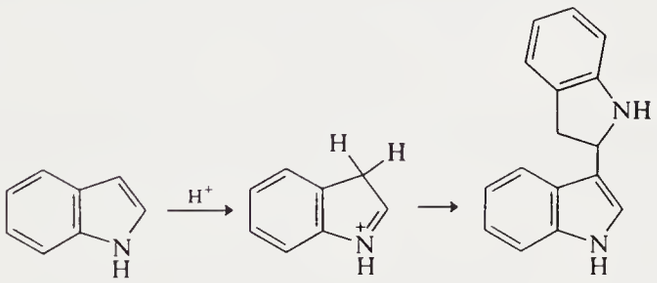
Stable α-protonated pyrrolium salts have been obtained by treating di- and tri-*t*-butylpyrroles with tetrafluoroboric acid ⟨81LA789⟩ and stable α-protonated thiophenium salts result from the reaction of thiophenes with hydrogen chloride and aluminum trichloride in an inert solvent (*e.g.* methylene chloride) ⟨75ZOR424⟩.

(ii) Acid-catalyzed hydrogen exchange

The ring hydrogen atoms of pyrrole, furan and thiophene exchange in acid. Relative rates are in the order 2-pyrrole > 3-pyrrole > 2-thiophene > 3-thiophene ≈ 2-furan. No exchange of the 3-position in furan could be found; ring-opening intervened. For pyrrole the exchange rate is *ca.* 10^{15} times that for benzene.

The 1-position protons of pyrroles exchange in neutral solution, presumably *via* the anion (see Section 3.3.1.3.1).

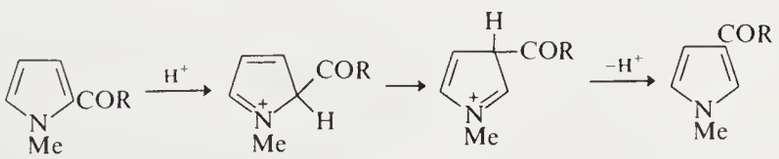
Indolizine gives a stable pyridinium ion and does not polymerize in the presence of acid. Indole undergoes acid-catalyzed dimerization; the 3*H*-indolium ion acts as an electrophile and attacks an unprotonated molecule to give the dimer (**49**). Protonation of the dimer in turn gives an electrophilic species from which a trimeric product can be derived ⟨77CPB3122⟩. *N*-Methylisoindole undergoes acid-catalyzed polymerization, indicating that protonation at C-1 gives a reactive electrophilic intermediate.



(**49**)

(iii) Rearrangement

The acid-catalyzed rearrangements of substituted pyrroles and thiophenes consequent on *ipso* protonation have been referred to previously (Section 3.3.1.4.2). There is some evidence that these rearrangements are intramolecular in nature since in the case of acid-induced rearrangement of 2-acylpyrroles to 3-acylpyrroles no intermolecular acylation of suitable substrates could be demonstrated (Scheme 9) ⟨81JOC839⟩.

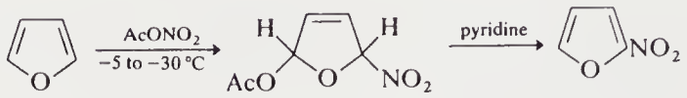


Scheme 9

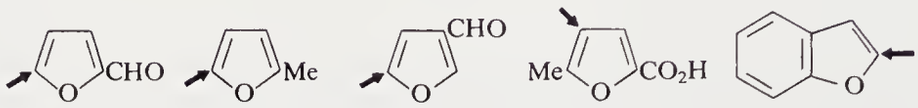
3.3.1.5.2 Nitration

The acid sensitivity of pyrrole dictates the use of acetyl nitrate as nitrating agent; the main product is the 2-nitro derivative together with some of the 3-nitro compound. The nitration of *N*-substituted pyrroles yields relatively more β-substituted product, and with electron-withdrawing groups such as acetyl or ethoxycarbonyl in the 2-position comparable amounts of 4- and 5-nitro derivatives are obtained. 3-Nitropyrrole is efficiently prepared by nitration of 1-benzenesulfonylpyrrole followed by hydrolysis of the blocking group ⟨81TL4899⟩.

Furan and acetyl nitrate give an addition product which is converted by pyridine into 2-nitrofuran (Scheme 10). The positions in which substituted furans undergo nitration with acetyl nitrate are shown in diagrams (**50**)–(**54**) and illustrate the rules of orientation.



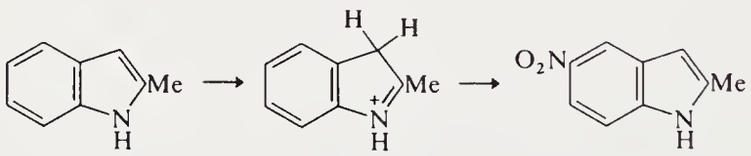
Scheme 10



(**50**) (**51**) (**52**) (**53**) (**54**)

Thiophene is nitrated by mild nitrating agents such as acetyl or benzoyl nitrate, mainly in the 2-position. The α selectivity decreases with increasing vigor of the reagent and up to 15% of the 3-isomer has been obtained. 2-Cyanothiophene is nitrated predominantly at position 4.

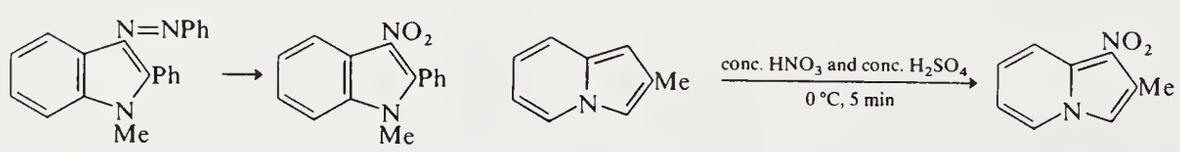
Indole with benzoyl nitrate at low temperatures gives 3-nitroindole. More vigorous conditions can be used for the nitration of 2-methylindole because of its resistance to acid-catalyzed polymerization. In nitric acid alone it is converted into the 3-nitro derivative, but in a mixture of concentrated nitric and sulfuric acids 2-methyl-5-nitroindole (**55**) is formed, by conjugate acid nitration. 3,3-Dialkyl-3*H*-indolium salts similarly nitrate at the 5-position.



(**55**)

There are examples of *ipso* attack during the nitration of pyrroles, furans and thiophenes and in the corresponding benzo-fused systems. Reactions resulting in nitro-dealkylation, nitro-deacylation, nitro-decarboxylation and nitro-dehalogenation are to be found in the monograph reactivity chapters of CHEC. Treatment of the 3-azophenylindole (**56**) with nitric acid in acetic acid at room temperature gives 80% of the 3-nitroindole (**57**) ⟨81JCS(P2)628⟩.

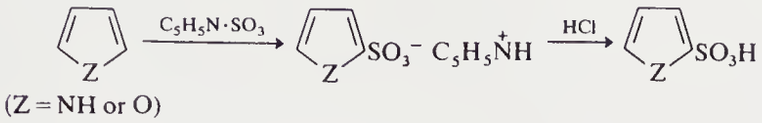
Nitration of benzo[*b*]thiophene (HNO_3/AcOH) yields mainly the 3-nitro derivative. Under these conditions the β to α ratio of substitution is approximately 5 : 1, which is significantly less than for indole itself which undergoes almost exclusive β substitution. Indolizines are readily nitrated, *e.g.* brief treatment of 2-methylindolizine with a mixture of concentrated nitric and sulfuric acids gives 2-methyl-1-nitroindolizine (**58**).



(**56**) (**57**) (**58**)

3.3.1.5.3 Sulfonation

Both pyrrole and furan can be sulfonated in the 2-position by treatment with the pyridine–sulfur trioxide complex (Scheme 11). Furan can be further sulfonated by this reagent to give the 2,5-disulfonate.



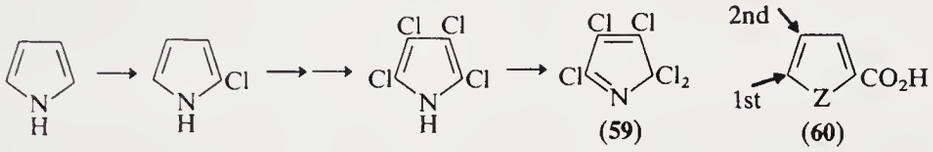
Scheme 11

Thiophene, which is more stable to acid, is readily sulfonated by shaking with concentrated sulfuric acid at room temperature. Benzene is not reactive under these conditions and this is the basis for the purification of benzene from thiophene contamination. With all three heterocycles, if the α-positions are blocked, then sulfonation occurs at the β-position.

Indole is sulfonated under similar conditions to pyrrole; the 3-sulfonic acid is formed. Benzo-[*b*]thiophene is also sulfonated in the 3-position ⟨71AHC(13)235⟩.

3.3.1.5.4 Halogenation

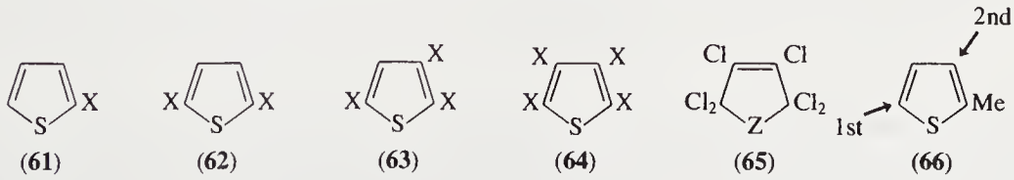
Pyrrole is readily halogenated. Chlorination with one mole of sulfuryl chloride in ether at 0 °C gives 2-chloropyrrole; further chlorination with this reagent yields di-, tri- and tetra-chloro derivatives and ultimately pentachloropyrrolenine (**59**) ⟨62JOC2585⟩.



Treatment of pyrrole, 1-methyl-, 1-benzyl- and 1-phenyl-pyrrole with one mole of *N*-bromosuccinimide in THF results in the regiospecific formation of 2-bromopyrroles. Chlorination with *N*-chlorosuccinimide is less selective ⟨81JOC2221⟩. Pyrrole with bromine in acetic acid gives 2,3,4,5-tetrabromopyrrole and iodine in aqueous potassium iodide yields the corresponding tetraiodo compound.

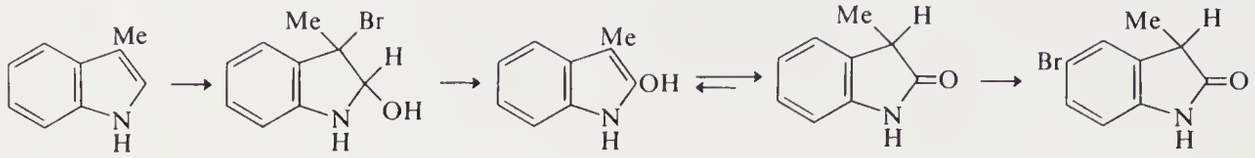
Furan reacts vigorously with chlorine and bromine at room temperature to give polyhalogenated products. Low temperature (−40 °C) reaction of furan with chlorine in dichloromethane yields mainly 2-chlorofuran and reaction of furan with dioxane dibromide at 0 °C affords 2-bromofuran in good yield. Furans stabilized by electron-withdrawing groups are halogenated more smoothly; thus, 2-furoic acid is brominated to form successively the 5-monobromo and 4,5-dibromo derivatives (*cf.* **60**; Z = O). 2-Iodofuran is obtained by treatment of 2-furoic acid with iodine and potassium iodide in aqueous sodium hydroxide.

Chlorine and bromine react with thiophene to give successively the halogenation products shown (**61**–**64**). The bromination can be interrupted at the intermediate stages; monochloro and dichloro derivatives have been obtained preparatively by chlorination with MeCONHCl. Addition products are also formed during chlorination; prolonged action (with Cl_2–I_2) gives the dihydrothiophene derivative (**65**; Z = S). Iodination (I_2–HgO) results in mono- and di-iodothiophenes (**61**) and (**62**) only. Substituted compounds are halogenated as expected, *e.g.* (**66**).



3-Chloroindole has been prepared from indole and sulfuryl chloride ⟨66JOC2627⟩ and 3-bromo- and 3-iodo-indole have been obtained by direct halogenation in DMF ⟨82S1096⟩. 2-Methylindole

reacts with sodium hypochlorite in carbon tetrachloride to give a 2:1 mixture of 1,3- and 3,3-dichloro derivatives ⟨81JOC2054⟩. 3-Substituted indoles are halogenated to yield 3-haloindolenium ions which react in a variety of ways, as illustrated by the reaction of 3-methylindole with NBS in aqueous acetic acid (Scheme 12).



Scheme 12

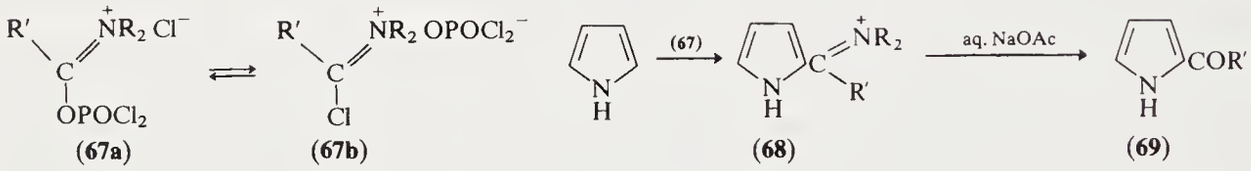
Halogens react with benzo[*b*]furan by an addition–elimination mechanism to give 2- and 3-substituted products ⟨76JCS(P2)266⟩. Treatment of benzo[*b*]thiophene with chlorine or bromine in acetic acid gives predominantly 3-substituted products ⟨71JCS(B)79⟩. 2,2,3,3,4,5,6,7-Octachloro-2,3-dihydrobenzothiophene is obtained when benzo[*b*]thiophene is treated with chlorine in the presence of 1 mole of iodine ⟨80JOC2151⟩.

3.3.1.5.5 Acylation

(i) Pyrroles

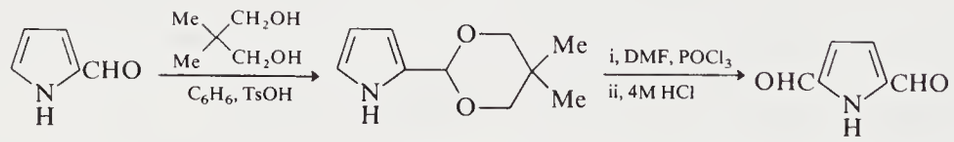
Pyrrole and alkylpyrroles are acylated by acid anhydrides above 100 °C. Pyrrole itself gives a mixture of 2-acetyl- and 2,5-diacetyl-pyrrole on heating with acetic anhydride at 150–200 °C. *N*-Acylpyrroles are obtained by reaction of the alkali metal salts of pyrrole with an acyl halide. *N*-Acetylimidazole efficiently acetylates pyrrole on nitrogen ⟨65CI(L)1426⟩. Pyrrole-2-carbaldehyde is acetylated on nitrogen in 80% yield by reaction with acetic anhydride in methylene chloride and in the presence of triethylamine and 4-dimethylaminopyridine ⟨80CB2036⟩.

The most useful general method for the *C*-acylation of pyrroles is the Vilsmeier–Haack procedure with the phosphoryl chloride complex (**67a, b**) of an *N,N*-dialkylamide. The intermediate imine salt (**68**) is hydrolyzed subsequently under mildly alkaline conditions to give the acylated pyrrole (**69**). On treatment of the imminium salt (**68**; R′ = H) with hydroxylamine hydrochloride and one equivalent of pyridine and heating in DMF, 2-cyanopyrrole is formed ⟨80CJC409⟩.



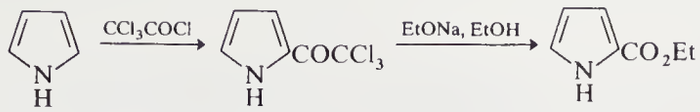
(67a) **(67b)** **(68)** **(69)**

No significant amounts of diacylated products are obtained under Vilsmeier–Haack conditions; an indirect method for preparing pyrrole-2,5-dicarbaldehydes is outlined in Scheme 13 ⟨78S295, 82CJC383⟩.



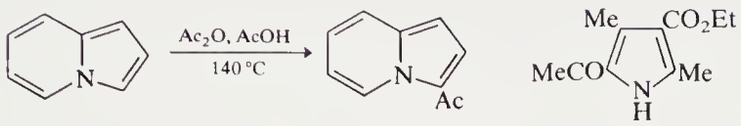
Scheme 13

3-Aroyl- and 3-acetyl-pyrroles can be obtained by Friedel–Crafts acylation of 1-benzenesulfonylpyrrole followed by removal of the blocking group by mild alkaline hydrolysis ⟨81TL4899, 81TL4901⟩. However, using dichloromethyl methyl ether as the acylating agent, substitution occurs at the 2-position to give 2-formyl-1-benzenesulfonylpyrrole, exclusively. 2-Trichloroacetylpyrrole, formed on treating pyrrole with trichloroacetyl chloride, is readily transformed into 2-ethoxycarbonylpyrrole (**70**) ⟨71OS(51)100⟩.



(70)

Indole with acetic anhydride at 140 °C gives 1,3-diacetylindole by way of the 3-acetyl compound. In the presence of sodium acetate, acetic anhydride gives exclusively 1-acetylindole. The Vilsmeier–Haack reaction is an efficient route to 3-acylindoles. The usual difference in orientation of substitution is observed in the acetylation ($Ac_2O/SnCl_4$/dichloroethane) of benzo[*b*]furan and benzo[*b*]thiophene. Thus the oxygen heterocycle yields mainly the 2-acetyl derivative and the sulfur heterocycle yields mainly the 3-acetyl derivative ⟨71AHC(13)235⟩. 1-Phenylisoindole readily undergoes acetylation to give a 3-acetyl derivative (Ac_2O/pyridine, room temperature) and indolizine gives a 3-acetyl derivative (**71**) on heating with acetic anhydride and acetic acid; it also undergoes Vilsmeier–Haack formylation.



(71) **(72)**

(ii) Furans

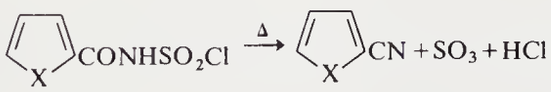
Furan can also be acylated by the Vilsmeier–Haack method or with acid anhydrides and acyl halides in the presence of Friedel–Crafts catalysts ($BF_3 \cdot Et_2O$, $SnCl_4$ or H_3PO_4). Reactive anhydrides such as trifluoroacetic anhydride, however, require no catalyst. Acetylation with acetyl *p*-toluenesulfonate gives high yields.

Pyrroles and furans also undergo the Gattermann aldehyde synthesis: with HCl and HCN, furan gives furfuraldehyde and 2-methylindole gives 2-methylindole-3-carboxaldehyde. The Houben–Hoesch ketone synthesis is also applicable to the preparation of acyl derivatives of furans and pyrroles, *e.g.* ethyl 2,4-dimethylpyrrole-3-carboxylate with MeCN and HCl yields (**72**).

(iii) Thiophenes

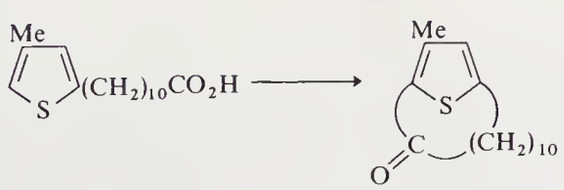
Thiophene is also readily 2-acylated under both Friedel–Crafts and Vilsmeier–Haack conditions. An almost quantitative conversion of thiophene into its 2-benzoyl derivative is obtained by reaction with 2-benzoyloxypyridine and trifluoroacetic acid ⟨80S139⟩

Acylation of either pyrrole or thiophene with chlorosulfonyl isocyanate gives a 2-substituted amide which fragments on heating to give the corresponding 2-cyano derivative (Scheme 14) ⟨81CJC2673, 70OS(50)52⟩. An alternative procedure for obtaining 2-cyanopyrrole and 3-cyanoindole involves treatment of the parent heterocycle with thiocyanogen and triphenylphosphine ⟨80JCS(P1)1132⟩.

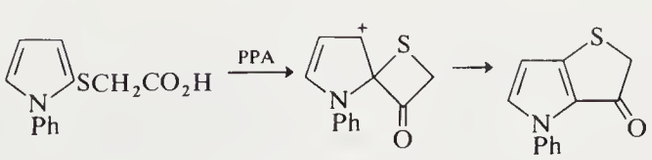


Scheme 14

A muscone synthesis involves selective intramolecular acylation at a vacant α-position (Scheme 15) ⟨80JOC1906⟩. In attempts to prepare 5,5-fused systems *via* intramolecular acylation reactions on to a β-position of a thiophene or a pyrrole, *ipso* substitution occurs in some cases with the result that rearranged products are formed (Scheme 16) ⟨82TH30200⟩.



Scheme 15



Scheme 16

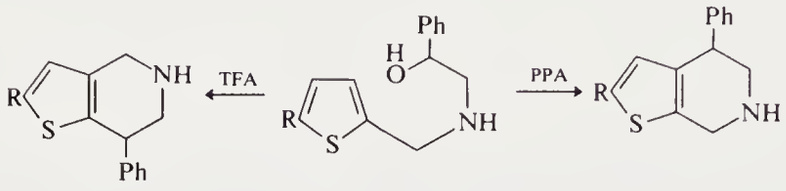
3.3.1.5.6 *Alkylation*

Pyrroles give polyalkylated products on reaction with methyl iodide at elevated temperatures and the more reactive allyl and benzyl halides under milder conditions in the presence of weak bases. Alkylation of pyrrole Grignard reagents gives mainly 2-alkylated pyrroles whereas *N*-alkylated pyrroles are obtained by alkylation of pyrrole alkali metal salts in ionizing solvents.

Alkylation of furan and thiophene has been effected with alkenes and catalysts such as phosphoric acid and boron trifluoride. In general, Friedel–Crafts alkylation of furans or thiophenes is not preparatively useful, partly because of polymerization by the catalyst and partly because of polyalkylation.

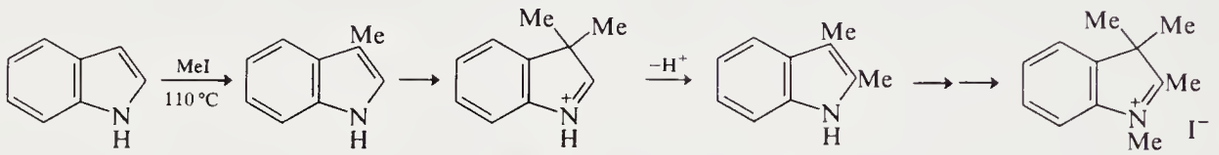
A successful procedure for the formation of 2,5-di-*t*-butylfuran involves reaction of the parent heterocycle with *t*-butyl chloride in the presence of iron(III) chloride and iron(III) oxide ⟨82CI(L)603⟩.

Ipso intramolecular alkylation to (**74**) occurs in the acid-promoted cyclization of the amino alcohols (**73**) with trifluoroacetic acid. Polyphosphoric acid gave the non-rearranged thienopyridine (**75**) ⟨82CC793⟩.



(**74**) (**73**) R = H or Me (**75**)

Reaction of indole with excess of methyl iodide at 110 °C gives a tetramethyl derivative (**78**). The intermediate 2,3-dimethylindole (**77**) is thought to arise by rearrangement of the 3,3-dimethyl-3*H*-indolium cation (**76**).



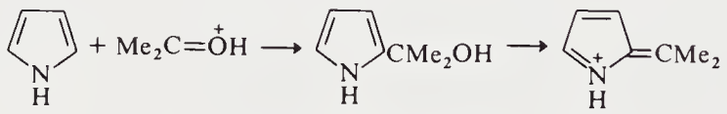
(**76**) (**77**) (**78**)

Pyrroles can be α-alkenylated by acetylenedicarboxylic ester, as discussed in Section 3.3.1.8.1.

3.3.1.5.7 *Reactions with aldehydes and ketones*

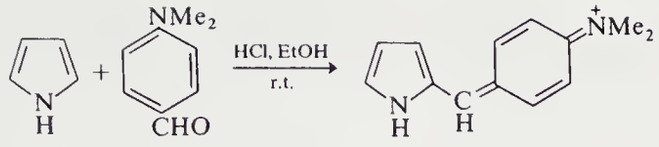
(i) Formation of carbinols or carbonium ions

Thiophenes, pyrroles and furans react with the conjugate acids of aldehydes and ketones to give carbinols (*e.g.* **79**) which cannot normally be isolated but which undergo proton-catalyzed loss of water to give reactive electrophiles (*e.g.* **80**).

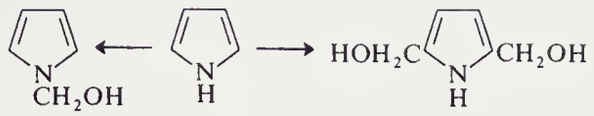


(**79**) (**80**)

By using an aromatic aldehyde carrying an electron-releasing group the intermediate cation can be stabilized. This is the basis of the widely used Ehrlich color reaction for pyrroles, indoles and furans which have a free reactive nuclear position (Scheme 17). As expected, pyrroles react preferentially in the α-position and indoles in the β-position, but if these positions are filled, reaction can occur at other sites.



Scheme 17

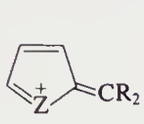


Scheme 18

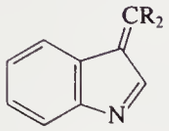
Pyrrole has been condensed under alkaline conditions with formaldehyde to give products of either *N*- or *C*-hydroxymethylation (Scheme 18).

(ii) Further reaction of carbonium ions

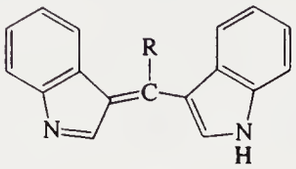
With *N*-unsubstituted pyrroles, ions of types (**81**; Z = NH) can lose a proton from the ring nitrogen, *e.g.* indole with Ph_2CO or PhCHO in HCl/EtOH gives products of type (**82**). Indole with HCO_2H or PhCOCl gives 'rosindoles' (**83**; R = H, Ph), involving the formation of ketones (*cf.* discussion in Section 3.3.1.5.5.i) and a subsequent reaction of this type with a second molecule of indole.



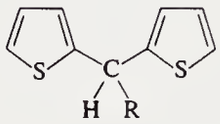
(**81**)



(**82**)

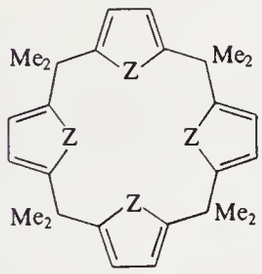


(**83**)

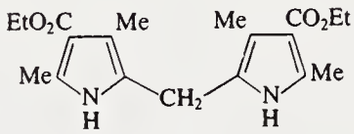


(**84**)

The ion (**81**), acting as an electrophilic reagent, can also attack another molecule of the heterocyclic compound. Thiophene with benzaldehyde or chloral gives the dinuclear product (**84**; R = Ph, CCl_3). Pyrrole and furan react with acetone to form tetranuclear derivatives of type (**85**; Z = NH, O). Pyrroles with a single free position react analogously to thiophene; *e.g.* two molecules of 3-ethoxycarbonyl-2,4-dimethylpyrrole with formaldehyde afford the dipyrromethane (**86**).

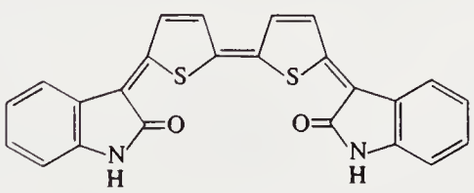


(**85**)

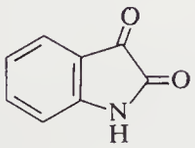


(**86**)

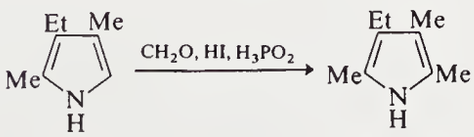
More rarely, ions of type (**81**) form dimeric products (possibly by initial loss of nuclear protons); thus, thiophenes with two free α-positions, or free adjacent α- and β-positions, give indophenines (*e.g.* **87**) with isatin (**88**). This reaction is used as a test for thiophene, the so-called 'indophenine test'.



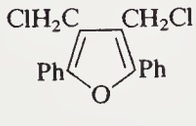
(**87**)



(**88**)



Scheme 19



(**89**)

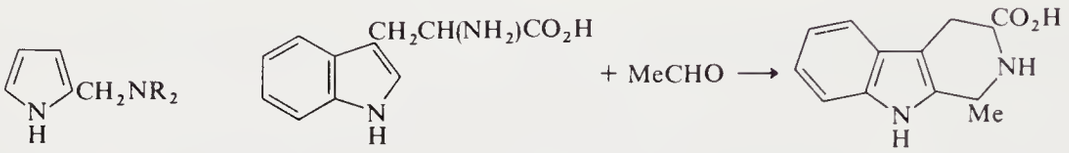
Although acid-catalyzed hydroxymethylation is not a practical possibility, by addition of a reducing agent to the reaction mixture overall reductive alkylation can be achieved (Scheme 19).

(iii) Chloromethylation

Thiophene and selenophene can be chloromethylated by treatment with formaldehyde and hydrochloric acid. Depending on the conditions, 2-chloromethyl or 2,5-bis(chloromethyl) derivatives are obtained. The chloromethylation of benzo[*b*]thiophene gives the 3-chloromethyl derivative and that of benzo[*b*]furan the 2-chloromethyl compound ⟨71AHC(13)235⟩. Furan is destroyed by this treatment, but 2,5-diphenylfuran, for example, gives the 3,4-bischloromethyl derivative (**89**).

(iv) Mannich reaction

Pyrrole is aminomethylated to give products of type (**90**). The intermediate immonium ion generated from formaldehyde, dimethylamine and acetic acid is not sufficiently reactive to aminomethylate furan, but it will form substitution products with alkylfurans. The Mannich reaction appears to be still more limited in its application to thiophene chemistry, although 2-aminomethylthiophene has been prepared by reaction of thiophene with formaldehyde and ammonium chloride. The use of *N,N*-dimethyl(methylene)ammonium chloride ($Me_2\overset{+}{N}{=}CH_2Cl^-$) has been recommended for the *N,N*-dimethylaminomethylation of thiophenes ⟨83S73⟩.

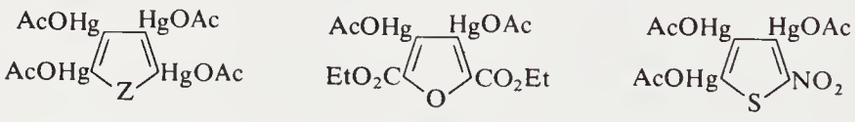


(**90**) (**91**)

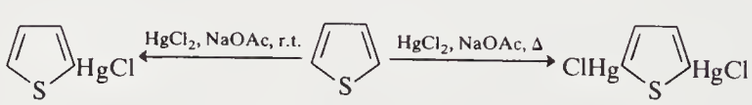
An important application of the Mannich reaction is in the synthesis of 3-dialkylaminoindoles. Intramolecular versions of this reaction are also possible, as illustrated by the formation of the β-carboline (**91**).

3.3.1.5.8 Mercuration

Mercury(II) acetate tends to mercurate all the free nuclear positions in pyrrole, furan and thiophene to give derivatives of type (**92**). The acetoxymercuration of thiophene proceeds *ca.* 10^5 times faster than that of benzene. Mercuration of rings with deactivating substituents such as ethoxycarbonyl and nitro is still possible with this reagent, as shown by the formation of compounds (**93**) and (**94**). Mercury(II) chloride is a milder mercurating agent, as illustrated by the chloromercuration of thiophene to give either the 2- or 2,5-disubstituted product (Scheme 20).



(**92**) Z = NH, O or S (**93**) (**94**)

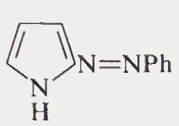


Scheme 20

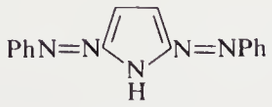
3.3.1.5.9 Diazo coupling

Diazo coupling occurs very readily between pyrroles and indoles and benzenediazonium salts. Reaction is much more rapid in alkaline solution when the species undergoing reaction is the *N*-deprotonated heterocycle. Depending on the conditions, pyrrole yields either 2-azo or 2,5-bis(azo) derivatives, *e.g.* (**95**) or (**96**), and indole gives a 3-substituted product (**97**).

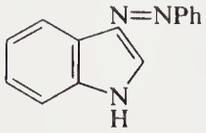
An α-demethylated product (**99**) is formed unexpectedly when the tetrasubstituted pyrrole (**98**) is reacted with *p*-nitrobenzenediazonium chloride ⟨82JOC1750⟩. *N*-*t*-Butylisoindole (**100**) couples with *p*-nitrobenzenediazonium fluoroborate to give the hydrazone (**101**) ⟨80AG(E)320⟩.



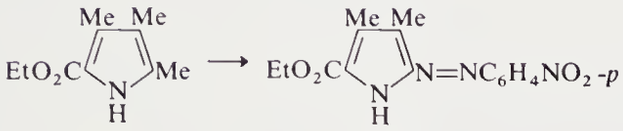
(**95**)



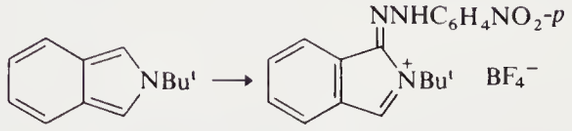
(**96**)



(**97**)

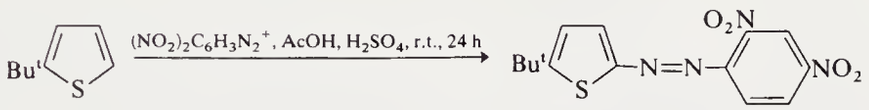


(**98**) (**99**)



(**100**) (**101**)

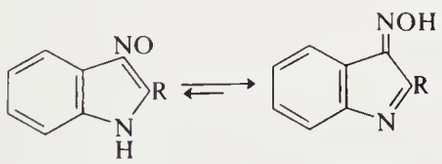
Furan undergoes phenylation rather than diazo coupling on reaction with benzenediazonium salts, and thiophene similarly yields 2- or 2,5-diaryl derivatives rather than coupled products (see Section 3.3.1.7.2). However, 2,5-dimethylfuran and 2-*t*-butylfuran give coupled products with 2,4-dinitrobenzenediazonium ion (Scheme 21).



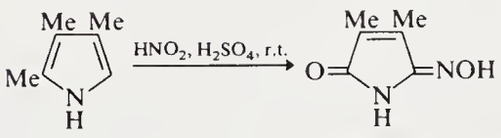
Scheme 21

3.3.1.5.10 Nitrosation

3-Nitroso derivatives (**102**) are obtained from indoles; they exist largely in oximino forms (**103**) ⟨80IJC(B)767⟩. Nitrosation of pyrrole or alkylpyrroles may result in ring opening or oxidation of the ring and removal of the alkyl groups. This is illustrated by the formation of the maleimide (**104**) from 2,3,4-trimethylpyrrole.



(**102**) (**103**)

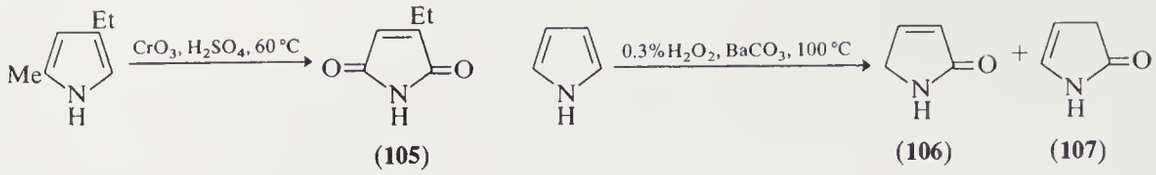


(**104**)

3.3.1.5.11 Electrophilic oxidation

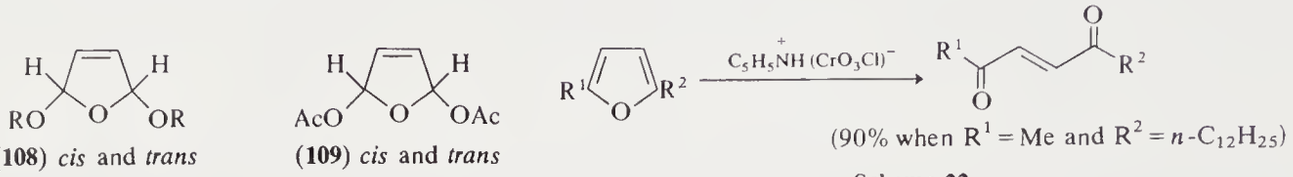
Pyrroles and furans are particularly easily oxidized. The mechanism of primary attack can be electrophilic, radical or cyclic transition state, and the assignment of individual reactions to these classes is sometimes arbitrary.

Simple pyrroles frequently give complex breakdown products. With strong oxidizing agents such as chromium trioxide in aqueous sulfuric acid, alkylpyrroles are converted into maleimides, *e.g.* (**105**). This oxidative technique played an important part in the classical determination of porphyrin structure. Milder oxidizing agents, such as hydrogen peroxide, convert pyrroles to pyrrolinones, *e.g.* oxidation of the parent heterocycle gives a tautomeric mixture of pyrrolin-2-ones (**106**) and (**107**).



(105) (106) (107)

Bromine or electrolytic oxidation of furan in alcoholic solution gives the corresponding 2,5-dialkoxy-2,5-dihydrofuran (**108**). Lead tetraacetate in acetic acid oxidation yields 2,5-diacetoxy-2,5-dihydrofuran (**109**).

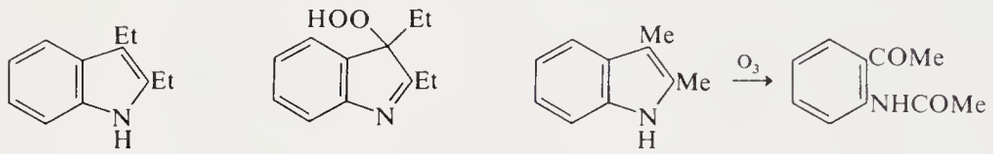


(**108**) *cis* and *trans* (**109**) *cis* and *trans* (90% when R^1 = Me and R^2 = *n*-$C_{12}H_{25}$)

Scheme 22

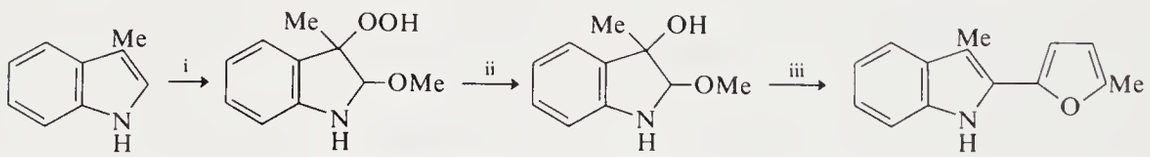
Oxidation of 2,5-dialkylfurans with pyridinium chlorochromate results in high yields of α,β-unsaturated γ-dicarbonyl compounds (Scheme 22) ⟨82S245, 80T661⟩.

Oxidants and electrophilic reagents attack pyrroles and furans at positions 2 and 5; in the case of indoles the common point of attack is position 3. Thus autoxidation of indoles (*e.g.* **110**) gives 3-hydroperoxy-3*H*-indoles (*e.g.* **111**). Lead tetraacetate similarly reacts at the 3-position to give a 3-acetoxy-3*H*-indole. Ozone and other oxidants have been used to cleave the 2,3-bond in indoles (**112**→**113**) ⟨81BCJ2369⟩.



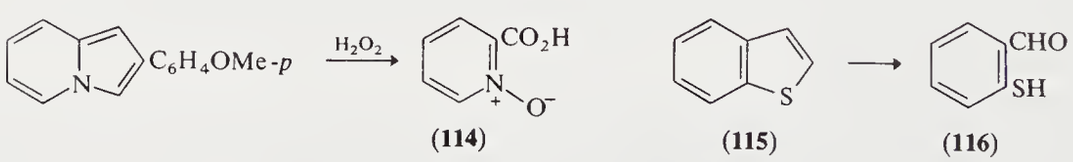
(**110**) (**111**) (**112**) (**113**)

Singlet oxygenation of 3-substituted indoles in the presence of alcohols followed by treatment with sodium borohydride gives 2-alkoxy-3-hydroxyindolines in high yields. Further reaction with a nucleophile and a Lewis acid forms the basis of a synthesis of 2-substituted indoles (Scheme 23) ⟨82CC977⟩. This represents an alternative approach to C—C bond formation at the 2-position of indoles to that involving the reaction of 2-lithioindoles with electrophiles. Isoindoles and indolizines are also preferentially oxidized in the five-membered ring to give phthalic acid and picolinic acid derivatives (**114**), respectively.



i, $^1O_2$, MeOH; ii, $NaBH_4$; iii, 2-methylfuran, $CF_3SO_3SiMe_3$

Scheme 23



(**114**) (**115**) (**116**)

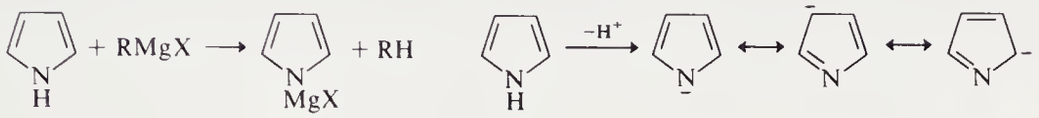
Thiophenes are reasonably stable to atmospheric oxidation. Ozone attacks the C=C bonds, *e.g.* benzothiophene (**115**) yields *o*-mercaptobenzaldehyde (**116**).

3.3.1.6 Reactions with Nucleophiles

Pyrrole, furan or thiophene reacts with nucleophilic reagents by proton transfer, and not by substitution or addition. However, the cationic species formed by reaction with electrophiles are highly susceptible to nucleophilic attack and we consider such reactions after discussion of proton loss from nitrogen and from carbon atoms.

3.3.1.6.1 Deprotonation at nitrogen

Pyrrole is very much less basic than secondary amines but much more acidic. Pyrrole is, however, still a very weak acid (pK_a 17.5). The nitrogen-bound proton can be abstracted from pyrrole by the use of strong bases such as sodium amide in liquid ammonia and *n*-butyllithium in hexane. Reaction of pyrrole with Grignard reagents results in the formation of halomagnesyl derivatives (**117**). The resulting anion (**118**) has ambident properties and may react with electrophiles at nitrogen, C-2 or C-3. *N*-Unsubstituted indoles similarly form metal derivatives when treated with a variety of reagents such as *n*-butyllithium, sodamide, potassium hydroxide ⟨81S461⟩, Grignard reagents and thallium(I) ethoxide ⟨81S389⟩.



(117) **(118a)** **(118b)** **(118c)**

The reactions of the pyrrole and indole anions with electrophiles are discussed in Section 3.3.1.3.1.

3.3.1.6.2 Deprotonation at carbon

The first proton to be removed from *N*-methylpyrrole by *n*-butyllithium is from an α-position; a second deprotonation occurs to give a mixture of 2,4- and 2,5-dilithiated derivatives. In both furan and thiophene initial abstraction of a proton at C-2 is followed by proton abstraction from C-5 ⟨77JCS(P1)887⟩. *N*-Methylindole, benzo[*b*]furan, benzo[*b*]thiophene, selenophene, benzo[*b*]selenophene, tellurophene and benzo[*b*]tellurophene similarly yield 2-lithio derivatives ⟨77AHC(21)119⟩.

Competitive metallation experiments with *N*-methylpyrrole and thiophene and with *N*-methylindole and benzo[*b*]thiophene indicate that the sulfur-containing heterocycles react more rapidly with *n*-butyllithium in ether. The comparative reactivity of thiophene and furan with butyllithium depends on the metallation conditions. In hexane, furan reacts more rapidly than thiophene but in ether, in the presence of tetramethylethylenediamine (TMEDA), the order of reactivity is reversed ⟨77JCS(P1)887⟩.

Directive effects on lithiation have also been studied. The regiospecific β-metallation of *N*-methylpyrrole derivatives and 2-substituted furans has been effected by employing the directive effect of the oxazolino group ⟨82JCS(P1)1343⟩. 2-Substituted furans and thiophenes are metallated in the 5-position. 2-Lithio-3-bromofuran forms on treatment of 3-bromofuran with lithium diisopropylamide (LDA) at −80 °C in THF ⟨77HCA2085⟩.

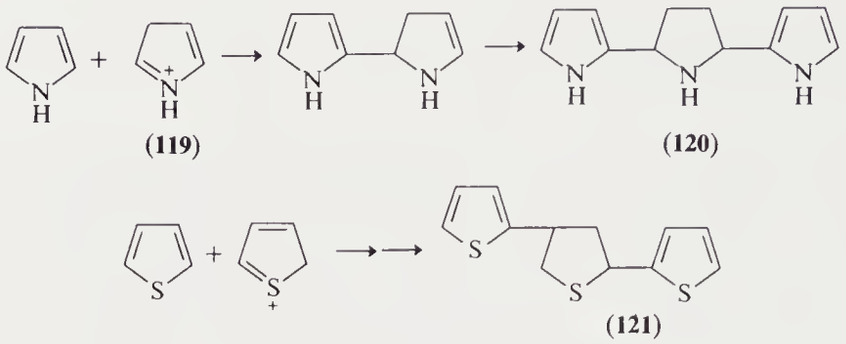
3-Methylthiophene is metallated in the 5-position whereas 3-methoxy-, 3-methylthio-, 3-carboxy- and 3-bromo-thiophenes are metallated in the 2-position ⟨80TL5051⟩. Lithiation of tricarbonyl(η^6-*N*-protected indole)chromium complexes occurs initially at C-2. If this position is trimethylsilylated, subsequent lithiation is at C-7 with minor amounts at C-4 ⟨81CC1260⟩. Tricarbonyl(η^6-1-triisopropylsilylindole)chromium(0) is selectively lithiated at C-4 by *n*-butyllithium–TMEDA.

The reactions of the lithiated derivatives are discussed in Section 3.3.7.8.

3.3.1.6.3 Reactions of cationic species with nucleophiles

Protonation of pyrrole, furan and thiophene derivatives generates reactive electrophilic intermediates which participate in polymerization, rearrangement and ring-opening reactions.

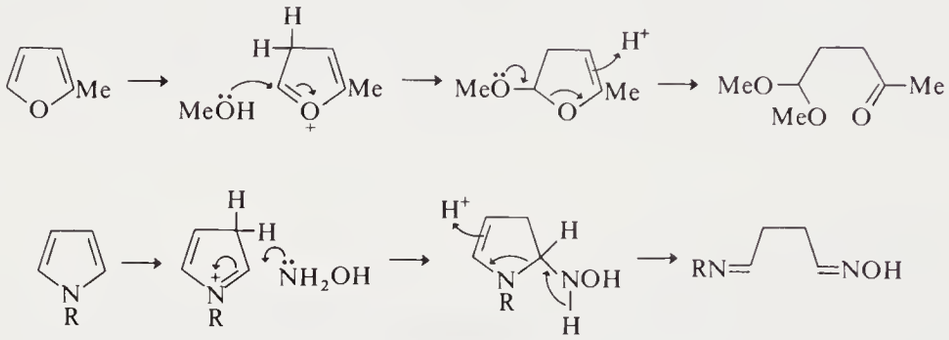
Pyrrole itself gives a mixture of polymers (pyrrole red) on treatment with mineral acid and a trimer (**120**) under carefully controlled conditions. Trimer formation involves attack on the neutral pyrrole molecule by the less thermodynamically favored, but more reactive, β-protonated pyrrole (**119**). The trimer (**121**) formed on treatment of thiophene with phosphoric acid also involves the generation of an α-protonated species.



(**119**) (**120**)

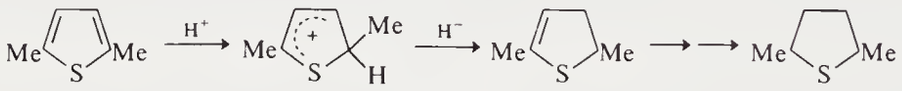
(**121**)

The chemical consequences of β-protonation are illustrated further by the ring-opening reactions of furans with methanolic hydrogen chloride and of *N*-substituted pyrroles with hydroxylamine hydrochloride (Scheme 24) ⟨82CC800⟩.



Scheme 24

The so-called ionic method for hydrogenating thiophenes ⟨78T1703⟩ is a further illustration of the chemical consequences of protonation. Protonation of the thiophene ring renders the ring susceptible to hydride ion attack, conveniently derived from triethylsilane (Scheme 25).



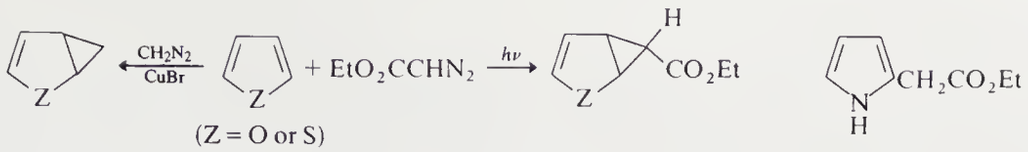
Scheme 25

Indole is reduced to 2,3-dihydroindole by sodium cyanoborohydride and acetic acid or triethylamineborane and hydrochloric acid. An alternative method for preparing indolines involves treatment of indoles with formic acid (or a mixture of formic acid and ammonium formate) and a palladium catalyst ⟨82S785⟩. Reduction of the heterocyclic ring under acidic conditions probably involves initial β-protonation followed by reaction with hydride ion.

3.3.1.7 Reactions with Radicals and Electron-deficient Species; Reactions at Surfaces

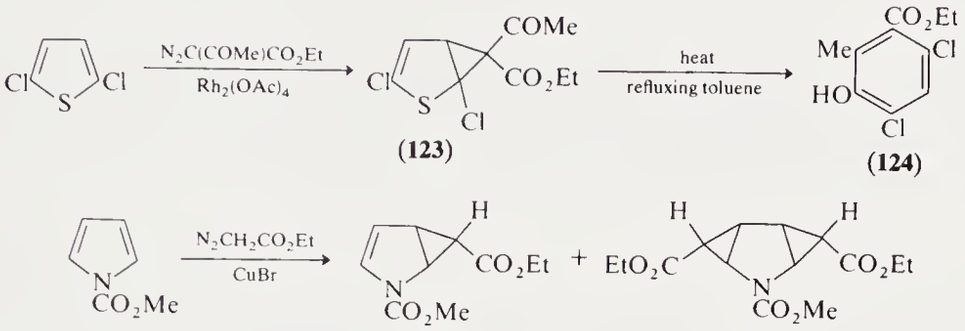
3.3.1.7.1 Carbenes and nitrenes

Furan and thiophene undergo addition reactions with carbenes. Thus cyclopropane derivatives are obtained from these heterocycles on copper(I) bromide-catalyzed reaction with diazomethane and light-promoted reaction with diazoacetic acid ester (Scheme 26). The copper-catalyzed reaction of pyrrole with diazoacetic acid ester, however, gives a 2-substituted product (**122**).



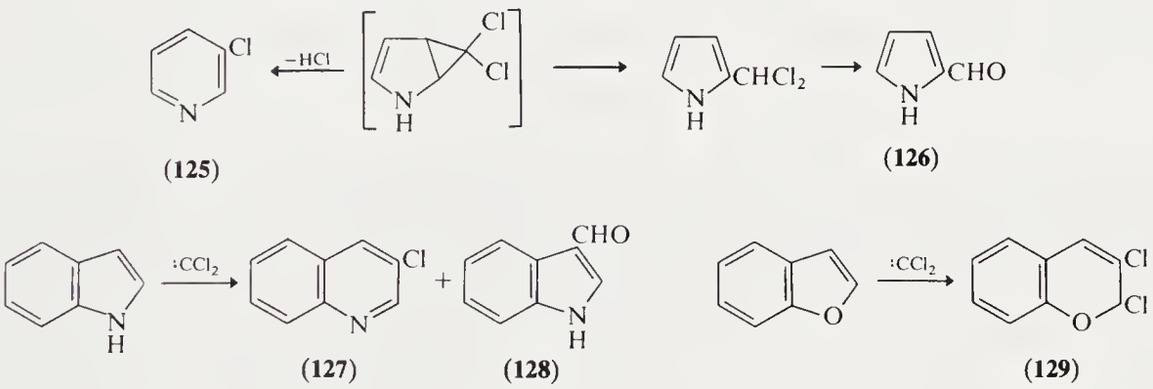
Scheme 26 **(122)**

Copper-promoted reaction of ethyl 2-diazoacetoacetate [$N_2C(COMe)CO_2Et$] and dimethyl diazomalonate [$N_2C(CO_2Me)_2$] with *N*-methylpyrrole also furnishes 2-substituted derivatives ⟨82JOC3000⟩. Indole similarly yields a 3-substituted product on reaction with diazoacetic acid ester. In the rhodium acetate-catalyzed reaction of 2,5-dichlorothiophene with ethyl 2-diazoacetoacetate, the initial 2,3-cycloadduct (**123**) fragments with sulfur extrusion and subsequent rearrangement yields the dichlorophenol (**124**) ⟨81T743⟩. A mixture of cyclopropanes is obtained, however, from the copper(I) bromide-catalyzed reaction of 1-methoxycarbonylpyrrole with diazoacetic acid ester. This is thought to be indicative of the reduced aromaticity of a pyrrole substituted on nitrogen with an electron-withdrawing substituent (Scheme 27).

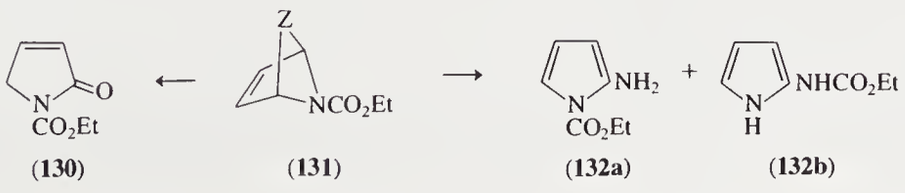


Scheme 27

The reaction of pyrrole with dichlorocarbene, generated from chloroform and strong base, gives a bicyclic intermediate which can be transformed to either 3-chloropyridine (**125**) or pyrrole-2-carbaldehyde (**126**). Indole gives a mixture of 3-chloroquinoline (**127**) and indole-3-carbaldehyde (**128**). The optimum conditions involve phase transfer ⟨76S249, 76S798⟩. Benzofuran reacts with dichlorocarbene in hexane solution to give the benzopyran (**129**), whereas benzothiophene fails to react.

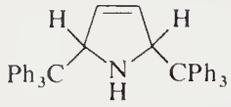


Furan undergoes 1,4-addition with ethoxycarbonylnitrene to give (**131**; Z = O) which rearranges to the pyrrolinone (**130**). The corresponding reaction with pyrrole gives a mixture of (**132a**) and (**132b**) ⟨64TL2185⟩.

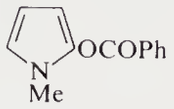


3.3.1.7.2 Free radical attack

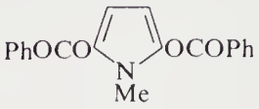
Pyrroles, furans and thiophenes react preferentially with free radicals at the 2-position. Thus reaction of pyrrole with benzyl radicals gives 2-benzylpyrrole. With triphenylmethyl radicals, pyrrole behaves like butadiene giving the adduct (**133**). *N*-Methylpyrrole undergoes free radical benzoyloxylation with dibenzoyl peroxide to give the 2-benzoyloxypyrrole (**134**) and 2,5-dibenzoyloxypyrrole (**135**). Furan, however, is converted in good yield to a mixture of *cis* and *trans* addition products analogous in structure to (**133**).



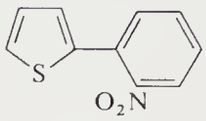
(**133**)



(**134**)



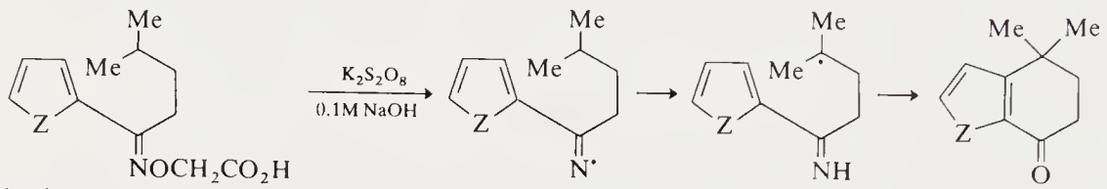
(**135**)



(**136**)

Arylation of *N*-substituted pyrroles, thiophenes and furans occurs preferentially in the 2-position, *e.g.* the *o*-nitrophenylation of thiophene by phase transfer catalysis yields (**136**) ⟨77TL1871⟩.

Thiophene reacts with phenyl radicals approximately three times as fast as benzene. Intramolecular radical attack on furan and thiophene rings occurs when oxime derivatives of type (**137**) are treated with persulfate ⟨81JCS(P1)984⟩. It has been found that intramolecular homolytic alkylation occurs with equal facility at the 2- and 3-positions of the thiophene nucleus whereas intermolecular homolytic substitution occurs mainly at position 2.

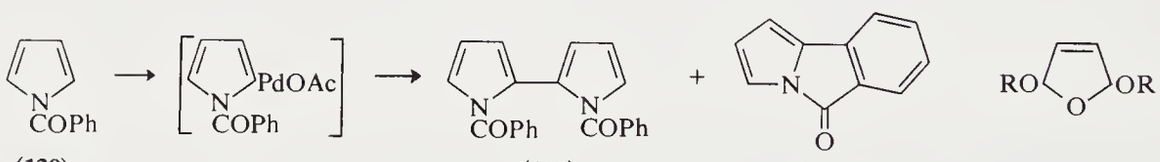


(**137**) Z = O or S

Pyrroles, furans and thiophenes undergo photoinduced alkylation with diarylalkenes provided that the alkene and the heteroaromatic compound have similar oxidation potentials, indicating that alkylation can occur by a non-ionic mechanism (Scheme 28) ⟨81JA5570⟩.

Scheme 28

1-Aroylpyrroles dimerize on treatment with palladium(II) salts; thus oxidation of 1-benzoylpyrrole (**138**) with palladium acetate in acetic acid gives the 2,2′-bipyrrole (**139**). The ring-closed compound (**140**) is formed as a by-product ⟨81CC254⟩.



(**138**) (**139**) (**140**) (**141**)

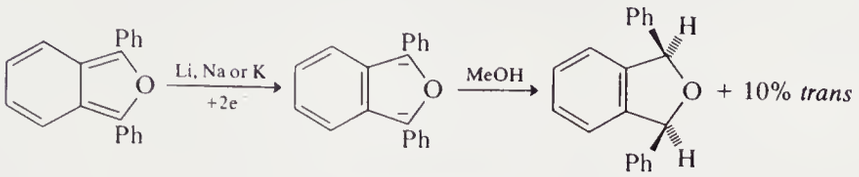
3.3.1.7.3 Electrochemical reactions

Electrolytic oxidation of furan in alcoholic solution gives the corresponding 2,5-dialkoxy-2,5-dihydrofuran (**141**).

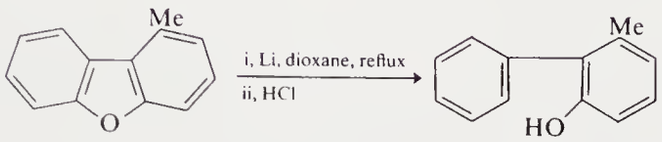
3.3.1.7.4 Reactions with free electrons

Pyrroles are not reduced by sodium in liquid ammonia, but the Birch reduction of 2-furoic acid with lithium in liquid ammonia gives the 2,5-dihydro derivative in 90% yield ⟨78OPP94⟩. Sodium–liquid ammonia–methanol reduction of thiophene gives a mixture of Δ^2- and Δ^3-dihydrothiophenes together with butenethiols. Reductive metallation of 1,3-diphenylisobenzofuran results in stereoselective formation of the *cis*-1,3-dihydro derivative (Scheme 29) ⟨80JOC3982⟩.

Regioselective cleavage of dibenzofuran derivatives has been achieved with lithium metal, as exemplified by the preparation of 3-methyl-2-phenylphenol (**142**) ⟨80S634⟩.



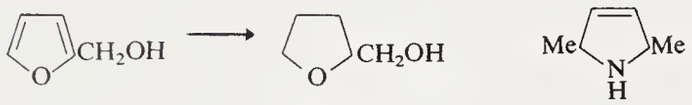
Scheme 29



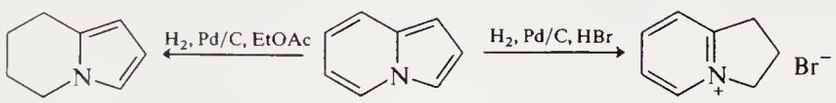
(142)

3.3.1.7.5 Catalytic hydrogenation

Catalytic reduction of pyrroles gives successively Δ^3-pyrroles and pyrrolidines. Tetrahydrofurans are formed by the catalytic reduction of furans with Raney nickel and hydrogen; ring cleavage products may also be formed, *e.g.* (**143**)→(**144**)→$Me(CH_2)_2CH(OH)CH_2OH + Me(CH_2)_4OH$.



(143) **(144)** **(145)**



Scheme 30

Vigorous catalytic reduction of indole (H_2/Pd/AcOH/HCl, 80 °C) results in the formation of *cis*-octahydroindole. Catalytic reduction of isoindoles occurs in the pyrrole ring. Reduction of indolizine with hydrogen and a platinum catalyst gives an octahydro derivative. With a palladium catalyst in neutral solution, reduction occurs in the pyridine ring but in the presence of acid, reduction occurs in the five-membered ring (Scheme 30).

3.3.1.7.6 Reduction by dissolving metals

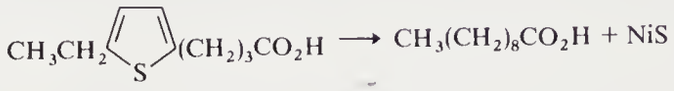
Δ^3-Pyrrolines, *e.g.* (**145**), are formed on the reduction of pyrroles and simple alkylpyrroles with zinc and acid. These are derived from the corresponding α-protonated species ⟨66JA1335⟩.

Reduction of thiophene and 2-ethylthiophene to the corresponding 2,5-dihydrothiophenes can be carried out with zinc and trifluoroacetic acid. The mechanism is again thought to involve protonation of the thiophene ring followed by transfer of two electrons from zinc and a second proton from the acid ⟨80CC766⟩.

Dissolving metals reduce the heterocyclic ring of isoindoles.

3.3.1.7.7 Desulfurization

Raney nickel desulfurization of thiophenes is an important technique of chain extension. Ring fission is accompanied by saturation of the ring carbon atoms and chain extension by four carbon atoms is effected. This method has been widely used to prepare alkanes, ketones and carboxylic acids and their derivatives ⟨B-74MI30200⟩. An illustrative example is given in Scheme 31; see also CHEC 1.16.



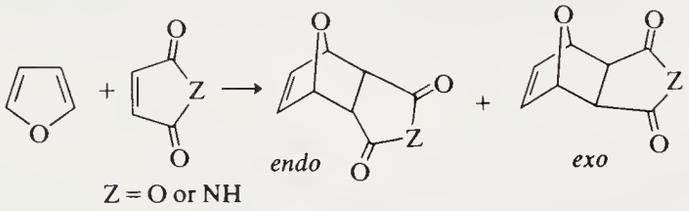
Scheme 31

3.3.1.8 Reactions with Cyclic Transition States

3.3.1.8.1 Reactions with dienophiles

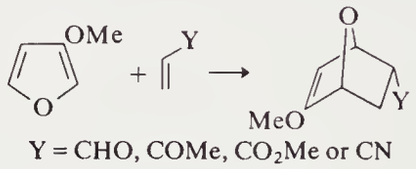
Furan has much greater reactivity in cycloaddition reactions compared with pyrrole and thiophene; the latter is the least reactive diene. *N*-Substituted pyrroles show enhanced diene character compared with the parent heterocycle.

Furan reacts as a diene with powerful dienophiles like maleic anhydride, maleimide and benzyne to give Diels–Alder adducts. The kinetically favored products are the *endo* adducts but the *exo* adducts are thermodynamically preferred (Scheme 32). Thus on prolonged reaction at room temperature, or on heating, the proportion of *exo* to *endo* adduct is increased ⟨78JOC518⟩. The reaction of furan with less reactive dienophiles such as acrylonitrile (CH_2=$CHCN$) and methyl acrylate (CH_2=$CHCO_2CH_3$) is greatly accelerated by zinc(II) iodide ⟨82TL5299⟩; copper(I) and copper(II) salts have been shown to catalyze the reaction of furan with α-acetoxyacrylonitrile (CH_2=$C(OAc)CN$) ⟨82HCA1700⟩. Alkoxy ⟨81CC221⟩ and silyloxy groups ⟨80TL3423⟩ activate the furan nucleus to cycloaddition reactions, *e.g.* 3-methoxyfuran readily undergoes [4+2] cycloaddition with electron-deficient dienophiles with regio-and stereo-control to give *endo* adducts (Scheme 33).



Z = O or NH

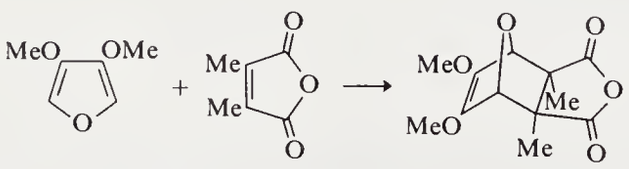
Scheme 32



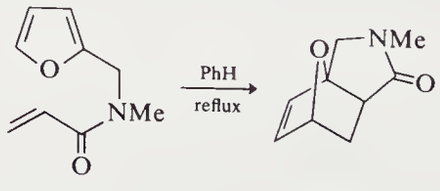
Y = CHO, COMe, CO_2Me or CN

Scheme 33

Conversely, furans with electron-withdrawing groups (*e.g.* CHO, CN, CO_2Me) in the 2-position show reduced Diels–Alder reactivity. Electron-withdrawing groups in the 3- or 4-position appear to have little effect on the diene character of the furan ring. Although 3,4-dimethoxyfuran readily undergoes [4 + 2] cycloaddition with maleic anhydride or methylmaleic anhydride, high pressure is required to carry out cycloaddition with dimethylmaleic anhydride (Scheme 34) ⟨82HCA1021⟩.



Scheme 34

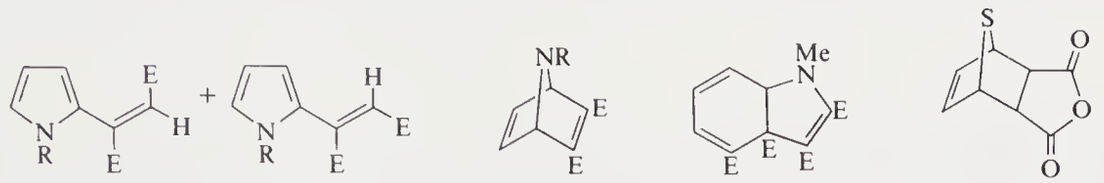


(146)

A number of intramolecular Diels–Alder addition reactions of furan derivatives have been reported ⟨78T1689, 82T245, 82T303, 81TL4877, 81CL917⟩. Noteworthy is the formation of compound **(146)** in quantitative yield even though the precursor incorporates an alkene group linked to only a single activating unsaturated group.

The reactions of pyrroles with dienophiles generally follow two different pathways involving either a [4 + 2] cycloaddition or a Michael-type addition to a free α-position of the pyrrole ring. Pyrrole itself gives a complex mixture of products with maleic anhydride or maleic acid.

The reactions of pyrroles with dimethyl acetylenedicarboxylate (DMAD) have been extensively investigated. In the presence of a proton donor the Michael adducts (**147**) and (**148**) are formed. However, under aprotic conditions the reversible formation of the 1 : 1 Diels–Alder adduct (**149**) is an important reaction. In the case of the adduct from 1-methylpyrrole, reaction with a further molecule of DMAD can occur to give a dihydroindole (**150**) ⟨82H(19)1915⟩.



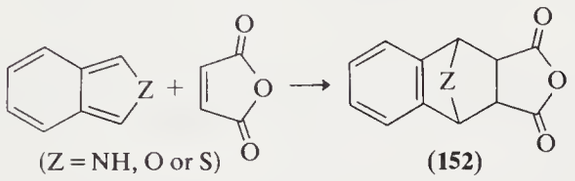
(**147**) (**148**) (**149**) (**150**) (**151**)

E = CO_2Me

N-Amino- and *N*-substituted amino-pyrroles readily undergo Diels–Alder additions and add to activated alkynes at room temperature.

Thiophene fails to undergo cycloaddition reactions with common dienophiles under normal conditions. However, when thiophene is heated under pressure with maleic anhydride, the *exo* adduct (**151**) is formed in moderate yield ⟨78JOC1471⟩.

Benzo[*b*]furans and indoles do not take part in Diels–Alder reactions. The benzo[*c*]-fused heterocycles function as highly reactive dienes in [4+2] cycloaddition reactions. Thus benzo-[*c*]furan, isoindole (benzo[*c*]pyrrole) and benzo[*c*]thiophene all yield Diels–Alder adducts (**152**) with maleic anhydride. Adducts of this type are used to characterize these unstable molecules and in a similar way benzo[*c*]selenophene, which polymerizes on attempted isolation, was characterized by formation of an adduct with tetracyanoethylene ⟨76JA867⟩.



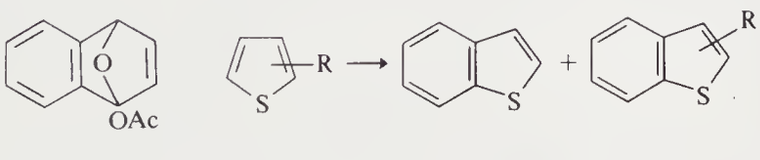
(Z = NH, O or S) (**152**)

Benzo[*c*]furan, generated *in situ* in boiling xylene in the presence of dimethylmaleic anhydride, gives mainly the *exo* adduct; furan itself fails to react with this dienophile ⟨82JOC4011⟩. 1,3-Diphenylbenzo[*c*]furan is also a reactive diene but the corresponding 1,3-dimesityl derivative is inert to several dienophiles, even under forcing conditions ⟨82CC766⟩.

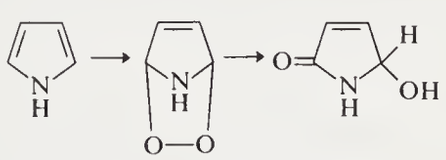
3.3.1.8.2 Reactions with benzynes and oxygen

Furans react readily with benzynes, *e.g.* 2-acetoxyfuran yields (**153**). *N*-Methylpyrrole also reacts normally across the 2,5-positions, but pyrrole itself yields 2-phenylpyrrole.

Benzyne, generated from diphenyliodonium 2-carboxylate, reacts with various thiophenes by addition to the sulfur and β-carbon to give, after loss of an acetylene moiety, benzo[*b*]thiophenes in low (< 4%) yield (Scheme 35) ⟨81CC124⟩.



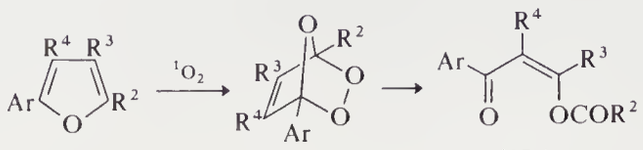
(**153**) **Scheme 35**



Scheme 36

The photosensitized reaction of pyrrole and oxygen yields 5-hydroxy-Δ^3-pyrrolin-2-one, probably by way of an intermediate cyclic peroxide (Scheme 36) ⟨76JA802⟩.

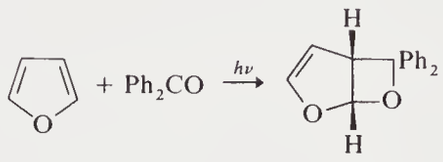
Furans also form cyclic peroxides on reaction with singlet oxygen ⟨81CC720, 80JCS(P1)1955⟩; these undergo some interesting rearrangements as shown by the formation of the 2-aroyl enol esters (**154**) from the peroxides derived from 2-arylfurans ⟨82S736⟩.



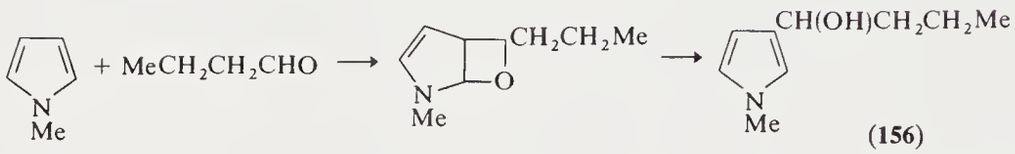
(**154**)

3.3.1.8.3 [2 + 2] Cycloaddition reactions

N-Substituted pyrroles, furans and dialkylthiophenes undergo photosensitized [2 + 2] cycloaddition reactions with carbonyl compounds to give oxetanes. Furan and benzophenone give the oxetane (**155**). The photochemical reaction of pyrroles with aliphatic aldehydes and ketones results in the regiospecific formation of 3-(1-hydroxyalkyl)pyrroles (*e.g.* **156**), *via* an intermediate oxetane which undergoes rearrangement under the reaction conditions ⟨79JOC2949⟩.

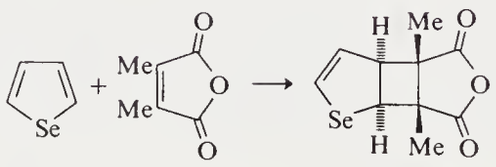


(**155**)



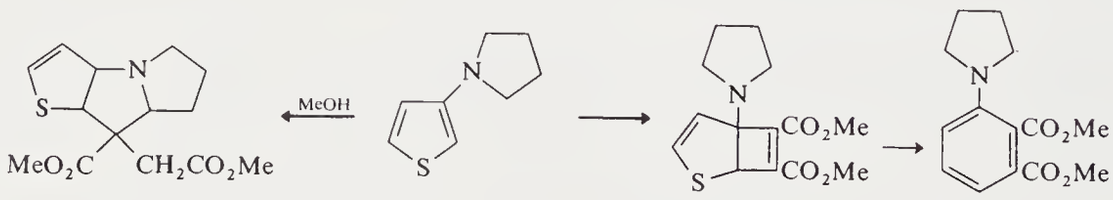
(**156**)

The photochemically induced [2 + 2] cycloaddition of selenophene with dimethylmaleic anhydride gives a 1 : 1 adduct (**157**), but attempts to form an oxetane by photoreaction with benzophenone failed ⟨80JHC1151⟩.



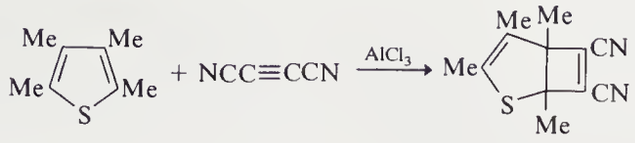
(**157**)

3-Aminothiophenes and 3-aminobenzo[*b*]thiophene undergo thermal [2 + 2] cycloaddition reactions with activated alkynes. The reactions are solvent dependent; thus in non-polar solvents at −30 °C, 3-pyrrolidinothiophene adds to DMAD to give a [2 + 2] cycloadduct which is ultimately converted into a phthalic ester. In methanol, however, a tricyclic product is formed (Scheme 37) ⟨81JOC424⟩.



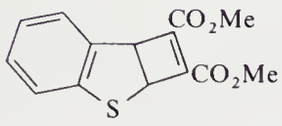
Scheme 37

Thiophenes have been observed to undergo aluminum chloride-catalyzed [2+2] cycloaddition with dicyanoacetylene (Scheme 38) ⟨82JOC967, 82JOC972⟩.

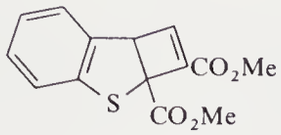


Scheme 38

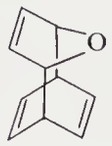
The benzo[*b*]-fused systems participate in a number of [2 + 2] cycloaddition reactions ⟨81JOC3939, 81TL521⟩. The photocycloaddition products of benzo[*b*]thiophenes and DMAD are dependent on the irradiation wavelength; at 330 nm (**158**) is formed, while at 360 nm the rearranged product (**159**) is produced.



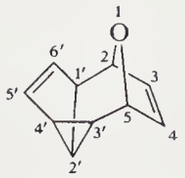
(**158**)



(**159**)



(**160**)

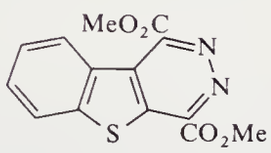


(**161**)

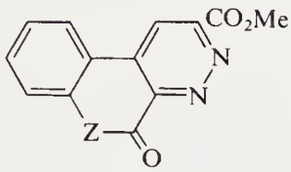
3.3.1.8.4 Other cycloaddition reactions

Photolysis of a mixture of furan and benzene gives mainly the [4 + 4] cycloadduct (**160**); a substantial amount of the adduct (**161**) derived by addition of carbons 2 and 5 of furan and 1 and 3 of benzene is also obtained ⟨81JOC2674⟩.

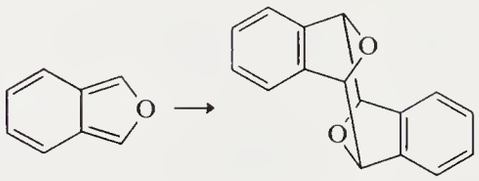
Benzo[*b*]thiophene reacts with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate in a cycloaddition-fragmentation reaction to yield (**162**), whereas benzo[*b*]furan and *N*-methylindole yield products (**163**) arising from ring opening and recyclization ⟨76AP679⟩.



(**162**)



(**163**) Z = NH or O



(**164**)

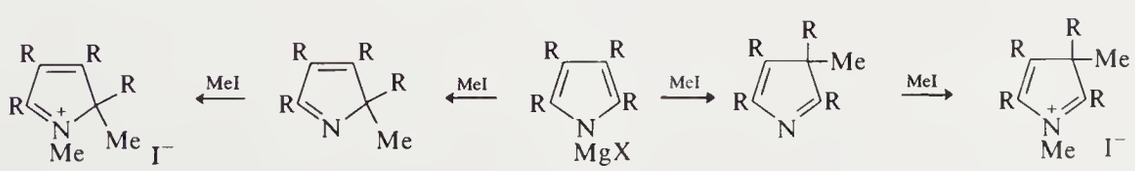
N-Methylisoindole and isobenzofuran give [8 + 8] photodimers. The [8 + 8] dimer (**164**) obtained from isobenzofuran at −60 °C has *anti* stereochemistry ⟨78HCA444, 82CC1195⟩.

3.3.2 REACTIVITY OF NON-AROMATIC COMPOUNDS

Before turning to the dihydro and tetrahydro derivatives of the fundamental ring systems, we deal with two special classes. The pyrrolenines and the thiophene sulfones both contain two double bonds in the heterocyclic ring, but in each case the conjugation does not include all the ring atoms. Finally we consider hydroxy derivatives, most of which exist predominantly as the non-aromatic carbonyl tautomers.

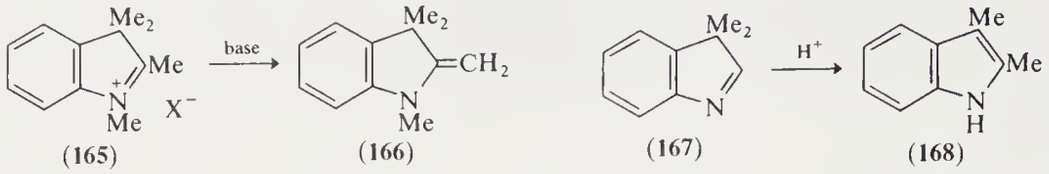
3.3.2.1 Pyrrolenines and Indolenines

Pyrrolenines and indolenines are much stronger bases than their aromatic analogues. Pyrrolenines readily undergo further alkylation to give quaternary salts (Scheme 39) and form stable hydrochlorides.



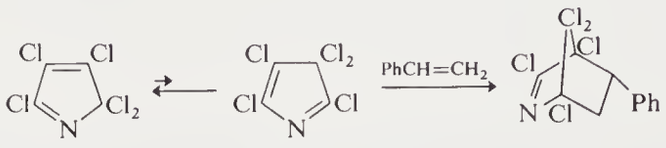
Scheme 39

The derived quaternary salts (*e.g.* **165**) give anhydro compounds (*e.g.* **166**) on treatment with alkali. β-Pentamethylpyrrolenine (2,3,3,4,5-pentamethylpyrrole) undergoes quantitative conversion to the α-isomer (2,2,3,4,5-pentamethylpyrrole) either on heating (>200°C) or in 1M HCl at room temperature ⟨71CC1093⟩. Indolenines also undergo acid-catalyzed rearrangement (*e.g.* **167**→**168**), known as the Plancher rearrrangement.



(165) (166) (167) (168)

Reduction of indolenines with sodium and ethanol gives indolines. The pentachloro-α-pyrrolenine (**169**) is in equilibrium with small but finite amounts of the isomeric β-pyrrolenine form (3*H*-pyrrole; **170**), since it forms cycloadduct (**171**) with styrene ⟨80JOC435⟩. Pentachloropyrrole acts as a dienophile in its reaction with cyclopentadiene *via* its ene moiety ⟨81JOC3036⟩.



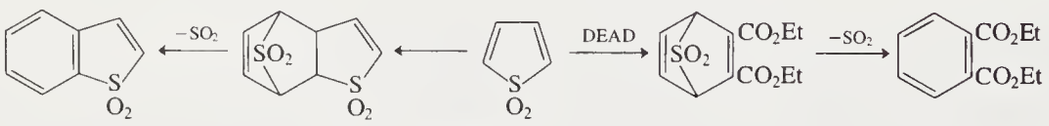
(169) (170) (171)

2*H*-Pyrrole 1-oxides undergo 1,3-dipolar cycloaddition with DMAD and with *N*-phenylmaleimide ⟨80TL1833⟩.

3.3.2.2 Thiophene Sulfones and Sulfoxides

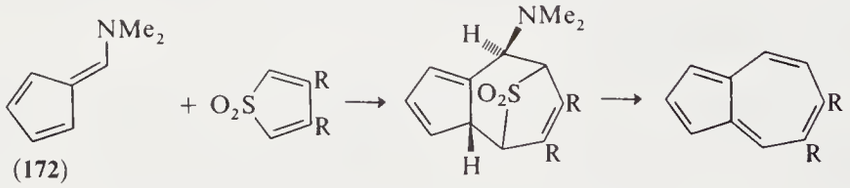
Thiophene sulfones show no aromatic character, they behave as dienes and also show reactions of compounds containing a C=C bond conjugated with an electron-withdrawing group. Thiophene sulfone itself is highly unstable, but alkyl and aryl groups and fused benzene rings increase the stability.

Thiophene sulfones undergo Diels–Alder reactions which are followed by spontaneous loss of sulfur dioxide from the products, *e.g.* Scheme 40.



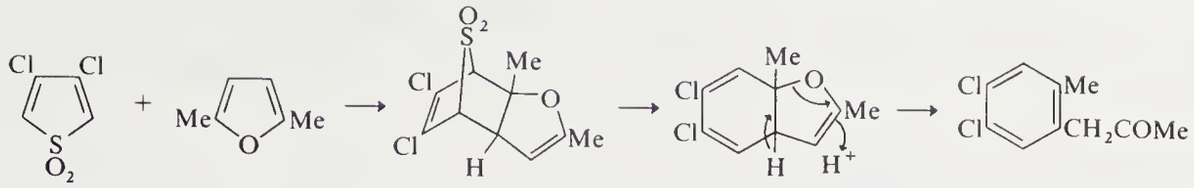
Scheme 40

An azulene synthesis involves the addition of 6-(*N*,*N*-dimethylamino)fulvene (**172**) to a thiophene sulfone ⟨77TL639, 77JA4199⟩.



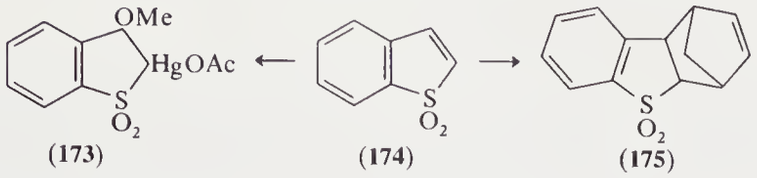
(172)

Halogenated thiophene sulfones (1,1-dioxides) are more stable than the parent sulfone. They have been employed as dienes in Diels-Alder reactions and found to add to a large variety of alkenic bonds, including the formal double bonds of *N*-methylpyrrole, furan and thiophene. The adducts subsequently lose sulfur dioxide and in some cases undergo further rearrangement and aromatization (Scheme 41) ⟨80JOC856, 80JOC867⟩. Reducing agents (*e.g.* Zn/HCl) convert thiophene sulfones to thiophenes; contrast the resistance to reduction of normal sulfones.



Scheme 41

Benzo[*b*]thiophene sulfone (**174**) reacts as a vinyl sulfone and forms adducts (**173**) and (**175**) when treated with mercury(II) acetate in methanol and with cyclopentadiene, respectively.

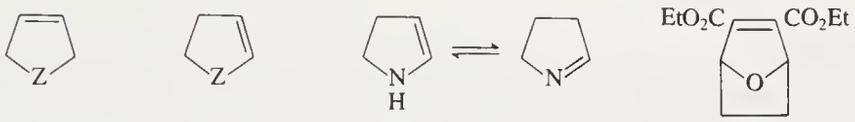


(**173**) (**174**) (**175**)

3.3.2.3 Dihydro Derivatives

There are two possible types of dihydro-furans and -thiophenes (*cf.* **176**, **177**) and examples of both are known. There are three possible classes of dihydropyrroles: *N*-unsubstituted 2-pyrrolines (**178**) are in tautomeric equilibrium with the corresponding 1-pyrrolines (**179**).

The reactions of these dihydro compounds can be divided into three categories: a pronounced tendency to aromatize, behavior analogous to aliphatic compounds of similar functionality, and other reactions. These are considered in turn.

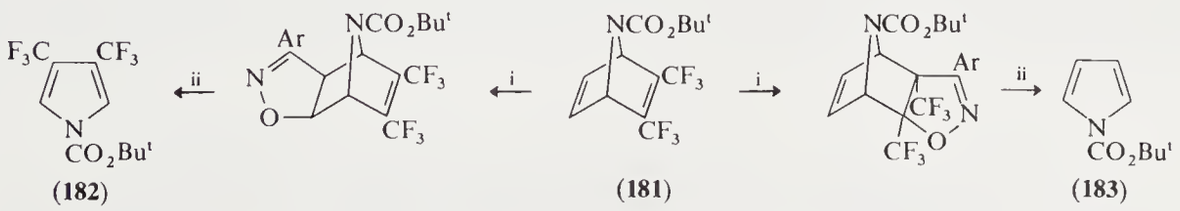


(**176**) (**177**) (**178**) (**179**) (**180**)

3.3.2.3.1 Aromatization of dihydro compounds

The following reactions illustrate some of the possible routes:

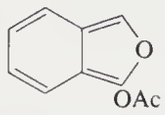
(a) Retro-Diels–Alder reaction: (**180**) on pyrolysis→ethyl 3,4-furandicarboxylate and ethylene. Similarly, azanorbornadienes with bulky or electron-withdrawing substituents undergo retro Diels–Alder extrusion of acetylene to give 3,4-disubstituted pyrroles. The adduct (**181**) from *N*-*t*-butoxycarbonylpyrrole and hexafluorobutyne with 2,4,6-trimethylbenzonitrile oxide gives a product mixture which undergoes smooth fragmentation to give mainly the 3,4-bis(trifluoromethyl)pyrrole (**182**) together with some *N*-*t*-butoxycarbonylpyrrole (**183**) ⟨82S313⟩. Alternatively, selective hydrogenation of adducts of type (**181**) at the less hindered double bond, followed by thermal extrusion of ethylene, provides a convenient route to 3,4-bis(trifluoromethyl)pyrroles ⟨82JOC4778⟩ (see CHEC 3.11.2.7.1). The cycloadduct from 2-acetoxyfuran and benzyne has been used in an analogous manner in the preparation of 1-acetoxybenzo[*c*]furan (**184**) ⟨81AJC1223⟩.



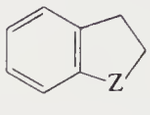
(**182**) (**181**) (**183**)

Ar=2,4,6-trimethylphenyl
i, 2,4,6-trimethylbenzonitrile oxide; ii, heat, 160 °C

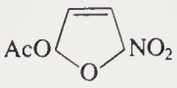
(b) Dehydrogenation: indoline (**185**; Z = NH) + chloranil → indole.
(c) Loss of acetic acid; (**186**) → 2-nitrofuran.
(d) Disproportionation: Δ^3-pyrroline heated over Pt → pyrrole + pyrrolidine.



(**184**)



(**185**)

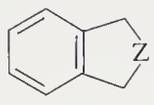


(**186**)

3.3.2.3.2 Behavior analogous to aliphatic analogues

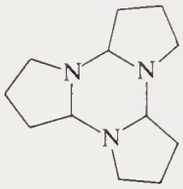
In many reactions, the dihydro compounds resemble their aliphatic analogues. Thus, when Z is nitrogen, (**187**) behaves as a benzylamine, (**185**; Z = NH) as an aromatic amine, and (**188**) as a Schiff's base. Similar comparisons apply when Z is oxygen or sulfur; (**185**; Z = O) is an aromatic ether, (**187**; Z = O) is a dibenzyl-type ether, and (**185**; Z = S) is an aromatic sulfide. Some of this behavior is illustrated by the following examples.

1-Pyrrolines readily form trimers of type (**189**). The trimer dissociates in boiling THF to 1-pyrroline; trimerization is relatively slow at −78 °C and the monomer can be trapped by reaction with acylating reagents to give *N*-acyl-2-pyrrolines, *e.g.* (**190**) with $ClCO_2Me$ ⟨81JOC4791⟩.

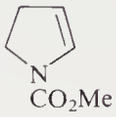


(**187**)

(**188**)



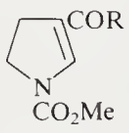
(**189**)



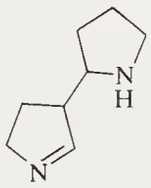
(**190**)

N-Methoxycarbonyl-2-pyrroline undergoes Vilsmeier formylation and Friedel–Crafts acylation in the 3-position to give products of type (**191**) ⟨82TL1201⟩. At pH 7, two molecules of 2,3-dihydropyrrole add together to give (**192**), thus exemplifying the dual characteristics of 2,3-dihydropyrroles as imines and enamines.

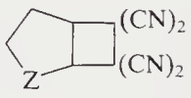
Both 2,3-dihydrofuran and 2,3-dihydrothiophene are converted into a [2 + 2] cycloadduct (**193**) on treatment with tetracyanoethylene under mild conditions ⟨80AG(E)831, 80AG(E)832⟩.



(**191**)



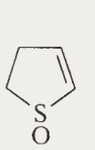
(**192**)

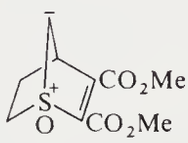


(**193**) Z = O or S

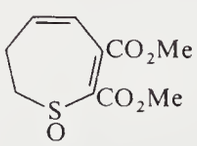
3.3.2.3.3 Other reactions

2,3-Dihydrothiophene and its 1-oxide undergo [2 + 3] cycloaddition with DMAD to give unstable sulfonium ylides (*e.g.* **194**). The latter undergoes ring expansion to give the thiepin 1-oxide (**195**) ⟨80AG(E)833⟩.

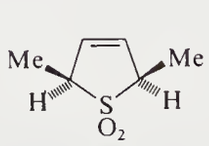




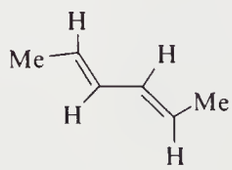
(**194**)



(**195**)



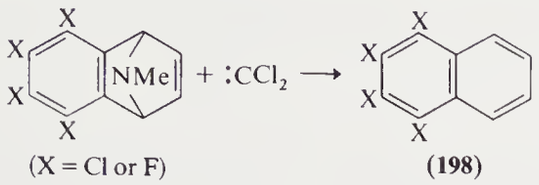
(**196**)



(**197**)

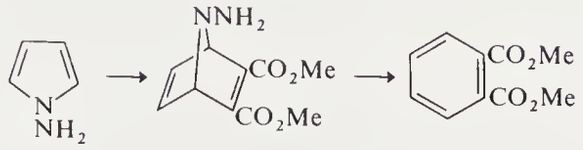
The thermal cheletropic extrusion of sulfur dioxide from both *cis* and *trans* isomers of 2,5-dihydrothiophene 1,1-dioxides is highly stereospecific. For example, *cis*- 2,5-dimethyl-2,5-dihydrothiophene 1,1-dioxide (**196**) yields (*E,E*)-hexa-2,4-diene (**197**) and sulfur dioxide ⟨75JA3666, 75JA3673⟩.

The benzyne adducts prepared from *N*-methylpyrrole (and *N*-methylisoindole) are deaminated conveniently by dichlorocarbene generated under phase-transfer conditions ⟨81JOC1025⟩ to give a convenient route to substituted naphthalenes (**198**) (and anthracenes) (Scheme 42).



(X = Cl or F) (**198**)

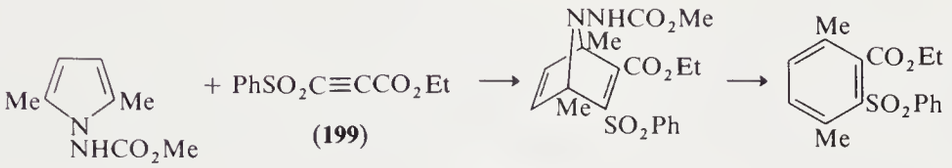
Scheme 42



Scheme 43

N-Amino- and *N*-substituted amino-pyrroles readily undergo Diels–Alder reactions and add to activated alkynes at room temperature. Loss of *N*-aminonitrene from the resulting adducts yields benzenoid derivatives (Scheme 43) ⟨81S753, 81TL1767⟩.

Ethyl β-phenylsulfonylpropiolate (**199**) is a superior dienophile to DMAD (Scheme 44).

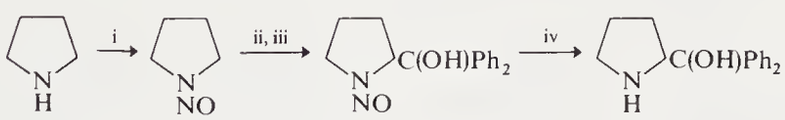


Scheme 44

3.3.2.4 Tetrahydro Derivatives

These show marked similarities to their acyclic counterparts, *e.g.* tetrahydrofuran closely resembles diethyl ether. Minor differences arise due to the less sterically hindered nature of the heteroatoms in the cyclic compounds. The basicities are: tetrahydropyrrole (pK_a 10.4), tetrahydrofuran (−2.1) and tetrahydrothiophene (thiolane) (−4.5).

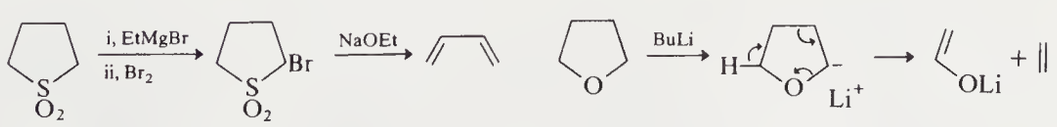
Pyrrolidine readily forms an *N*-nitroso derivative. This can be lithiated in the 2-position, and subsequent reaction with electrophiles and deprotection yields 2-substituted pyrrolidines ⟨78OS(58)113⟩, as illustrated in Scheme 45. The transformation of tetrahydrothiophene 1,1-dioxide (**200**) into its 2-bromo derivative (**201**) is similar in principle. This involves deprotonation with ethylmagnesium bromide followed by electrophilic attack by bromine. Sodium ethoxide treatment of (**201**) gives buta-1,3-diene in 74% yield ⟨80LA1540⟩.



i, EtONO; ii, LDA, THF, −78 °C; iii, Ph_2CO; iv, Raney Ni, H_2

Scheme 45

Although tetrahydrofuran is commonly used as a solvent in organometallic chemistry, it does undergo reaction with butyllithium. Proton–lithium exchange at an α-position is followed by cleavage to ethylene and the enolate anion of acetaldehyde. Its half-life is 10 min at 35 °C (Scheme 46) ⟨72JOC560⟩.



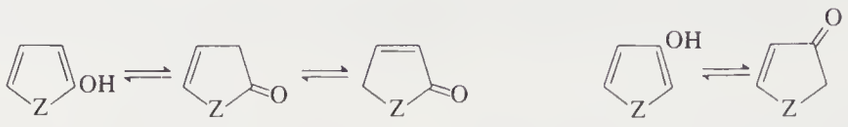
(**200**) (**201**)

Scheme 46

3.3.2.5 Ring Carbonyl Compounds and their Hydroxy Tautomers

3.3.2.5.1 Survey of structures

Hydroxy derivatives of thiophene, pyrrole and furan (**202** and **205**) are tautomeric with alternative non-aromatic carbonyl forms (**203**, **204** and **206**), as discussed in Section 2.3.5.2.



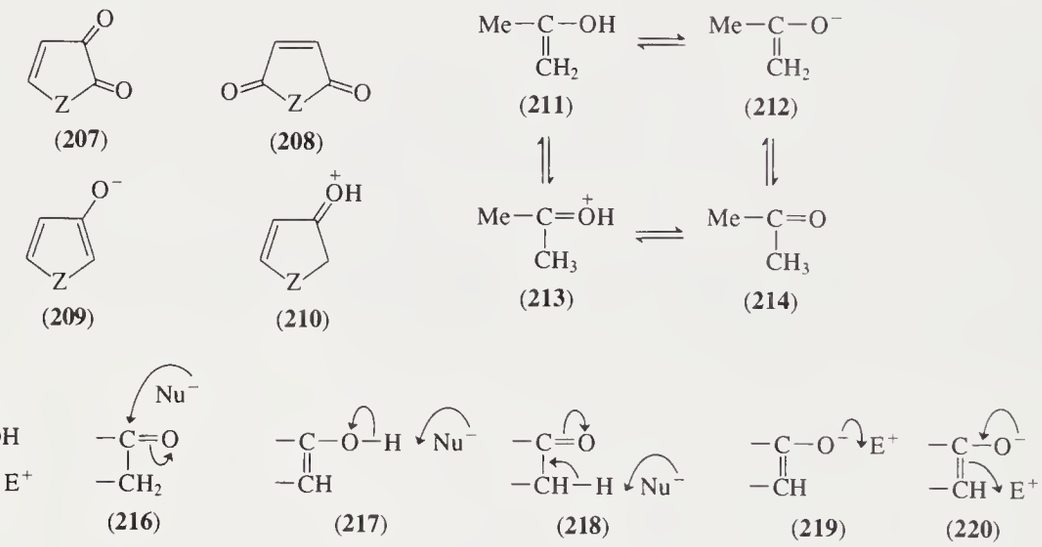
(**202**) (**203**) (**204**) (**205**) (**206**)

In the majority of cases, the equilibrium lies predominantly in favor of the carbonyl tautomer, and for this reason these compounds are considered in the present section. (Most amino and mercapto analogues, while also tautomeric, exist predominantly as such, and they are therefore considered as substituted aromatic compounds.)

Compounds of types (**207**) and (**208**) bear a formal structural resemblance to quinones but little similarity in properties; this can be ascribed to the lower aromaticity of the parent heterocyclic systems.

3.3.2.5.2 Interconversion and reactivity of tautomeric forms

Interconversion of the hydroxy and carbonyl forms of these heterocycles proceeds through an anion (as **209**) or a cation (as **210**) just as the enol (**211**) and keto forms (**214**) of acetone are interconverted through the ions (**212**) or (**213**). Reactions of the various species derived from the heterocyclic compounds are analogous to those of the corresponding species from acetone: hydroxy forms react with electrophilic reagents (**215**) and carbonyl forms with nucleophilic reagents (**216**). In addition, either form can lose a proton (**217**, **218**) to give an anion which reacts very readily (more so than the parent heterocycles) with electrophilic reagents on either oxygen (**219**) or carbon (**220**).

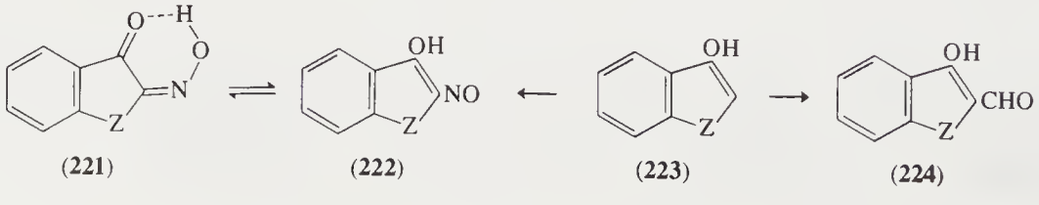


(**207**) (**208**) (**209**) (**210**) (**211**) (**212**) (**213**) (**214**) (**215**) (**216**) (**217**) (**218**) (**219**) (**220**)

3.3.2.5.3 Reactions of hydroxy compounds with electrophiles

Electrophilic substitution reactions at low pH values probably involve the hydroxy form:

(a) Nitrosation ($NaNO_2 - H_2O - HCl$) to give tautomeric products, *e.g.* (**223**)→(**222**)⇌(**221**), Z = NH, O, S.

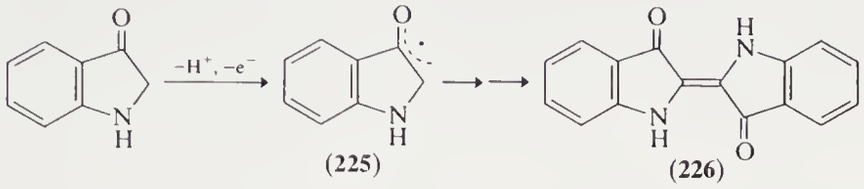


(**221**) (**222**) (**223**) (**224**)

(b) Gattermann reaction (**223**→**224**).
(c) Coupling with diazonium salts (Scheme 47).

Scheme 47

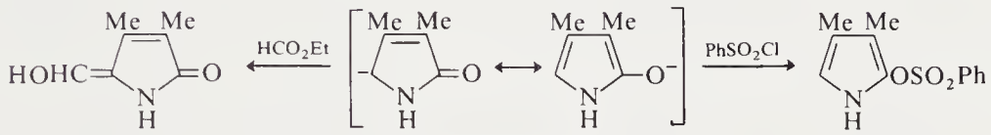
Indoxyl and thioindoxyl are easily oxidized, *e.g.* by $K_3Fe(CN)_6$, to indigo (**226**) and thioindigo, respectively, *via* dimerization of radical intermediates (**225**).



(**225**) (**226**)

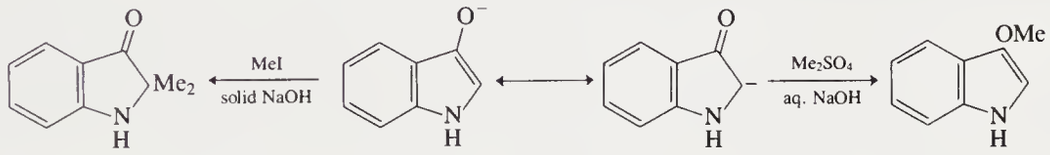
3.3.2.5.4 Reactions of anions with electrophiles

These heterocyclic compounds undergo many reactions which are similar to those of the acetone enolate. Thus, Claisen condensation and *o*-sulfonylation are exemplified by Scheme 48.



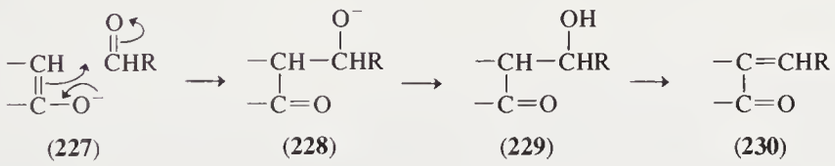
Scheme 48

The indoxyl (3-hydroxyindole) anion undergoes carbon or oxygen alkylation (Scheme 49).



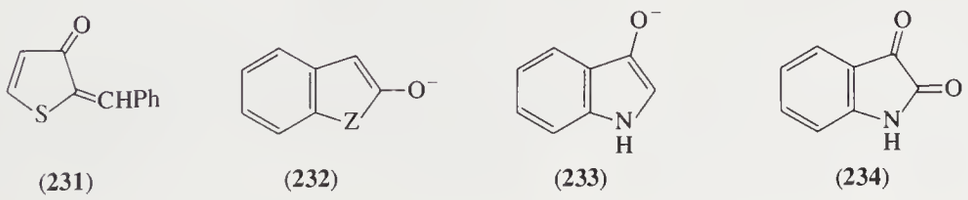
Scheme 49

Aldol condensation with aldehydes and ketones gives hydroxy compounds (**227** → **229**) which usually spontaneously lose water (by a reverse Michael addition) to give unsaturated compounds (**230**).

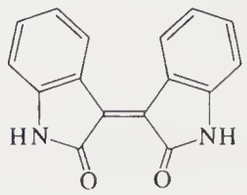


(**227**) (**228**) (**229**) (**230**)

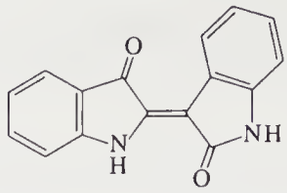
The following exemplify reactions of the aldol type. 3-Hydroxythiophene with benzaldehyde forms (**231**). Anions derived from oxindole (**232**; Z = NH) and indoxyl (**233**) react with isatin (**234**) to give isoindigo (**235**) and indirubin (**236**).



(**231**) (**232**) (**233**) (**234**)



(235)



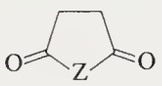
(236)

3.3.2.5.5 *Reactions of carbonyl compounds with nucleophiles*

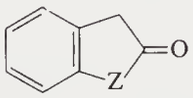
Nucleophilic reagents attack the carbonyl carbon atom; the subsequent course of this reaction parallels that in aliphatic chemistry. If the carbonyl group and the heteroatom are adjacent, the ring is usually opened. If they are not adjacent, a carbonyl addition compound results, which often eliminates water spontaneously. The reactions of carbonyl groups in both environments are discussed.

(i) Carbonyl adjacent to heteroatom

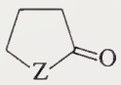
Ring opening by nucleophilic reagents necessitates group Z gaining a negative charge, the ease of which depends on the heteroatom (S > O ≫ NH) and on the ring type (*e.g.* **237** > **238** > **239**). Succinic (**237**; Z = O), maleic and phthalic anhydrides and imides behave similarly to the acyclic acid anhydrides and imides.



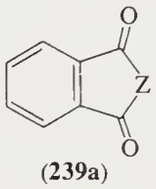
(237)



(238)

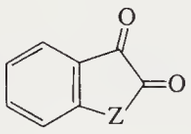


(239)

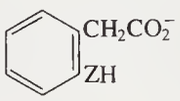


(239a)

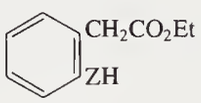
The ring opening of phthalimides (**239a**; Z = NR) by hydrazine to give a primary amino compound and 1,4-phthalazinedione (**239a**; Z = NH—NH) (Ing–Manske reaction) is important in the modified Gabriel synthesis. 2-Coumaranone, its S-analogue (**238**; Z = O, S) and the diones (**240**; Z = O, S) react reversibly with hydroxide and alkoxide ions to give salts (as **241**) and esters (as **242**) of the ring-opened acid. The corresponding reactions with indoxyl (**243**; Z = NH) are much more difficult, but in the case of isatin (**234**), the second carbonyl group facilitates ring fission, *e.g.* treatment of (**234**) with sodium hydroxide gives sodium isatinate.



(240)



(241)



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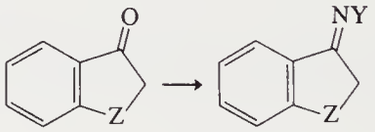
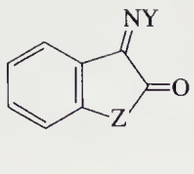


(243) (244)

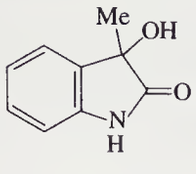
(ii) Carbonyl not adjacent to heteroatom

Carbonyl groups not adjacent to a heteroatom are less stabilized by resonance and react with the relatively weakly nucleophilic 'ketonic' reagents. If carbonyl groups of both types are present, as in (**240**; Z = O, NH), then the carbonyl group not adjacent to the heteroatom is preferentially attacked. Thus, isatin and indoxyl and their O- and S-analogues (**240**, **243**) react with hydroxylamine, hydrazine, phenylhydrazine, semicarbazide, *etc.*, to give oximes, hydrazones, phenylhydrazones, semicarbazones, *etc.* (**243**→**244**; **240**→**245**).

The reactive 3-carbonyl group in compounds of type (**240**) undergoes aldol condensation with active methylene compounds; such reactions of isatin with indoxyl, oxindole (Section 3.3.2.5.4) and with thiophenes (Section 3.3.1.5.7. ii) have already been mentioned. These compounds also react with Grignard reagents and phosphorus halides as expected, *e.g.* isatin (**240**; Z = NH) with MeMgBr and PCl_3 yields (**246**) and (**247**), respectively.



(245)



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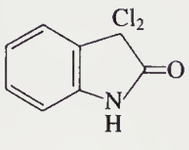
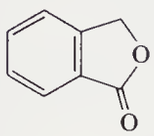
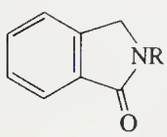


(247)



(248)



(249)

3.3.2.5.6 Reductions of carbonyl and hydroxy compounds

In cyclic anhydrides and imides, one carbonyl group is usually easily reduced; thus phthalic anhydride with H_2/Ni gives phthalide (**248**), and phthalimides with Zn/HCl yield phthalamides (**249**). Indoxyl and its O- and S-analogues can be reduced (Zn–HOAc) to indole, *etc.*

3.3.3 REACTIVITY OF SUBSTITUENTS

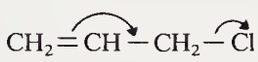
3.3.3.1 General Survey of Reactivity

In general, substituents attached to furan, thiophene and pyrrole ring carbon atoms (we consider separately substituents attached to pyrrole nitrogen or thiophene sulfur) react similarly to those on benzenoid nuclei, but there are some important differences:

(a) Some reactions requiring vigorous conditions which succeed in the benzene series fail because the heterocyclic rings are susceptible to attack by electrophilic reagents; see Section 3.3.1.4.

(b) Hydroxy groups attached directly to the heterocyclic nuclei usually exist largely, or entirely, in an alternative, non-aromatic tautomeric form (Section 2.3.5.2); their reactions show little resemblance to those in phenols, and have been considered with the non-aromatic compounds in Section 3.3.2.5. Amino derivatives, although highly reactive, generally exist in the amino form (see Section 3.3.3.4.2).

(c) Benzyl and allyl halides are more reactive than other alkyl halides because the halogen is labilized by electronic shifts of the type shown below; these shifts are enhanced in thienyl- and especially in pyrryl- and furyl-methyl halides.



(d) Hydroxymethyl and aminomethyl groups on the heterocyclic compounds are activated in a manner similar to, although less marked than, the chloromethyl derivatives.

The validity of the Hammett relationship $\log K/K_0 = \rho\sigma$ has been extensively investigated for five-membered heteroaromatic compounds and their benzo analogues. The ratio ρ(heterocycle)/ρ(benzene) is closest to unity for thiophene. Judged from work on the polarographic reduction of nitro compounds, the ability to transmit electronic effects is HC=CH ≈ S < O < NH.

3.3.3.2 Fused Benzene Rings

3.3.3.2.1 Electrophilic attack

Most common reactions of benzene rings involve attack by electrophilic reagents; since thiophene, pyrrole and furan are more readily attacked than benzene, reaction in fused-ring compounds should occur at a free position in the heterocyclic ring in preference to the benzene ring. This generalization may become invalid if (a) there is a strongly deactivating substituent (*e.g.* CHO, CO_2Et, NO_2) in the heterocyclic ring or (b) a strongly activating substituent (*e.g.* NH_2, OH) is present in the benzene ring. When both positions of the heterocyclic ring are substituted, substitution in the benzene ring is generally observed, though many examples of substituent displacement (*ipso* substitution) are known.

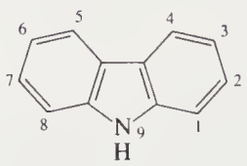
Carbazole (**250**), dibenzofuran (**251**; Z = O) and dibenzothiophene (**251**; Z = S) behave as diphenylamine, diphenyl ether and diphenyl sulfide in their substitution reactions and thus electrophilic substitution occurs at the positions *para* to the heterocyclic atom, as exemplified for:

(a) Dibenzofuran (**251**; Z = O): bromination (Br_2–CS_2), sulfonation ($ClSO_3H$) and formylation (HCN–HCl–$AlCl_3$).

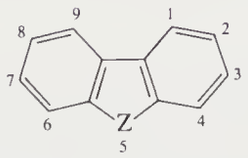
(b) Dibenzothiophene (**251**; Z = S): nitration (HNO_3–AcOH) and bromination (Br_2–CS_2).

(c) Carbazole (**250**): acylation ($RCOCl-AlCl_3$), halogenation ($SOCl_2$ or Br_2-CS_2) and sulfonation (H_2SO_4).

(d) Dibenzoselenophene and dibenzotellurophene (**251**; Z = Se, Te) undergo nitration in the 2-position.



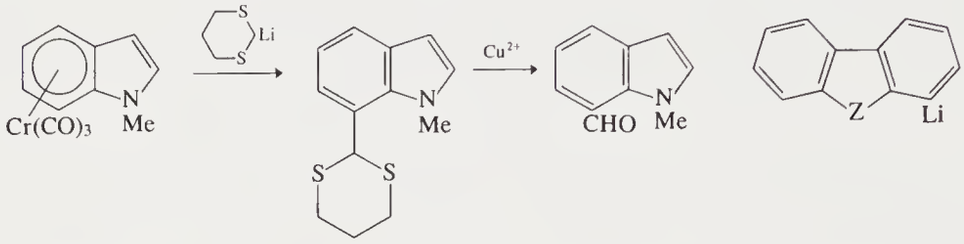
(**250**)



(**251**) Z=O, S, Se or Te

3.3.3.2.2 Nucleophilic attack

The possibility of activating the indole nucleus to nucleophilic substitution has been realized by formation of chromium tricarbonyl complexes. For example, the complex from *N*-methylindole (**252**) undergoes nucleophilic substitution with 2-lithio-1,3-dithiane to give a product (**253**) which can be transformed into 1-methylindole-7-carbaldehyde (**254**) ⟨78CC1076⟩.



(**252**) (**253**) (**254**) (**255**)

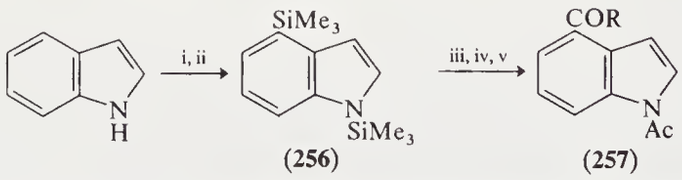
Alkyllithium compounds metallate dibenzofuran, dibenzothiophene and *N*-alkylcarbazoles (in increasing order of difficulty) to form compounds of type (**255**); substitution occurs *ortho* to the heteroatom as expected from benzene chemistry.

3.3.3.2.3 Reactions with electrons

Selective reduction of indole in the benzene ring can be achieved by treatment with lithium in liquid ammonia, which gives a mixture of the 4,7-dihydro and 4,5,6,7-tetrahydro derivatives.

Birch reduction of indole with lithium metal in THF in the presence of trimethylsilyl chloride followed by oxidation with *p*-benzoquinone gave 1,4-bis(trimethylsilyl)indole (**256**). This is readily converted in two steps into 1-acetyl-4-trimethylsilylindole. Friedel–Crafts acylation of the latter compound in the presence of aluminum chloride yields the corresponding 4-acylindole (**257**) ⟨82CC636⟩.

For the reduction of indolizine see Section 3.3.1.7.5.

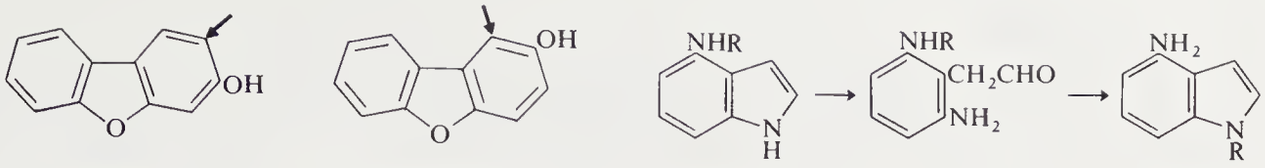


(**256**) (**257**)

i, Li, THF, Me_3SiCl; ii, *p*-benzoquinone; iii, aqueous MeOH; iv, NaH, AcCl; v, RCOCl, CH_2Cl_2, $AlCl_3$, r.t.

3.3.3.2.4 Reactions of substituents on benzene rings

Substituents on fused benzene rings undergo the usual reactions expected in the benzene series. The orientation in the diazo coupling reactions with hydroxy compounds (**258**) and (**259**) indicates that there is little 'bond fixation' in dibenzofuran, a distinct contrast to naphthalene.



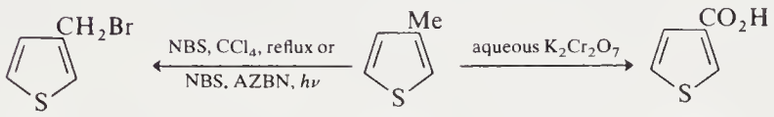
(258) (259) (260) (261)

4-Alkylaminoindoles (**260**) rearrange to 4-amino-1-alkylindoles (**261**) when heated with *p*-toluenesulfonic acid hydrate ⟨82CC1356⟩.

3.3.3.3 Other *C*-Linked Substituents

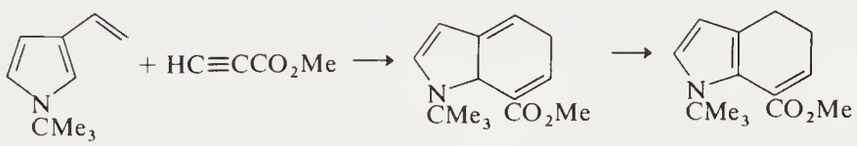
3.3.3.3.1 Alkyl and vinyl groups

The reactivity of alkyl groups on five-membered rings with one heteroatom is similar to that of alkyl groups on benzenoid rings. Because of the high reactivity of the heterocyclic nuclei, specific reactions of the alkyl groups may be difficult to carry out . However, oxidation of alkyl to carboxyl can be achieved (*e.g.* **263**→**264**) ⟨65JOC1453⟩ and selective bromination of alkyl groups (*e.g.* **263**→**262**) has been reported ⟨76SC475⟩. Further bromination of (**262**) yields the dibromomethyl derivative. The practical application of these reactions may require either nuclear deactivation by substitution of electron-withdrawing groups or, in the case of halogenation, that all the nuclear carbon atoms carry substituents.



(262) (263) (264)

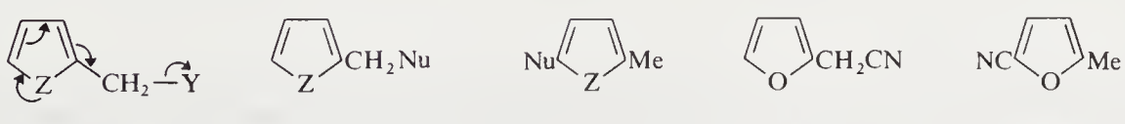
2-Vinylfuran reacts in high yield with maleic anhydride in ether at room temperature to form the adduct involving the exocyclic double bond. Similarly, 2- and 3-vinylpyrroles react with π-electron-deficient alkenes and alkynes under relatively mild conditions to give the corresponding tetrahydro- and dihydro-indoles (Scheme 50) ⟨80JOC4515⟩. 2-Vinylbenzo[*b*]furan and 2- and 3-vinylindoles similarly give adducts involving the exocyclic double bond.



Scheme 50

3.3.3.3.2 Substituted alkyl groups: general

As discussed previously (Section 3.3.3.1), halomethyl, hydroxymethyl and aminomethyl groups show enhanced reactivity toward nucleophilic attack because of the ease with which the halogen, hydroxy or amino group is lost (**265**). Both side-chain (**266**) and nuclear substitution products (**267**) have been obtained (Scheme 51). These two possibilities are exemplified by the reaction of furfuryl chloride with sodium cyanide to give (**266a**) and (**267a**).

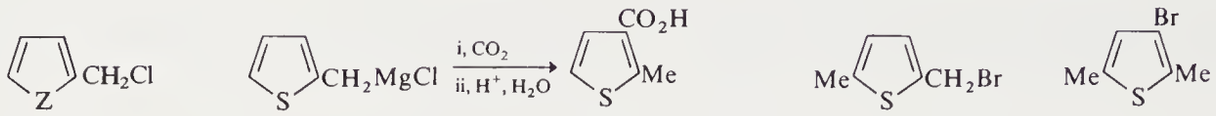


(265) (266) (267) (266a) (267a)

Scheme 51

3.3.3.3.3 Halomethyl

The furfuryl halides (*cf.* **268**; Z = O) are exceedingly reactive; they are usually not isolated but are used in solution as intermediates because of their instability. The halogen may be replaced directly by amino or alkoxy groups, but with potassium cyanide the S_N' product (**267a**) is also formed.



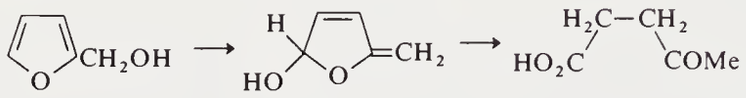
(268) **(269)** **(270)** **(271)** **(272)**

2-Chloromethylthiophene shows similar reactivity to benzyl chloride, in that it is readily converted into 2-cyanomethylthiophene, thiophene-2-carbaldehyde (by treatment with hexamethylenetetramine) and a Grignard reagent (**269**). The latter reacts with electrophiles to give 2-methyl-3-substituted thiophenes (*e.g.* **270**).

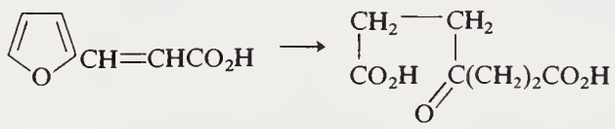
2-Bromomethyl-5-methylthiophene gives normal displacement products with amines but it is isomerized on attempted reaction with copper(I) cyanide (**271**→**272**) ⟨48MI130200⟩.

3.3.3.3.4 Hydroxymethyl

Whereas 2-hydroxymethylthiophene reacts normally with hydrogen halides to give 2-halomethylthiophenes, reaction of 2-hydroxymethylfuran (2-furfuryl alcohol) with hydrochloric acid results in formation of laevulinic acid (**274**) *via* the S_N' intermediate (**273**). The conversion of 2-furanacrylic acid (**275**) into an ester of γ-oxopimelic acid (**276**) by ethanolic hydrochloric acid is a related reaction involving an analogous intermediate.



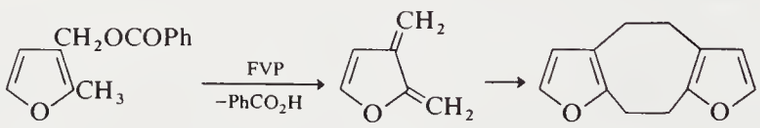
(273) **(274)**



(275) **(276)**

Reduction of 2-hydroxymethylpyrroles with lithium aluminum hydride or diborane yields the corresponding 2-methylpyrroles.

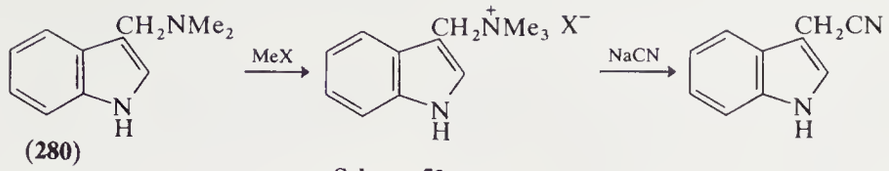
The diene (**278**), generated by flash vacuum pyrolysis of 2-methyl-3-furylmethyl benzoate (**277**), on dimerization yields 51% of compound (**279**). Diene (**278**) has been trapped by addition of methyl acrylate ⟨81JA6691⟩.



(277) **(278)** **(279)**

3.3.3.3.5 Aminomethyl

Aminomethylindoles are particularly important synthetic intermediates. 3-Dimethylaminomethylindole (gramine) (**280**) and especially its quaternary salts readily undergo displacement reactions with nucleophiles (Scheme 52).



(280)

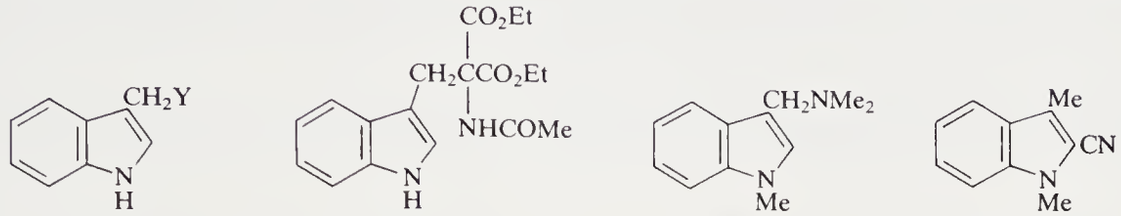
Scheme 52

(a) Potassium cyanide gives 3-indoleacetonitrile which can in turn be reduced to tryptamine (**281**; $Y = CH_2NH_2$), or hydrolyzed to 3-indoleacetic acid (**281**; $Y = CO_2H$).

(b) Diethyl acetamidomalonate gives (**282**), which can be hydrolyzed to tryptophan.

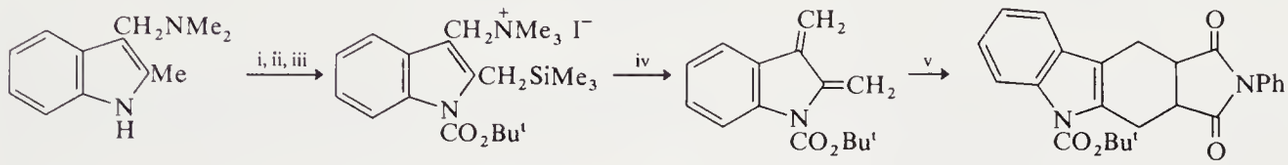
(c) Nitroethane forms (**281**; $Y = CHMeNO_2$).

1-Methylgramine (**283**) generally reacts analogously to gramine, but with potassium cyanide it yields a mixture of the 2-cyano-3-methyl (**284**) (by S_N' reaction) and the 3-cyanomethyl derivatives.



(281) **(282)** **(283)** **(284)**

Indole-2,3-quinodimethanes, generated from 2-methylgramine as shown in Scheme 53, undergo intermolecular cycloaddition reactions with dienophiles to yield carbazole derivatives ⟨82T2745⟩.



i, Na dimsylate, Bu^tOCON_3; ii, LTMP/THF, −78 °C, $ClSiMe_3$; iii, MeI;
iv, $Bz_4\overset{+}{N}F^-$ v, *N*-phenylmaleimide

Scheme 53

3.3.3.3.6 Carboxylic acids, esters and anhydrides

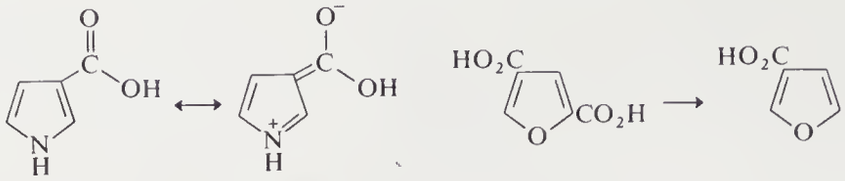
Carboxylic acids show most of the standard reactions of benzoic acid. Amides, esters, hydrazides, azides and nitriles can be prepared by standard methods. Thiophenes form stable acid chlorides, furans unstable ones, and *N*-unsubstituted pyrroles do not form them.

The acid dissociation constants of some representative carboxylic acids are given in Table 3.

Table 3 pK_a Values of Pyrrole-, Furan-, Thiophene-, Selenophene- and Tellurophene-carboxylic Acids

Acid	pK_a (H_2O, 25 °C)
Pyrrole-2-carboxylic acid	4.4
Pyrrole-3-carboxylic acid	5.0
Furan-2-carboxylic acid	3.15
Furan-3-carboxylic acid	4.0
Thiophene-2-carboxylic acid	3.5
Thiophene-3-carboxylic acid	4.1
Selenophene-2-carboxylic acid	3.6
Tellurophene-2-carboxylic acid	4.0
Benzoic acid	4.2

Pyrrole-3-carboxylic acid (**285**) is appreciably weaker than benzoic acid and this is attributed to the stabilization of the undissociated acid by electron release from nitrogen. The 2-carboxylic acids of furan, thiophene, selenophene and tellurophene are all stronger acids than benzoic acid ⟨77AHC(21)119⟩.



(285a) (285b) Scheme 54

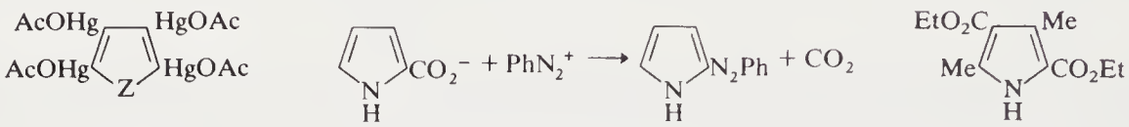
Pyrrole-2-carboxylic acid easily loses the carboxylic group thermally. Pyrrole-3-carboxylic acid and furan-2- and -3-carboxylic acids also readily decarboxylate on heating to about 200 °C. Thiophenecarboxylic acids require higher temperatures or a copper–quinoline catalyst. In furans, 2-carboxylic acid groups are lost more readily than 3-carboxylic acid groups (Scheme 54).

Decarboxylation often takes place during electrophilic substitution of the nucleus, for example:

(a) Thiophene-2-carboxylic acid and mercuric acetate give tetraacetoxymercurithiophene (**286**; Z = S).

(b) 2-Furoic acid and acetyl nitrate give 2-nitrofuran.

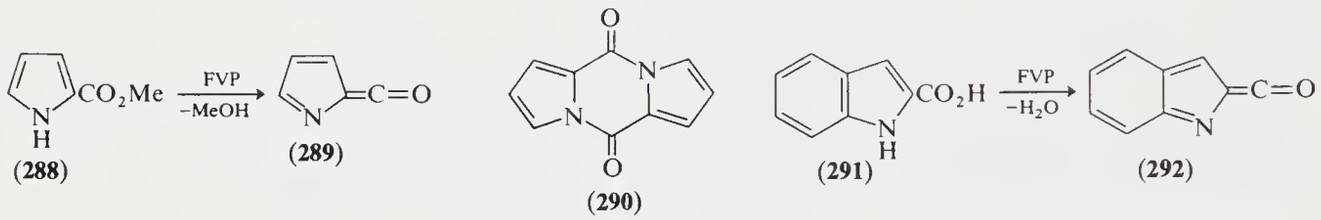
(c) Reaction of the anion of pyrrole-2-carboxylic acid with benzenediazonium ion results in the displacement of carbon dioxide rather than hydrogen (Scheme 55).



(286) Scheme 55 (287)

In the pyrrole series, ester groups α to nitrogen are more readily hydrolyzed by alkali, but those in a β position more readily by acid. Thus, in compounds such as diethyl 2,4-dimethylpyrrole-3,5-dicarboxylate (**287**) either ethoxycarbonyl group may be selectively hydrolyzed and, if desired, subsequently eliminated by decarboxylation.

Flash vacuum pyrolysis of 2-methoxycarbonylpyrrole (**288**) gives the ketene (**289**), characterized by IR absorption at 2110 cm^{-1}. On warming to −100 to −90 °C the dimer (**290**) is formed ⟨82CC360⟩. Flash vacuum pyrolysis of indole-2-carboxylic acid (**291**) results in loss of water and the formation of a ketene (**292**) showing absorption at 2106 cm^{-1} ⟨82CC360⟩.

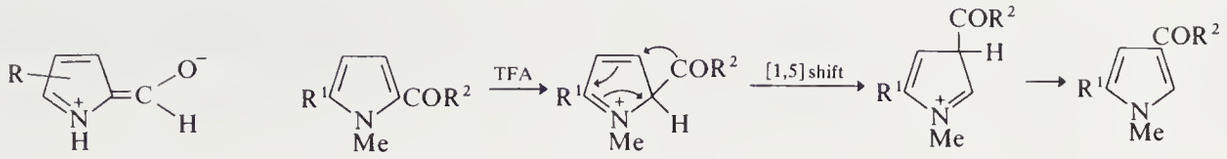


(288) (289) (290) (291) (292)

The anhydride of thiophene-2,3-dicarboxylic acid is a precursor of 2,3-didehydrothiophene which is trapped as [4 + 2] and [2 + 2] cycloaddition products with dienes ⟨81T4151⟩.

3.3.3.3.7 Acyl groups

The carbonyl reactivity of pyrrole-, furan-, thiophene- and selenophene-2- and -3-carbaldehydes is very similar to that of benzaldehyde. A quantitative study of the reaction of *N*-methylpyrrole-2-carbaldehyde, furan-2-carbaldehyde and thiophene-2-carbaldehyde with hydroxide ions showed that the difference in reactivity between furan- and thiophene-2-carbaldehydes was small but that both of these aldehydes were considerably more reactive to hydroxide addition at the carbonyl carbon than *N*-methylpyrrole-2-carbaldehyde ⟨76JOC1952⟩. Pyrrole-2-aldehydes fail to undergo Cannizzaro and benzoin reactions, which is attributed to mesomerism involving the ring nitrogen (see **293**). They yield 2-hydroxymethylpyrroles (by $NaBH_4$ reduction) and 2-methylpyrroles (Wolff–Kishner reduction). The IR spectrum of the hydrochloride of 2-formylpyrrole indicates that protonation occurs mainly at the carbonyl oxygen atom and only to a limited extent at C-5.

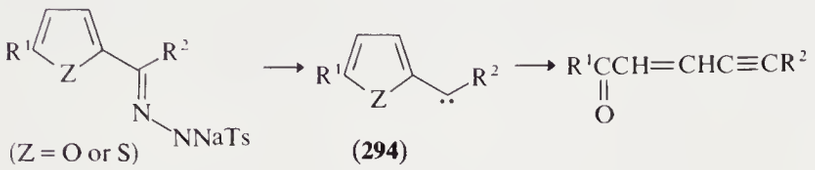


(293) **Scheme 56**

Acyl-pyrroles, -furans and -thiophenes in general have a similar pattern of reactivity to benzenoid ketones. Acyl groups in 2,5-disubstituted derivatives are sometimes displaced during the course of electrophilic substitution reactions. *N*-Alkyl-2-acylpyrroles are converted by strong anhydrous acid to *N*-alkyl-3-acylpyrroles. Similar treatment of *N*-unsubstituted 2- or 3-acylpyrroles yields an equilibrium mixture of 2- and 3-acylpyrroles; pyrrolecarbaldehydes also afford isomeric mixtures ⟨81JOC839⟩. The probable mechanism of these rearrangements is shown in Scheme 56. A similar mechanism has been proposed for the isomerization of acetylindoles.

Diborane reduction of pyrrole and indole ketones affords the corresponding alkyl-pyrroles and -indoles ⟨68T1145⟩.

Carbenes of type (**294**), generated by thermal decomposition of the appropriate tosylhydrazone salts, undergo ring opening more readily when the ring heteroatom is oxygen than when it is sulfur ⟨78JA7927⟩.

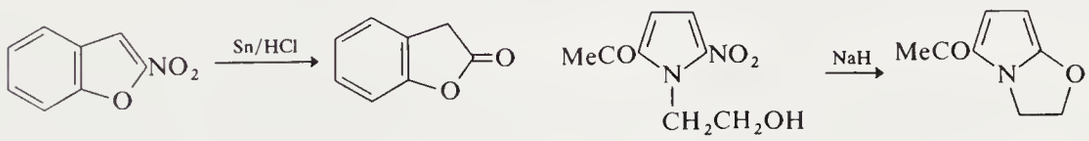


(Z = O or S) (**294**)

3.3.3.4 *N*-Linked Substituents

3.3.3.4.1 Nitro

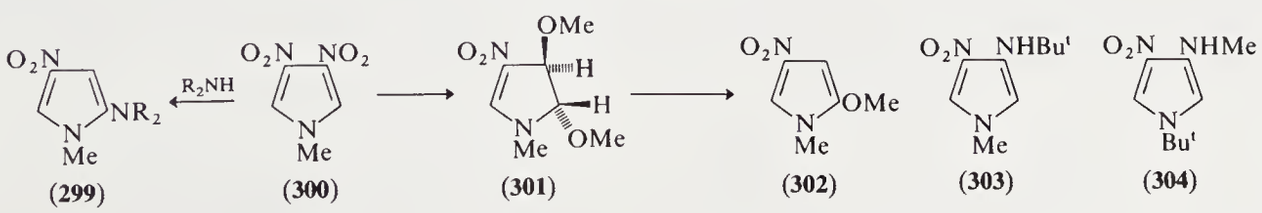
Both 2- and 3-nitrothiophenes are reduced by tin and hydrochloric acid to the corresponding aminothiophenes. 2-Acetamidofurans are prepared by the reduction of 2-nitrofurans in the presence of acetic anhydride. Benzofuranone (**296**) and not 2-aminobenzofuran is obtained from tin and hydrochloric acid reduction of 2-nitrobenzo[*b*]furan (**295**).



(**295**) (**296**) (**297**) (**298**)

Although in general the π-excessive nature of the heterocyclic rings under discussion reduces their reactivity to nucleophilic substitution, a number of interesting reactions have been reported in which the leaving group is a nitro group. An example of intramolecular nucleophilic displacement of a pyrrole nitro group is provided by the base-induced cyclization of 2-acetyl-1-(2-hydroxyethyl)-5-nitropyrrole (**297**→**298**) ⟨71JCS(C)2554⟩.

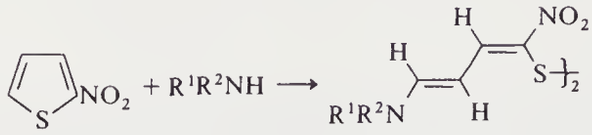
1-Methyl-3,4-dinitropyrrole (**300**) with methanolic sodium methoxide yields product (**301**) which on treatment with trifluoroacetic acid gives the 2-methoxypyrrole (**302**) ⟨78CC564⟩.



(**299**) (**300**) (**301**) (**302**) (**303**) (**304**)

With secondary amines such as piperidine or dimethylamine the formal products (**299**) of *cine* substitution are obtained; with primary amines (*e.g.* *t*-butylamine), in addition to the displacement

product (**303**), a rearranged product (**304**) is obtained in which the nitrogen-bearing methyl becomes exocyclic ⟨80CC123⟩. Earlier studies on the reaction of 2-nitrothiophene with secondary amines showed that ring-opened products (**305**) are obtained ⟨74JCS(P1)2357⟩.

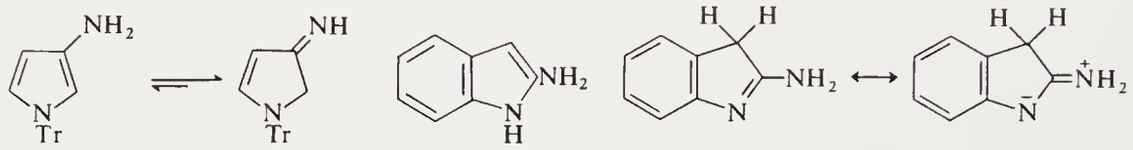


(**305**)

3.3.3.4.2 Amino

The free bases are much less stable than aniline, particularly 2-amino-pyrroles and -furans which are very easily oxidized or hydrolyzed. 2-Aminofurans substituted with electron-withdrawing groups (*e.g.* NO_2) are known and 3-amino-2-methylfuran is a relatively stable amine which can be acylated and diazotized. 2-Aminothiophene can be diazotized and the resulting diazonium salt coupled with *β*-naphthol.

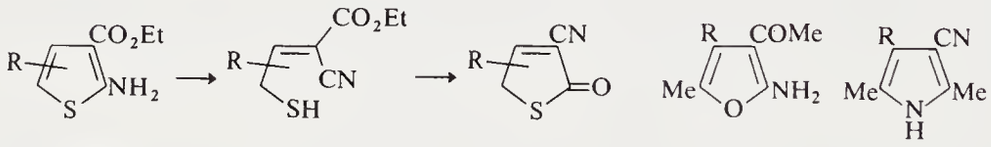
Most of these compounds exist predominantly in the amino form. However, there are exceptions. 3-Amino-1-tritylpyrrole (**306**) appears to exist in solution exclusively in the imino-Δ^4-pyrroline form (**307**) ⟨83JCS(P1)93⟩. 2-Aminoindole (**308**) is unusual in that it exists mainly as the 3*H*-tautomer (**309**), which is stabilized by amidine resonance.



(**306**) (Tr = CPh_3) (**307**) (**308**) (**309a**) (**309b**)

The amino compounds form salts and acylamino derivatives which are considerably more stable.

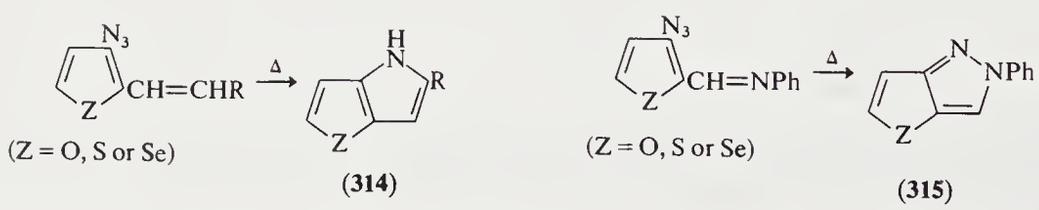
Interesting ring-opening reactions can be initiated by proton loss from the amino group. Thus, 2-amino-3-ethoxycarbonylthiophenes (**310**) with ethanolic sodium ethoxide give cyanothiolenones (**311**) ⟨75JPR861⟩. In a similar sequence 2-amino-3-acetylfurans (**312**) are converted into 3-cyano-2-methylpyrroles (**313**) by aqueous ammonia. ⟨78JOC3821⟩.



(**310**) (**311**) (**312**) (**313**)

3.3.3.4.3 Azides

Five-membered ring heterocyclic azides are readily reduced (H_2S, $LiAlH_4$) to the corresponding amines ⟨82JOC3177⟩. On thermolysis they lose nitrogen, thereby generating nitrenes. For example, thermolysis of 3-azido-2-vinyl derivatives in xylene at 120–130 °C yields [3,2-*b*]-fused pyrroles (**314**); nitrene insertion into an *ortho*-disposed imino function similarly yields [3,2-*b*]-fused pyrazoles (**315**) ⟨76ACS(B)391, 77CS(12)1⟩.



(Z = O, S or Se) (**314**) (Z = O, S or Se) (**315**)

3.3.3.5 *O*-Linked Substituents

Hydroxy compounds are considered in Section 3.3.2.5, with their non-aromatic carbonyl tautomers.

3.3.3.6 *S*-Linked Substituents

Thiophene-2-sulfonic acid is a strong acid, similar to benzenesulfonic acid. It forms a sulfonyl chloride with phosphoryl chloride which on reduction with zinc yields thiophene-2-sulfinic acid.

Pyrrolethiols, readily obtained from the corresponding thiocyanates by reduction or treatment with alkali, rapidly oxidize to the corresponding disulfides. They are converted into thioethers by reaction with alkyl halides in the presence of base. Pyrrole-, furan- and thiophene-thiols exist predominantly as such rather than in tautomeric thione forms.

3.3.3.7 Halo Groups

3.3.3.7.1 Nucleophilic displacement

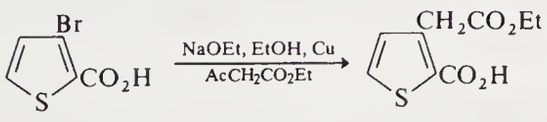
Halopyrroles do not readily undergo nucleophilic displacement.

Halogen-substituted furans and thiophenes are also relatively inert, although their reactivity is somewhat greater than that of the corresponding aryl halides. Kinetic data are available for the nucleophilic displacement of halogen from 2-halofurans with piperidine. 2-Chlorofuran has about the same reactivity as bromobenzene and 2-chloro- and 2-bromo-thiophene have about a tenfold greater rate of reaction than the corresponding benzene compounds ⟨57JOC133⟩. As in the benzene series, the introduction of powerfully electron-withdrawing groups, such as nitro, carboxy or ester groups, greatly facilitates nucleophilic substitution. Halothiophenes which contain a nitro group react very much faster with nucleophilic reagents than the corresponding benzene derivatives, as shown by the rate data in Table 4.

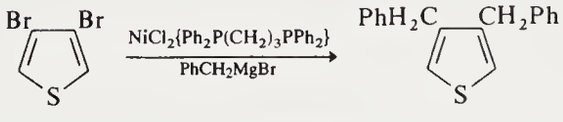
Table 4 Relative Pseudo-first-order Rates of Displacement of Bromonitrothiophenes and Bromonitrobenzenes with Piperidine at 25 °C ⟨57NKK954⟩

Compound	*Rate*
m-Bromonitrobenzene	1
p-Bromonitrobenzene	1.85×10^{2}
o-Bromonitrobenzene	1.62×10^{3}
5-Bromo-2-nitrothiophene	2.84×10^{4}
2-Bromo-3-nitrothiophene	6.32×10^{5}
5-Bromo-3-nitrothiophene	Very fast
4-Bromo-2-nitrothiophene	1.36×10^{3}
4-Bromo-3-nitrothiophene	Very fast

As in benzenoid chemistry, numerous nucleophilic displacement reactions are found to be copper catalyzed. Illustrative of these reactions is the displacement of bromide from 3-bromothiophene-2-carboxylic acid and 3-bromothiophene-4-carboxylic acid by active methylene compounds (*e.g.* $AcCH_2CO_2Et$) in the presence of copper and sodium ethoxide (Scheme 57) ⟨75JCS(P1)1390⟩.



Scheme 57

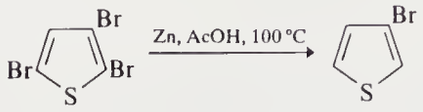


Scheme 58

3-Bromothiophenes give cross-coupled products by reaction with Grignard reagents in the presence of a nickel catalyst (Scheme 58) ⟨80TL4017⟩.

3.3.3.7.2 Reductive dehalogenation

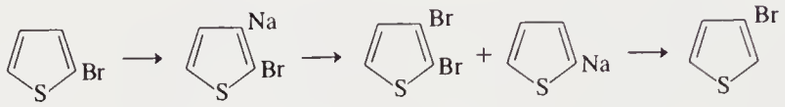
Halogen can be removed by catalytic hydrogenation and so it is possible to use halogen as a blocking group in pyrrole chemistry. In the thiophene and selenophene series, α-halogens are preferentially removed by reduction with zinc and acetic acid, as illustrated by the preparation of 3-bromothiophene (**317**) from 2,3,5-tribromothiophene (**316**) ⟨81SC25⟩.



(**316**) (**317**)

3.3.3.7.3 Rearrangement

3-Bromothiophene can also be prepared by rearrangement of the 2-bromo compound on brief treatment with sodamide in liquid ammonia. The corresponding reaction with potassamide yields 3-aminothiophene ⟨71JOC2690⟩. The mechanism of the rearrangement is given in Scheme 59. The second step is a disproportionation between two molecules.



Scheme 59

3.3.3.7.4 Formation of Grignard reagents

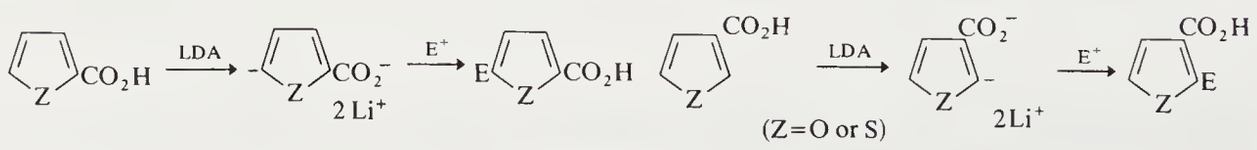
Grignard reagents can be prepared from 2-bromothiophene and 2-iodofuran; these Grignard reagents show normal reactivity. 3-Iodothiophenes also react with magnesium but 3-bromothiophene only reacts by the entrainment method. The 3-bromo compound, however, reacts smoothly with butyllithium at −70 °C to give 3-thienyllithium. If the reaction is carried out at room temperature, 3-thienyllithium acts as a lithiating agent and an equilibrium mixture of thiophene, 2-lithiothiophene and 3-bromo-2-lithiothiophene is formed. 3-Lithiofurans can similarly be obtained from 3-halofurans and butyllithium.

3.3.3.8 Metallo Groups

3.3.3.8.1 General

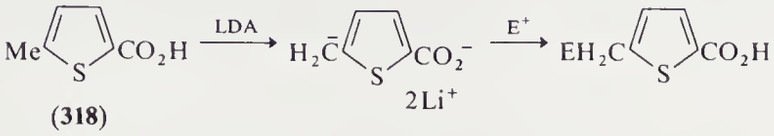
Although a limited range of Grignard reagents is available, the most widely used group is undoubtedly the lithio group introduced by direct lithiation (see Section 3.3.1.6.2). The ready formation of the lithio derivatives of pyrroles, furans and thiophenes and their benzo-fused derivatives has had a most important impact on the chemistry of these heterocyclic systems. Reaction of the lithiated heterocycles with an extremely wide range of electrophiles leads to heterocyclic derivatives with carbon, nitrogen, oxygen, sulfur and halogen linked substituents.

The dianions derived from furan- and thiophene-carboxylic acids by deprotonation with LDA have been reacted with various electrophiles (Scheme 60). The furan dianions reacted efficiently with aldehydes and ketones but not so efficiently with alkyl halides or epoxides. The thiophene dianions reacted with allyl bromide, a reaction which failed in the case of the dianions derived from furancarboxylic acids, and are therefore judged to be the softer nucleophiles ⟨81JCS(P1)1125, 80TL5051⟩.



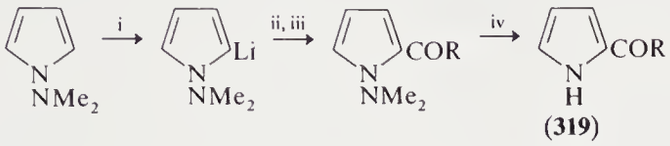
Scheme 60

The dianions of methylated thiophenecarboxylic acids (*e.g.* **318**) are also readily generated by reaction with LDA; they undergo preparatively useful reactions with a range of carbon electrophiles ⟨80JOC4528⟩.



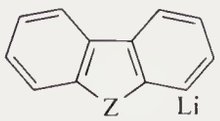
(318)

To exploit the reactions of the *C*-lithio derivatives of *N*-unsubstituted pyrroles and indoles, protecting groups such as *t*-butoxycarbonyl, benzenesulfonyl and dimethylamino have been used ⟨81JOC157⟩. This is illustrated by the scheme for preparing *C*-acylated pyrroles (**319**) ⟨81JOC3760⟩.



(319)

i, BuLi; ii, RCHO; iii, MnO_2; iv, $Cr_2(OAc)_4 \cdot 2H_2O$



(320) Z = NR, O or S

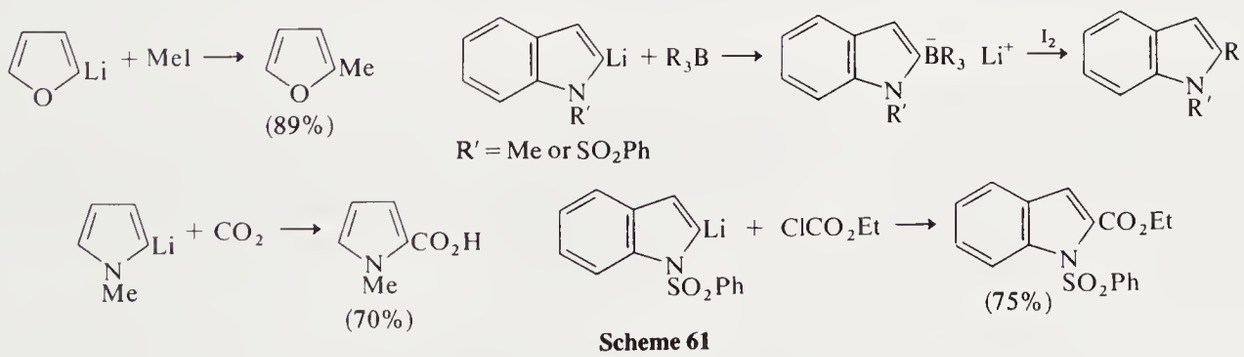
The reactions of the lithio derivatives of benzo[*b*]-fused systems indole, benzo[*b*]furan and benzo[*b*]thiophene are similarly diverse. Since indole and benzo[*b*]thiophene undergo electrophilic substitution mainly in the 3-position, the ready availability of 2-lithio derivatives by deprotonation with *n*-butyllithium is particularly significant and makes available a wide range of otherwise inaccessible compounds. The ready availability of 3-iodoselenophene and hence of 3-lithioselenophene ⟨73CHE845⟩ provides a convenient route to 3-substituted selenophenes. 2-Lithiotellurophenes are especially important precursors of tellurophene derivatives because of the restricted range of electrophilic substitution reactions which are possible on tellurophenes ⟨77AHC(21)119⟩.

Two cautions regarding the use of lithio derivatives need to be given: the possible incursion of rearrangement and ring-opening reactions ⟨78CHE353⟩. For synthetic applications of ring-opening reactions see Section 3.3.3.8.7.

The lithio derivatives of the dibenzo heterocycles (**320**) are also preparatively useful since electrophiles attack these systems *para* to the heteroatom. For a review on the lithio heterocycles see ⟨79OR(26)1⟩.

3.3.3.8.2 Formation of C—C bonds

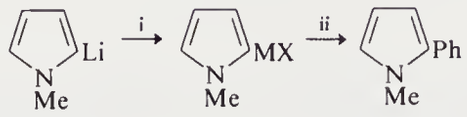
The reaction of lithio derivatives with appropriate electrophiles has been utilized in the preparation of alkyl, aryl, acyl and carboxylic acid derivatives. Representative examples of these conversions are given in Scheme 61. Noteworthy is the two-step method of alkylation involving reaction with trialkylborane followed by treatment with iodine ⟨78JOC4684⟩.



Scheme 61

Other carbon electrophiles which are frequently employed include aldehydes, ketones, esters, nitriles and amides of the type $RCONMe_2$. An indirect method of acylation involves the initial reaction of a lithio compound with an aldehyde followed by oxidation of the resulting secondary alcohol to the corresponding acyl derivative.

The transmetallation of lithio derivatives with either magnesium bromide or zinc chloride has been employed to increase further their range of synthetic application. While the reaction of 1-methyl-2-pyrrolyllithium with iodobenzene in the presence of a palladium catalyst gives only a poor yield (29%) of coupled product, the yield can be dramatically improved (to 96%) by first converting the lithium compound into a magnesium or zinc derivative (Scheme 62) ⟨81TL5319⟩.



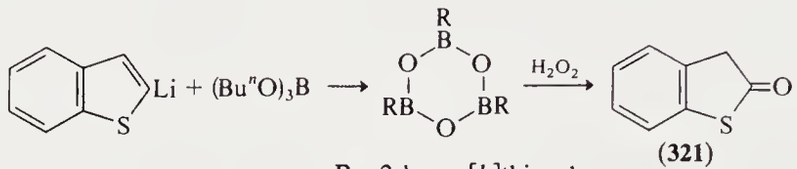
MX=MgBr or ZnCl

i, MgBr or $ZnCl_2$ in THF at r.t.; ii, PhI, $PdCl_2$(dppb), r.t. [dppb = 1,4-bis(diphenylphosphino)butane]

Scheme 62

3.3.3.8.3 Formation of C—O bonds

This can be achieved by an indirect method. The lithio derivative is first reacted with a borate ester. Sequential acid hydrolysis and oxidation yields the corresponding hydroxy derivative. This procedure is illustrated by the conversion of 2-lithiobenzo[*b*]thiophene to 2-hydroxybenzo[*b*]-thiophene, which exists predominantly in the 2(3*H*)-one tautomeric form (**321**) ⟨70JCS(C)1926⟩.

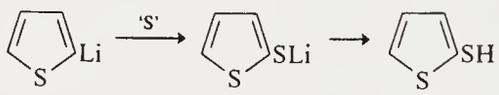


(**321**)

R = 2-benzo[*b*]thienyl

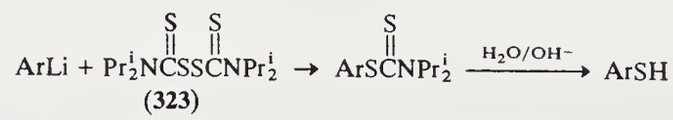
3.3.3.8.4 Formation of C—S bonds

Carbon–sulfur bonds can be formed by the reaction of elemental sulfur with a lithio derivative, as illustrated by the preparation of thiophene-2-thiol (**322**) ⟨70OS(50)104⟩. If dialkyl or diaryl disulfides are used as reagents to introduce sulfur, then alkyl or aryl sulfides are formed; sulfinic acids are available by reaction of lithium derivatives with sulfur dioxide.



(**322**)

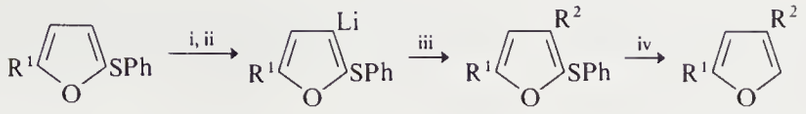
Tetraisopropylthiuram disulfide (**323**) is a reagent of choice for preparing thiols from the corresponding lithio derivatives (Scheme 63) ⟨82TL2001⟩. 2,4-Disubstituted furans, difficult to prepare by classical methods, have been prepared from 2-phenylthio-5-alkylfurans as shown in Scheme 64. The starting material is obtained by treatment of 2-alkylfurans with *n*-butyllithium followed by diphenyl disulfide ⟨81JOC2473⟩. The practicality of this approach thus illustrates the potential of the phenylthio group as a protecting group.



(**323**)

Ar=2-furyl, 2-thienyl, 2-benzo[*b*]thienyl or 4-dibenzothienyl

Scheme 63

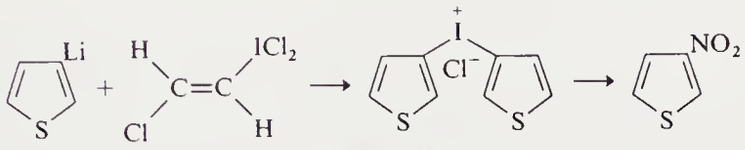


i, Br_2; ii, Bu^{t}Li; iii, alkyl iodide, aldehyde, carbon dioxide or trimethylsilyl chloride; iv, Raney Ni

Scheme 64

3.3.3.8.5 Formation of C—N bonds

Azides are formed by the reaction of lithio derivatives with *p*-toluenesulfonyl azide ⟨69JOC3430, 82JOC3177; see also 82TL699⟩, and these in turn can be converted into the corresponding amino compounds by a variety of reductive procedures. Nitro compounds are available by a novel reversal of the general pattern of reaction with electrophiles. This approach requires the initial conversion of the lithio compound into an iodonium salt followed by reaction with nitrite ion. This is illustrated by the preparation of 3-nitrothiophene (Scheme 65) ⟨72CS(2)245⟩. Other nucleophiles such as thiocyanate ion, which yields the 3-thiocyanate, can be employed. The preparative significance of these reactions is again that products not accessible by electrophilic substitution can be obtained.



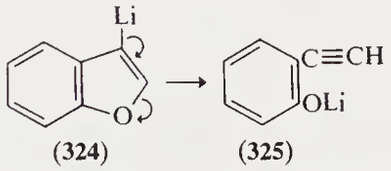
Scheme 65

3.3.3.8.6 Formation of C—halogen bonds

Synthetic procedures are available for the preparation of fluoro, chloro, bromo and iodo compounds from the corresponding lithio derivatives. Perchloryl fluoride ($FClO_3$) *N*-chlorosuccinimide, bromine and iodine are examples of reagents which can be used to introduce fluorine, chlorine, bromine and iodine, respectively.

3.3.3.8.7 Ring-opening reactions

The 3-lithio derivative of 1-benzenesulfonylindole, generated from the 3-iodo compound by low temperature (−100 °C) treatment with *t*-butyllithium, rearranges on warming to room temperature to the thermodynamically more stable 2-lithio species ⟨82JOC757⟩. The ring-opening reactions of lithiated derivatives have been reviewed comprehensively. A well-known example of this latter possibility is the ring-opening of 3-lithiobenzo[*b*]furan (**324**) to the lithium salt of 2-ethynylphenol (**325**) ⟨78CHE353⟩.

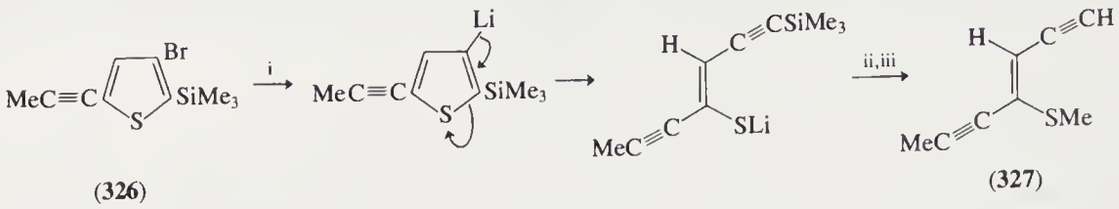


(**324**) (**325**)

The tendency for the 3-lithio derivatives of furans and thiophenes to undergo ring opening has been exploited for the synthesis of polyunsaturated acyclic compounds. A trimethylsilyl group in the 2-position increases the ring-opening tendency of 3-thienyllithium derivatives. For example, the trimethylsilyl derivative (**326**), prepared by lithiating the 3-bromothiophene with LDA followed by reaction with trimethylsilyl chloride, smoothly ring opened on treatment with butyllithium. Subsequent reaction with methyl iodide and desilylation with potassium fluoride gave the terminal alkyne (**327**) ⟨82JOC374⟩. This sequence also shows that *o*-halolithiothiophenes are significantly

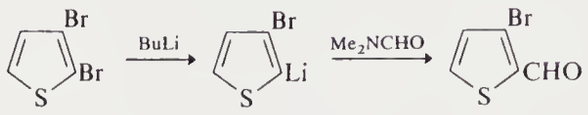
more stable than the corresponding benzenoid derivatives which are used as benzyne precursors. The preparation of 3-bromothiophene-2-carbaldehyde (**328**) also illustrates this point.

3-Lithio-2,5-dimethylselenophene shows a much greater tendency to undergo ring opening than 3-lithio-2,5-dimethylthiophene ⟨77JHC1085⟩.



(**326**) (**327**)

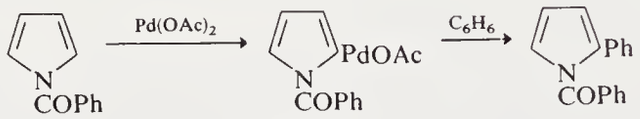
i, BuLi, hexane, ether, −20 °C, 30 min; ii, MeI; iii, $KF{\cdot}2H_2O$, DMF



(**328**)

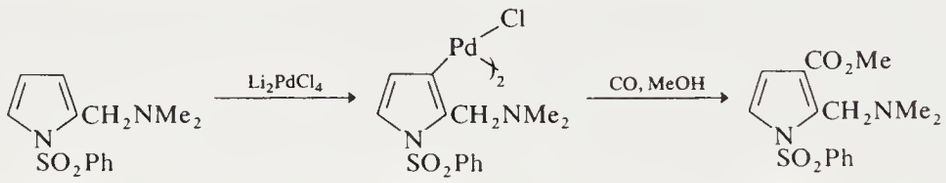
3.3.3.8.8 Palladium and mercury derivatives

There are reports of an increasing number of palladium-assisted reactions, in some of which the palladium has a catalytic function. Thus furan and thiophene undergo facile palladium-assisted alkenylation giving 2-substituted products. Benzo[*b*]furan and *N*-acetylindole yield cyclization products, dibenzofurans and carbazoles respectively, in addition to alkenylated products ⟨81JOC851⟩. The arylation of pyrroles can be effected by treatment with palladium acetate and an arene (Scheme 66) ⟨81CC254⟩.



Scheme 66

The *N*-protected pyrrole (**329**) can be palladiated, but not lithiated, in the 3-position to give the stable complex (**330**); this is readily converted into the 3-methoxycarbonylpyrrole (**331**) ⟨82JOM(234)123⟩. The use of palladium derivatives thus further increases the range of transformations made possible through the intermediacy of metallo groups.

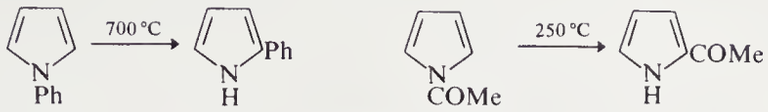


(**329**) (**330**) (**331**)

The classical uses of organomercurials include the replacement of the mercuri group (R—HgCl or R—HgOAc) by hydrogen or halogen. Chloromercurated derivatives of furan, thiophene and selenophene can be acylated with acyl halides ⟨69JOM(17)P21⟩; the range of application of organomercurials seems likely to grow since they have been shown to undergo transmetallation by a variety of transition metal reagents, particularly palladium salts, thus increasing their synthetic potential ⟨82T1713⟩.

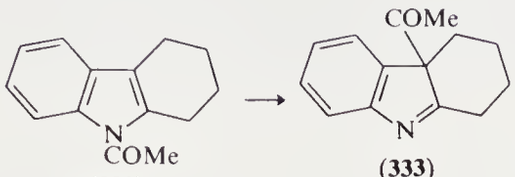
3.3.3.9 Substituents Attached to the Pyrrole Nitrogen Atom

The thermal reactions of pyrroles include the rearrangement of *N*-substituted pyrroles to *C*-substituted derivatives (Scheme 67). The rearrangement of *N*-acylpyrroles has also been reported to occur in the vapor phase on irradiation.



Scheme 67

Photoisomerization of 1-acylindoles yields 3-acylindolenines, as exemplified by the conversion of compound (**332**) into compound (**333**) ⟨81JA6990⟩.

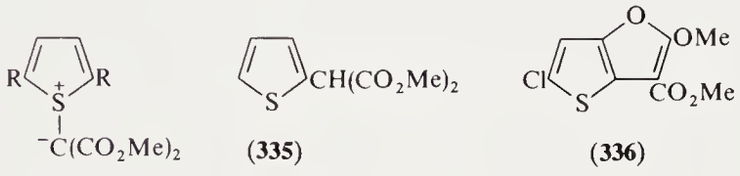


(**332**) (**333**)

Thermal rearrangement of *N*-chloropyrrole in methanol yields 2-chloropyrrole whereas acid-catalyzed rearrangement gives a mixture of 2- and 3-chloropyrrole and some 2,5-dichloropyrrole ⟨82JOC1008⟩.

3.3.3.10 Substituents Attached to the Thiophene Sulfur Atom

On heating the sulfonium ylide (**334**; R = H) the isomeric bis(methoxycarbonyl)methylthiophene (**335**) is formed ⟨78CC85⟩. Thermolysis of the ylide (**334**; R = Cl) yields the thienofuran (**336**) ⟨79CC366⟩. When heated in the presence of copper or rhodium catalysts, (**334**; R = Cl) undergoes cleavage of the carbon–sulfur bond resulting in the formation of carbenoid intermediates which can be trapped with activated aromatic substrates or alkenes to yield the corresponding arylmalonates or cyclopropanes, respectively ⟨78CC83, 79CC50⟩.



(**334**) (**335**) (**336**)

3.4

Reactivity of Five-membered Rings with Two or More Heteroatoms*

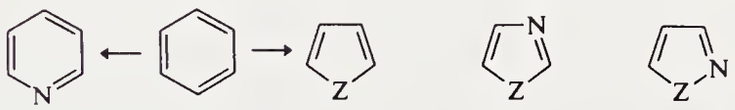
3.4.1 REACTIONS AT HETEROAROMATIC RINGS

3.4.1.1 General Survey of Reactivity

In this initial section the reactivities of the major types of azole aromatic rings are briefly considered in comparison with those which would be expected on the basis of electronic theory, and the reactions of these heteroaromatic systems are compared among themselves and with similar reactions of aliphatic and benzenoid compounds. Later in this chapter all the reactions are reconsidered in more detail. It is postulated that the reactions of azoles can only be rationalized and understood with reference to the complex tautomeric and acid–base equilibria shown by these systems. Tautomeric equilibria are discussed in Chapter 2.4. Acid–base equilibria are considered in Section 3.4.1.3 of the present chapter.

3.4.1.1.1 Reactivity of neutral azoles

Replacing a CH group of benzene with a nitrogen atom gives pyridine (**1**); replacing a CH=CH group of benzene with NH, O or S gives pyrrole, furan or thiophene (**3**), respectively.



(**1**) (**2**) (**3**) (**4**) (**5**)

The azoles (**4**) and (**5**) may be considered to be derived from benzene by two successive steps, one of each of these types. Hence, the chemistry of five-membered aromatic rings with two or more heteroatoms shows similarities to both that of the five- and that of the six-membered aromatic rings containing one heteroatom. Thus, electrophilic reagents attack lone electron pairs on multiply bonded nitrogen atoms of azoles (*cf.* pyridine) (see Section 3.4.1.3), but they do not commonly attack electron pairs on heterocyclic nitrogen atoms in NR groups or on heterocyclic oxygen or sulfur atoms (*cf.* pyrrole, furan, thiophene) (for example, see Section 3.4.1.5.1).

The carbon atoms of azole rings can be attacked by nucleophilic (Section 3.4.1.6), electrophilic (Section 3.4.1.4) and free radical reagents (Section 3.4.1.8.2). Some systems, for example the thiazole, imidazole and pyrazole nuclei, show a high degree of aromatic character and usually 'revert to type' if the aromatic sextet is involved in a reaction. Others such as the isoxazole and oxazole nuclei are less aromatic, and hence more prone to addition reactions.

Electron donation from pyrrole-like nitrogen, or to a lesser extent from analogous sulfur or oxygen atoms, helps electrophilic attack at azole carbon atoms, but as the number of heteroatoms in the ring increases, the tendency toward electrophilic attack at both C and N decreases rapidly.

Just as electron displacement toward the nitrogen atom allows nucleophilic reagents to attack pyridines at the α-position, similar displacements toward the nitrogens of the azoles also facilitate nucleophilic attack at carbon. As in similar reactions with pyridine, formation of the initial adduct

*Chapter 4.02 of 'Comprehensive Heterocyclic Chemistry', by A. R. Katritzky, University of Florida, and J. M. Lagowski, The University of Texas at Austin.

involves dearomatization of the ring. The subsequent fate of the adduct depends in part on the degree of aromaticity. Those derived from highly aromatic azoles tend to rearomatize, whereas those of lower aromaticity can take alternative reaction paths. For most neutral azoles, nucleophilic attack at a ring carbon atom is only possible with very strong nucleophiles.

Where azoles contain ring NH groups, this group is acidic and nucleophiles can remove a proton. Nucleophilic species can also remove ring-hydrogen atoms, particularly those which are α to a sulfur or oxygen atom, as in base-catalyzed hydrogen exchange and metallation reactions (Section 3.4.1.7).

3.4.1.1.2 Azolium salts

All neutral azoles possess positively charged azolium counterparts. In addition, as discussed in Chapter 2.4, certain 'olylium' species exist which have no neutral counterparts, for example dithiolylium salts.

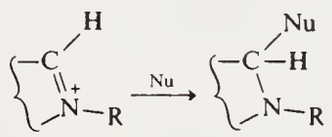
Azolium systems show much lower reactivity than the corresponding neutral azoles toward electrophiles at ring carbon. Even if an azolium ion contains an additional unquaternized pyridine-like nitrogen, this nitrogen is hardly basic in character. By contrast, azolium cations show a great reactivity toward nucleophiles: at ring carbon atoms, at the hydrogen of ring CH and NH groups, and even at ring sulfur atoms.

In all these azoliums, oxolyliums and thiolyliums the positive charge facilitates attack by nucleophilic reagents at ring carbon atoms α or γ to the charged heteroatom (Section 3.4.1.6). Hydroxide, alkoxide, sulfide, cyanide and borohydride ions, certain carbanions, amines and organometallic compounds react under mild conditions, usually at a position α to the quaternary center as in (**6**), to give initial non-aromatic adducts (**7**) which can be isolated in certain cases but undergo further reaction with alacrity. The most important of these subsequent reactions include:

(i) oxidation, *e.g.* the formation of cyanine dyes in the thiazole series (Section 3.4.1.6.5 ii);

(ii) ring opening with subsequent closure, *e.g.* the reaction of dithiolylium salts with amines (Section 3.4.1.6.2);

(iii) ring opening without subsequent closure, *e.g.* the reactions of oxazoliums with hydroxide ion (Section 3.4.1.6.5.ii).



(**6**) (**7**)

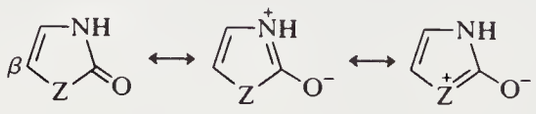
Ring hydrogen atoms can be abstracted from the α-carbon atoms of azolium ions by strong bases, as demonstrated in base-catalyzed hydrogen exchange (Section 3.4.1.7.2).

3.4.1.1.3 Azole anions

Azole anions are derived from imidazoles, pyrazoles, triazoles or tetrazoles by proton loss from a ring NH group. In contrast to the neutral azoles, azole anions show enhanced reactivity toward electrophiles, both at the nitrogen (Section 3.4.1.3.6) and carbon atoms (Section 3.4.1.4.1.i). They are correspondingly unreactive toward nucleophiles.

3.4.1.1.4 Azolinones, azolinethiones, azoliniminies

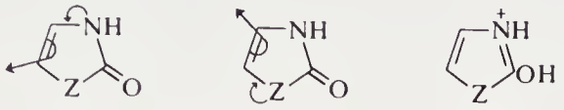
These compounds are usually written in the unionized form as in (**8**; Z = NH, NR, O, S). Canonical forms of types (**9**) or (**10**) are important, *i.e.* these compounds can also be considered as betaines formally derived from azolium ions. Many compounds of this type are tautomeric and such tautomerism is discussed in Section 2.4.5.2.



(**8**) (**9**) (**10**)

Reactions of these compounds follow logically from the expected electron displacements in the molecules. Their very varied chemical reactivity includes four main possibilities for heterolytic reactions: electrophilic attack at a ring carbon atom β to a ring heteroatom (*e.g.* Section 3.4.1.4.2), or at a carbonyl oxygen atom (Section 3.4.3.7), a thiocarbonyl sulfur atom (Section 3.4.3.8.2) or an imine nitrogen atom (Section 3.4.3.5.5). Nucleophilic attack to remove hydrogen from an NH group (Section 3.4.1.3.6) or at a ring carbon atom α to a ring heteroatom (Section 3.4.3.12.3) also needs to be considered.

The mode of attack of electrophilic reagents (E^+) at ring carbon atoms is β to the heteroatoms as shown, for example, in (**11**) and (**12**); the intermediates usually revert to type by proton loss. Halogenation takes place more readily than it does in benzene (Section 3.4.1.4.5). Nitration and sulfonation also occur; however, in the strongly acidic environment required the compounds are present mainly as less reactive hydroxyazolium ions, *e.g.* (**13**).



(**11**) (**12**) (**13**)

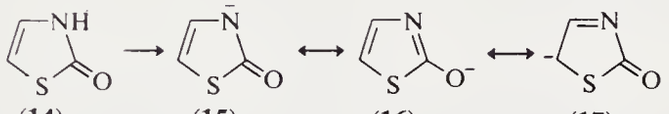
The reactions of electrophilic reagents at a carbonyl oxygen atom, a thiocarbonyl sulfur, and an imino nitrogen atom are considered as reactions of substituents (see Sections 3.4.3.7, 3.4.3.8.2, 3.4.3.5.4 and 3.4.3.5.5).

The removal of a hydrogen atom from a heterocyclic nitrogen atom of azolones by nucleophiles acting as bases, *e.g.* (**14**)→(**15**), gives mesomeric anions, *e.g.* (**15**)↔(**16**)↔(**17**), which react exceedingly readily with electrophilic reagents, typically:

(i) at nitrogen, *e.g.* with alkyl halides (Section 3.4.1.3.9);

(ii) at oxygen, *e.g.* with acylating reagents (Section 3.4.3.7);

(iii) at the β-carbon atoms, *e.g.* with halogens (Section 3.4.1.4.5), and in the Reimer–Tiemann reaction (Section 3.4.1.4.6).

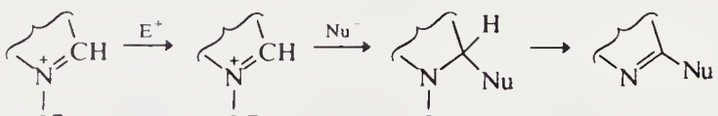


(**14**) (**15**) (**16**) (**17**)

3.4.1.1.5 N-*Oxides*, N-*imides*, N-*ylides of azoles*

Azole *N*-oxides, *N*-imides and *N*-ylides are formally betaines derived from *N*-hydroxy-, *N*-amino- and *N*-alkyl-azolium compounds. Whereas *N*-oxides (Section 3.4.3.12.6) are usually stable as such, in most cases the *N*-imides (Section 3.4.3.12.5) and *N*-ylides (Section 3.4.3.12.3) are found as salts which deprotonate readily only if the exocyclic nitrogen or carbon atom carries strongly electron-withdrawing groups.

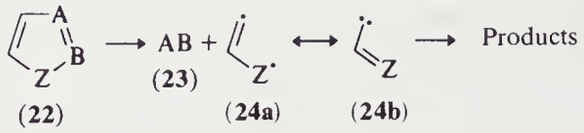
The reactivity of these compounds is somewhat similar to that of the azolonium ions, particularly when the cationic species is involved. However, although the typical reaction is with nucleophiles, the intermediate (**20**) can lose the *N*-oxide group to give the simple α-substituted azole (**21**). Benzimidazole 3-oxides are readily converted into 2-chlorobenzimidazoles in this way.



(**18**) (**19**) (**20**) (**21**)

3.4.1.2 Thermal and Photochemical Reactions Formally Involving No Other Species

We consider here fragmentations and rearrangements which involve only the azole molecule itself, without the vital involvement of any substituent or other molecule. Many fragmentations of azoles can be summarized by the transformation (**22**)→(**23**) + (**24**), where (**23**) represents a stable fragment, particularly N_2, but also CO_2, N_2O, COS or HCN.



(22) (23) (24a) (24b)

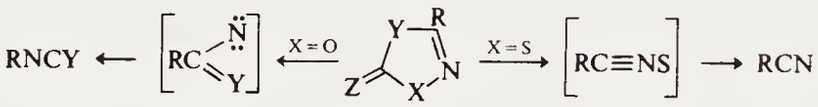
3.4.1.2.1 Thermal fragmentation

Thermal and photochemical fragmentation are often related to the mass spectroscopic breakdown of azole molecules (see Section 2.4.3.8), the latter often providing an indication of the behavior of a given molecule under such stimuli. Such fragmentations are facilitated in the polynitrogenous azoles, and azoles containing several nitrogen atoms undergo ring fission with loss of nitrogen. This is particularly noticeable when two adjacent pyridine-like nitrogen atoms are present. Thermolysis of (**25**) to give N_2 and a 1,3-dipole, such as PhC≡$\overset{+}{N}$—$\bar{O}$, is a useful and general reaction. Azoles containing only two heteroatoms, such as the pyrazole and thiazole systems, are thermally very stable.

(25) (26)

Although unsubstituted 1,2,5-thiadiazole is stable on heating at 220 °C, 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide (**26**) decomposes into benzonitrile and sulfur dioxide at 250 °C ⟨68AHC(9)107⟩.

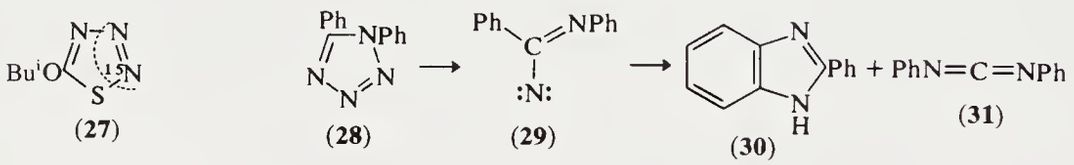
Thermal reactions of 1,4,2-dioxazoles, 1,4,2-oxathiazoles and 1,4,2-dithiazoles are summarized in Scheme 1. The reactive intermediates generated in these thermolyses can often be trapped, *e.g.* the nitrile sulfide dipole with DMAD.



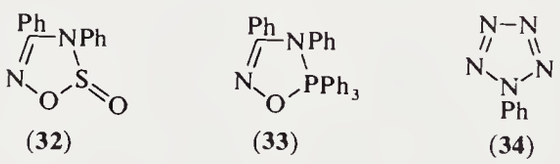
Scheme 1

1,2,3,4-Thiatriazoles readily decompose thermally into nitrogen, sulfur and an organic fragment, usually a cyanide, *e.g.* (**27**)→($Bu^iOCN + {}^{15}N^{14}N + S$ ⟨76AHC(20)145⟩.

Other classes of heterocycles undergo thermolytic fragmentation to give imidolynitrenes. As typified by the thermolysis of 1,5-diphenyltetrazole (**28**), the intermediates (**29**) can either cyclize on to aromatic rings to form benzimidazoles (**30**) or undergo a Wolff-type rearrangement to carbodiimides (**31**) ⟨81AHC(28)231⟩. Compounds (**32**) and (**33**) thermolyze to give mainly the carbodiimides (**31**) ⟨79JA3976⟩. Pentazoles (**34**) spontaneously form azides, usually below 20 °C.



(27) (28) (29) (30) (31)

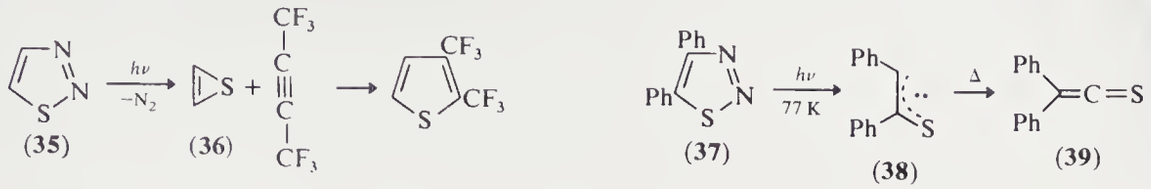


(32) (33) (34)

3.4.1.2.2 Photochemical fragmentation

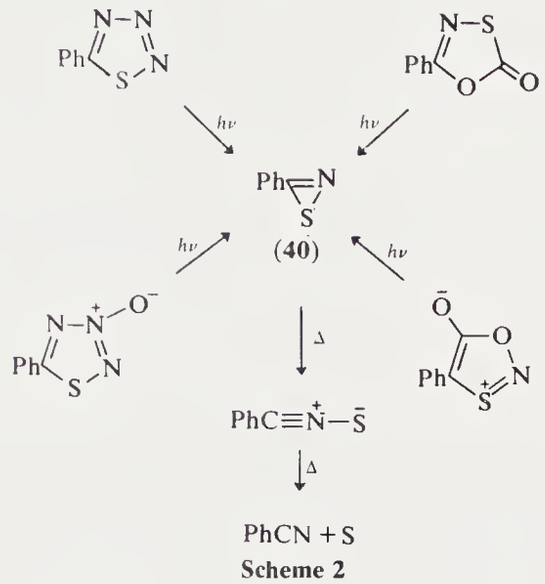
Photolysis of 1,2,3-thiadiazole (**35**) gives thiirene (**36**) which can be trapped by an alkyne ⟨70AHC(11)1⟩. 4,5-Diphenyl-1,2,3-thiadiazole (**37**) is photolyzed at low temperatures to

the thiobenzoylphenylcarbene triplet (**38**). Diphenylthioketene (**39**) is formed on warming ⟨81AHC(28)231⟩.



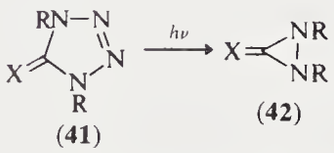
(**35**) (**36**) (**37**) (**38**) (**39**)

3-Phenylthiazirine (**40**) can be isolated as an intermediate in the photolysis of 5-phenyl-1,2,3,4-thiatriazole and also from other five-membered ring heterocycles capable of losing stable fragments; see Scheme 2 ⟨81AHC(28)231⟩. Photolysis of 5-phenylthiatriazole in the presence of cyclohexene yields cyclohexene episulfide ⟨60CB2353⟩ by trapping the sulfur atom.



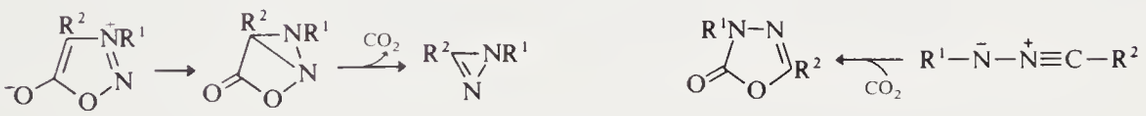
Scheme 2

Diaziridine derivatives (**42**) can be obtained from tetrazoles of type (**41**).

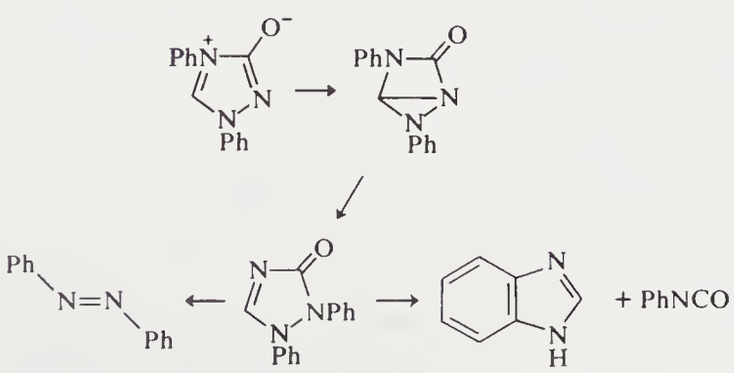


(**41**) (**42**)

Mesoionic compounds undergo a variety of photochemical fragmentations. Examples are shown in which CO_2 or PhNCO is extruded (Schemes 3 and 4, respectively) ⟨76AHC(19)1⟩.



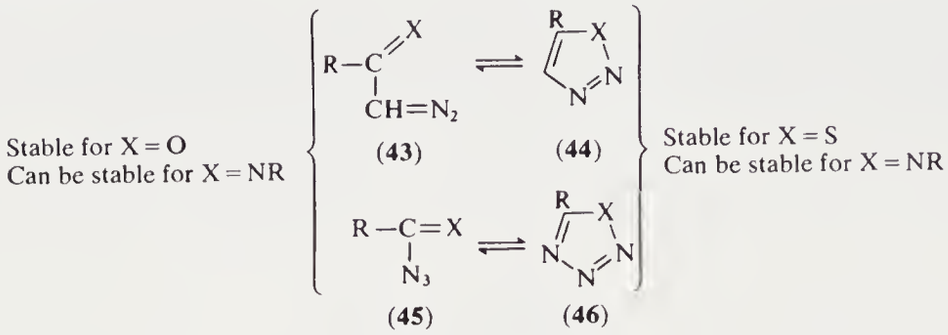
Scheme 3



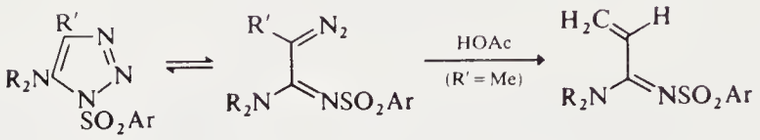
Scheme 4

3.4.1.2.3 Equilibria with open-chain compounds

Azoles of types (**44**) and (**46**) are isomeric with the open-chain compounds (**43**) and (**45**), respectively. Rearrangement between the two pairs is rapid and the thermodynamically stable isomer is encountered. Thus diazoketones (**43**; X = O) exist as such, but diazothioketones (**43**; X = S) spontaneously ring-close to thiadiazoles (**44**). 1,2,3-Triazoles generally exist as such unless the nitrogen carries a strong electron-withdrawing substituent. Thus 1-cyano- and 1-arenesulfonyl-1,2,3-triazoles (**47**) undergo easy, reversible ring-opening to diazo-imine tautomers ⟨74AHC(16)33⟩.

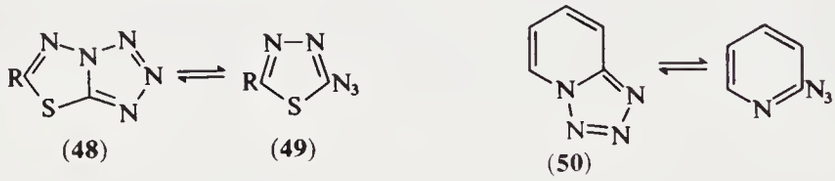


(**43**) (**44**) (**45**) (**46**)



(**47**)

A similar situation exists for molecules containing an azide group bonded to a doubly bound carbon atom as in (**45**). When X is oxygen, the acylazide exists in the acyclic form (**45**), but when X is sulfur the cyclic thiatriazole (**46**) predominates. When X is nitrogen, as in tetrazoles, the imidoylazide (**45**) or the tetrazole (**46**) may predominate, or both may exist in equilibrium. The position of the tetrazole–imidoylazide equilibrium depends on the following factors: (1) electron-withdrawing substituents favor the azide form; (2) higher temperature favors the azide form; and (3) polar solvents tend to favor the tetrazole form, and non-polar solvents the azide form. Ring strain is also important and two fused five-membered rings are in general avoided. For example, in the thiadiazolotetrazole equilibrium (**48**)⇌(**49**), the system exists in the bicyclic form in the solid state and in the azide form in carbon tetrachloride solution ⟨77AHC(21)323⟩. Fusion with six-membered rings generally is more favorable to a bicyclic tetrazole form. For example, pyridine fusion gives essentially all tetrazole (**50**) ⟨69TL2595⟩.



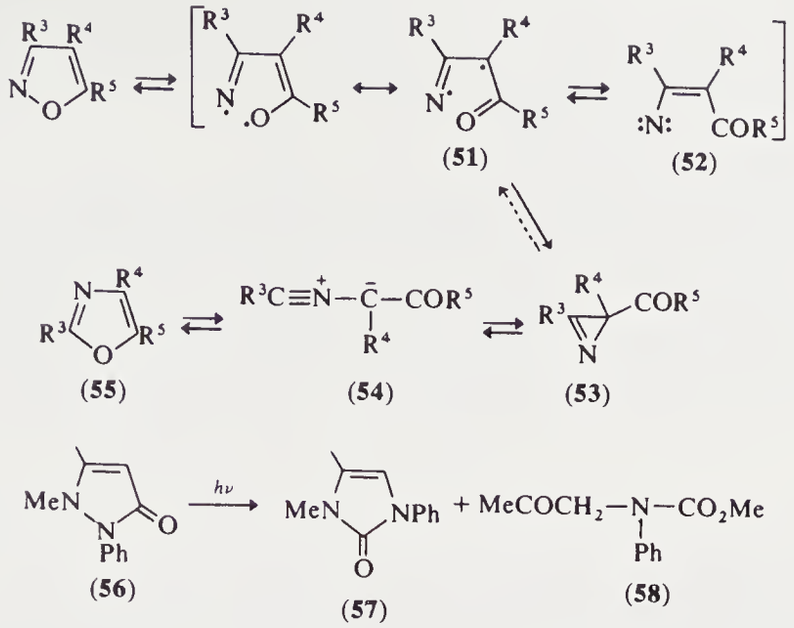
(**48**) (**49**) (**50**)

3.4.1.2.4 Rearrangement to other heterocyclic species

Many examples are known of rearrangement of azoles involving scrambling of the ring atoms to give a new isomeric azole molecule. Different mechanisms are involved.

For isoxazoles the first step is the fission of the weak N—O bond to give the diradical (**51**) which is in equilibrium with the vinylnitrene (**52**). Recyclization now gives the substituted 2*H*-azirine (**53**) which *via* the carbonyl-stabilized nitrile ylide (**54**) can give the oxazole (**55**). In some cases the 2*H*-azirine, which is formed both photochemically and thermally, has been isolated; in other cases it is transformed quickly into the oxazole ⟨79AHC(25)147⟩.

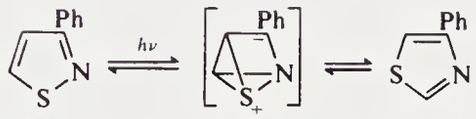
The photorearrangement of pyrazoles to imidazoles is probably analogous, proceeding *via* iminoylazirines ⟨82AHC(30)239⟩; indazoles similarly rearrange to benzimidazoles ⟨67HCA2244⟩. 3-Pyrazolin-5-ones (**56**) are photochemically converted into imidazolones (**57**) and open-chain products (**58**) ⟨70AHC(11)1⟩. The 1,2- and 1,4-disubstituted imidazoles are interconverted photochemically.



(51) (52) (55) (54) (53)

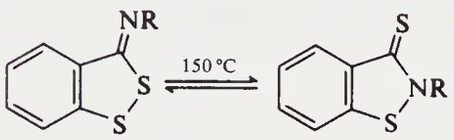
(56) (57) (58)

Irradiation of isothiazole gives thiazole in low yield. In phenyl-substituted derivatives an equilibrium is set up between the isothiazole (**59**) and the thiazole (**61**) *via* intermediate (**60**) ⟨72AHC(14)1⟩.



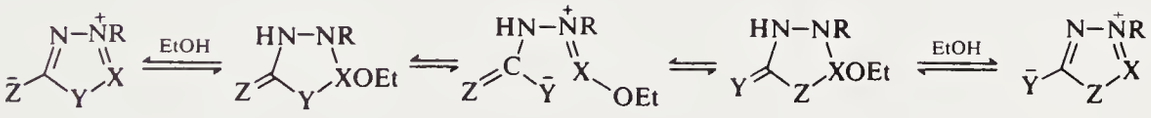
(59) (60) (61)

Iminobenzodithioles (**62**) and benzisothiazolethiones (**63**) thermally equilibrate ⟨72AHC(14)43⟩.



(62) (63)

Mesoionic compounds of the type designated ⟨76AHC(19)1⟩ as 'A' are capable of isomerism. In one case in the 1,2,4-triazole series, isomerism of the pair (**64**)⇌(**65**) has been demonstrated ⟨67TL4261⟩.



(64) (65)

3.4.1.2.5 Polymerization

Imidazoles and pyrazoles with free NH groups form hydrogen-bonded dimers and oligomers ⟨66AHC(6)347⟩.

3.4.1.3 Electrophilic Attack at Nitrogen

3.4.1.3.1 Introduction

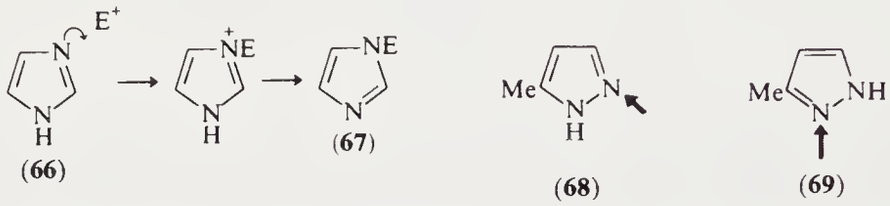
Reactions of this type can be related to the chemistry of simple tertiary aliphatic amines. Thus the lone pair of electrons on the nitrogen atom in trimethylamine reacts under mild conditions with the following types of electrophilic reagents:

(i) proton acids give salts;
(ii) Lewis acids give coordination compounds;
(iii) transition metal ions give complex formation;
(iv) reactive halides give quaternary salts;
(v) halogens give adducts;
(vi) certain oxidizing agents give amine oxides.

The analogous reactions of pyridines with these electrophilic reagents at the lone pair on the nitrogen atom are well known. All neutral azoles contain a pyridine-like nitrogen atom and therefore similar reactions with electrophiles at this nitrogen would be expected. However, the tendency for such reactions varies considerably; in particular, successive heteroatom substitutions markedly decrease the ease of reaction. One convenient quantitative measure of the tendency for such reactions to occur is found in the basicity of these compounds; this is treated in Section 3.4.1.3.5.

3.4.1.3.2 Reaction sequence

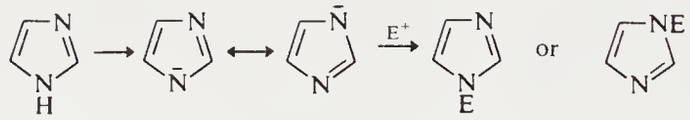
In azoles containing at least two annular nitrogen atoms, one of which is an NH group and the other a multiply bonded nitrogen atom, electrophilic attack occurs at the latter nitrogen. Such an attack is frequently followed by proton loss from the NH group, *e.g.* (**66**)→(**67**). If the electrophilic reagent is a proton, this reaction sequence simply means tautomer interconversion (see Section 2.4.5), but in other cases leads to the product.



(**66**) (**67**) (**68**) (**69**)

Since the electrophilic reagent attacks the multiply bonded nitrogen atom, as shown for (**68**) and (**69**), the orientation of the reaction product is related to the tautomeric structure of the starting material. However, any conclusion regarding tautomeric equilibria from chemical reactivity can be misleading since a minor component can react preferentially and then be continually replenished by isomerization of the major component.

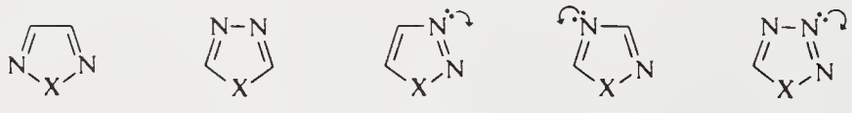
In addition to reaction sequences of type (**66**)→(**67**), electrophilic reagents can attack at either one of the ring nitrogen atoms in the mesomeric anions formed by proton loss (*e.g.* **70**→**71** or **72**; see Section 3.4.1.3.6). Here we have an ambident anion, and for unsymmetrical cases the composition of the reaction product (**71**) + (**72**) is dictated by steric and electronic factors.



(**70**) (**71**) (**72**)

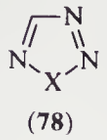
3.4.1.3.3 Orientation in azole rings containing three or four heteroatoms

Such compounds contain two or three pyridine-like heteroatoms. For the symmetrical systems (**73**) and (**74**), no ambiguity occurs, but for systems (**75**)–(**78**) there are at least two alternative reaction sites. It appears that reaction takes place at the nitrogen atom furthest away from the pyrrole-like heteroatom, as shown in (**75**)–(**77**) where evidence is available from reactions with alkylating reagents (Section 3.4.1.3.8).

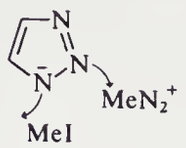


(**73**) (**74**) (**75**) (**76**) (**77**)

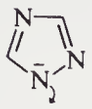
Similar ambiguities arise in the reactions of azole anions. At least as regards alkylation reactions in the 1,2,3-triazole series (**79**), the product appears to depend on the reagent used. In the 1,2,4-triazole series (**80**) a single product is formed, whereas tetrazole (**81**) gives mixtures.



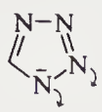
(**78**)



(**79**)



(**80**)



(**81**)

3.4.1.3.4 Effect of azole ring structure and of substituents

The ease of attack by an electrophilic reagent at the nitrogen atom of any azole is proportional to ΔE between the ground state and transition state energies. However, ground state structure largely controls the variation in these differences, which hence depend on the electron density on the basic nitrogen atom and the degree of steric hindrance. The number, orientation and type of heteroatoms are very important in determining electron density. Additional pyridine-like nitrogen atoms always reduce the electron density at another pyridine-like nitrogen (compare the reduced basicities of diazines relative to pyridine). Unshared electron pairs on two pyridine-like nitrogen atoms can interact, but the effect on reactivity appears to be small ⟨78AHC(22)71⟩. In the case of pyrrole-like nitrogen, oxygen and sulfur there are two mutually opposed effects: base-strengthening mesomeric electron donation and base-weakening inductive electron withdrawal. The latter is particularly strong for heteroatoms in the α-position and in fact for oxygen and sulfur always dominates over the base-strengthening effect.

The effects of substituents may be rationalized as follows:

(i) Strongly electron-withdrawing substituents (*e.g.* NO_2, COR, CHO) make these reactions more difficult by decreasing the electron density on the nitrogen atom(s). The effect is largely inductive and therefore is particularly strong from the α-position.

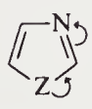
(ii) Strongly electron-donating substituents (*e.g.* NH_2, OR) facilitate electrophilic attack by increasing the electron density on the nitrogen. This is caused by the mesomeric effect and is therefore strongest from the α- and γ-positions.

(iii) Fused benzene rings, aryl and alkyl groups, and other groups with relatively weak electronic effects have a relatively small electronic influence.

The foregoing electronic effects are illustrated by the pK_a values given in Section 3.4.1.3.5. Reactions other than proton addition are hindered by all types of α-substituents. However, steric hindrance is less in these five-membered ring heterocycles than that in pyridines because the angle subtended between the nitrogen lone pair and the α-substituent is significantly greater in the five-membered ring compounds and thus the substituent is held further away from the lone pair.

3.4.1.3.5 Proton acids on neutral azoles: basicity of azoles

Mesomeric shifts of the types shown in structures (**82**) and (**83**) increase the electron density on the nitrogen atom and facilitate reaction with electrophilic reagents. However, the heteroatom Z also has an adverse inductive effect; the pK_a of NH_2OH is 6.0 and that of N_2H_4 is 8.0, both considerably lower than that of NH_3 which is 9.5.



(**82**)

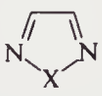
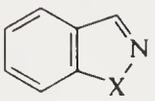
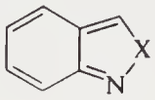
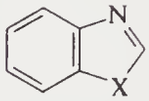
(**83**)

Gas-phase pK_a values for azoles are unavailable except for imidazole and 1-methylimidazole. Imidazole is *ca.* 75 kJ mol^{-1} more basic than ammonia, *i.e.* approximately the same as pyridine; 1-methylimidazole is about 29 kJ mol^{-1} more basic than imidazole ⟨82PC40200⟩.

Tetrazoles are preferentially protonated at N-4.

The basicities of the parent azole systems in water are shown in Table 1. When both heteroatoms are nitrogen, the mesomeric effect predominates when the heteroatoms are in the 1,3-positions, whereas the inductive effect predominates when they are in the 1,2-positions. The predominance of the mesomeric effect is illustrated by the pK_a value of imidazole (**82**; Z = NH), which is 7.0, whereas that of pyrazole (**83**; Z = NH) is 2.5 (*cf.* pyridine, 5.2). An *N*-methyl group is base-strengthening in imidazole, but base-weakening in pyrazole, probably because of steric hindrance to hydration. When the second heteroatom is oxygen or sulfur the inductive, base-weakening effect increases; the pK_a of thiazole (**82**; Z = S) is 3.5 and that of isoxazole (**83**; Z = O) is 1.3.

Table 1 pK_a Values for Proton Addition ⟨63PMH(1)1, 71PMH(3)1, B-76MI40200, B-76MI40201⟩

X	*Ring systems*				
					
NH	2.52	6.95	1.17	2.45	(1.17)
NMe	2.06	7.33	1.25	3.20	<1
O	−2.97	0.8	—	—	—
S	−0.51	2.53	—	—	−4.9
					
NH	1.31	—	5.53		
NMe	0.42	2.02	5.57		
O	−4.7	−2.20	−0.13		
S	—	−0.05	1.2		

Substituents are expected to alter the electron density at the multiply bonded nitrogen atom, and therefore the basicity, in a manner similar to that found in the pyridine series. The rather limited data available appear to bear out these assumptions. The additional ring nitrogen atoms in triazoles, oxadiazoles, *etc.* are quite strongly base-weakening; this is as expected since diazines are weaker bases than pyridine. As regards *C*-substituents, their effects on the pK_a of the parent compounds are as follows:

(i) Methyl groups are weakly base-strengthening due to their mesomeric and inductive electron donor effect: thus in the methylthiazoles the base strengths decrease in the order 2 > 4 > 5.

(ii) Phenyl groups are weak resonance donors, but inductive acceptors. Phenyl groups are therefore expected to reduce the basicity of azoles.

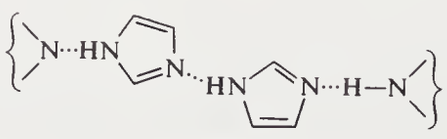
(iii) Amino groups are strong resonance electron donors and hence base-strengthening, particularly if directly conjugated with the basic center.

(iv) Methoxy groups are resonance donors but inductive acceptors. The inductive effect would be expected to be dominant for azoles.

(v) Halogen atoms are inductive acceptors (and weak resonance donors); they are expected to cause a marked decrease in basicity, especially from α-positions.

(vi) Fused benzene rings usually have little effect; *cf.* the pK_a values of imidazole and benzimidazole. Substituents on the benzene ring in benzazoles should have little effect on the basicity.

Annular nitrogen atoms can form hydrogen bonds, and if the azole contains an NH group, association occurs. Imidazole (**84**) shows a cryoscopic molecular weight in benzene 20 times that expected. Its boiling point is 256 °C, which is higher than that of 1-methylimidazole (198 °C).



(**84**)

3.4.1.3.6 Proton acids on azole anions: acidity of azoles

The acidities of the five parent compounds are compared with that of pyrrole in Table 2. The acidity of the ring system increases as the number of nitrogens increases, the acidity of pyrrole increasing by approximately 2, 4.5 and 5 pK_a units for each successive addition of a nitrogen atom. 1,2,3-Triazole is slightly more acidic than 1,2,4-triazole, but the effect on NH acidity of nitrogen orientation is much less than the effect of the total number of nitrogens ⟨71PMH(3)1⟩.

Table 2 pK_a Values of Azoles for Proton Loss ⟨B-76MI40200, B-76MI40201⟩

Nitrogen positions	pK_a	*Nitrogen positions*	pK_a
1	16.5	1,2,3	9.26
1,2	14.21	1,2,4	10.04
1,3	14.44	1,2,3,4	4.89

Ring substituents can have a considerable effect on the acidity of the system. In the 1,2,4-triazole series a 3-amino group decreases the acidity to 11.1, a 3-methyl group to 10.7, whereas a 3-phenyl group increases the acidity to 9.6, and 3,5-dichloro substitution to 5.2 ⟨71PMH(3)1⟩.

3.4.1.3.7 Metal ions

(i) Simple complexes

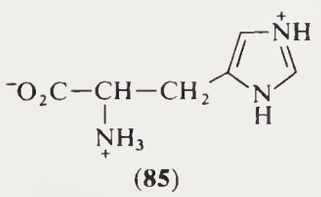
Many examples are known of complexes between metal cations and both neutral azoles and azole anions. Overlap between the *d*-orbitals of the metal atom and the azole π-orbitals is believed to increase the stability of many of these complexes.

Despite the weak basicity of isoxazoles, complexes of the parent methyl and phenyl derivatives with numerous metal ions such as copper, zinc, cobalt, *etc.* have been described ⟨79AHC(25)147⟩. Many transition metal cations form complexes with imidazoles; the coordination number is four to six ⟨70AHC(12)103⟩. The chemistry of pyrazole complexes has been especially well studied and coordination compounds are known with thiazoles and 1,2,4-triazoles. Tetrazole anions also form good ligands for heavy metals ⟨77AHC(21)323⟩.

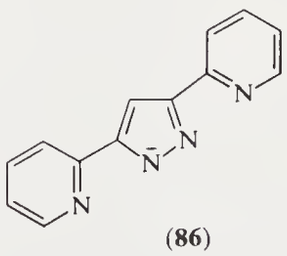
Isothiazoles react with hexacarbonyls $M(CO)_6$ to give *N*-coordinate $M(CO)_5$ derivatives.

(ii) Chelate complexes

Chelate rings can be formed by azoles containing α-substituents such as carbonyl or CH=NH groups. An important bidentate chelating agent is histidine (**85**), and many pyrazoles with substituent groups are known which form bis and tris complexes with many metals, *e.g.* (**86**). Similarly, 2- and 4-α-pyridylthiazoles are bidentate chelating agents. Complex formation of this type has analytical applications; thus 1,3,4-thiadiazole-2,5-dithione has been used as a spot test for bismuth and other metals ⟨58MI140200⟩.



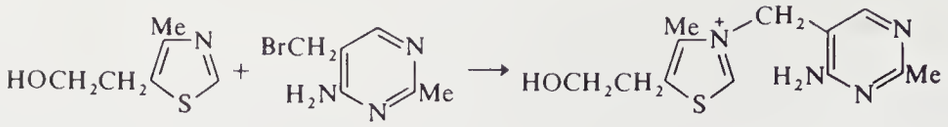
(**85**)



(**86**)

3.4.1.3.8 Alkyl halides and related compounds: azoles without a free NH group

Pyrazoles and imidazoles carrying a substituent on nitrogen, as well as oxazoles, thiazoles, *etc.*, are converted by alkyl halides into quaternary salts. This is illustrated by the preparation of thiamine (**89**) from components (**87**) and (**88**).



(87) (88) (89)

Azoles having heteroatoms in the 1,3-orientation are more reactive than those in which the arrangement is 1,2. However, the magnitude of the factor varies. Thus oxazole is 68 times more reactive than isoxazole, whereas benzoxazole quaternizes 26 times faster than does 1,2-benzisoxazole ⟨78AHC(22)71⟩.

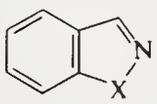
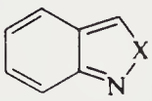
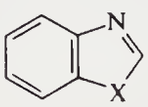
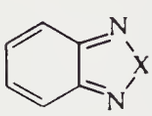
These reactions are of the S_N2 type and are sensitive to steric effects of substituents in the azole ring. However, these steric effects are significantly less than, for example, in the analogous pyridine derivatives because the angle subtended by the nitrogen lone pair and an α-substituent is about 70° in an azole as opposed to 60° in pyridine. Thus the rate constant for methylation of 2-*t*-butylthiazole by methyl iodide is only 40 times less than that for the corresponding 2-methyl compound. By comparison, in the pyridine series the retardation factor is over 2000 in the same solvent (nitrobenzene). As in six-membered rings, the kinetic consequences of the steric effects of *o*-alkyl groups are related to the E_s parameter. However, buttressing groups can cause special effects as has been investigated extensively in the thiazole series.

Annelation of a five-membered aza ring to a benzo ring generally leads to rate retardation in *N*-quaternization reactions similar in magnitude to that for six-membered rings. Exceptions are known: 2,1-benzisoxazole undergoes *N*-methylation faster than isoxazole, and in 2,1,3-benzoxadiazole and 2,1-benzisothiazole the rates are little changed from the corresponding monocyclic rings; however, here we are dealing with *o*-quinonoid structures. The more usual situation is rate retardation by a moderate amount. This is probably caused not by steric effects, but by electronic effects, as is shown by the corresponding influence on the pK_a values ⟨78AHC(22)71⟩.

Satisfactory Brönsted correlations for α-substituted azoles offer further evidence of the lesser importance of steric effects in the azole series ⟨78AHC(22)71⟩.

For both azole and benzazole rings the introduction of further heteroatoms into the ring affects the ease of quaternization. In series with the same number and orientation of heteroatoms, rate

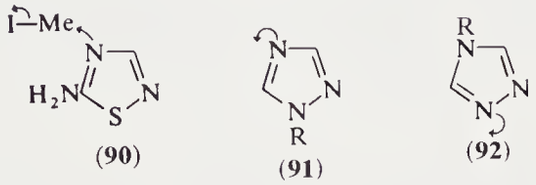
Table 3 Heteroatom and Benzo-fusion Effects on Relative Rate Constants for *N*-Methylation ⟨78AHC(22)71⟩

	k_{rel}		
Heterocycle	O	S	NMe
	1	6.9	120
	1	15 1	912 61
	1	20 1	56 2.8
	1	3.6 1	33 9.2
	1	9.3 1	708 76
	—	2.8	1

constants increase in the order X = O < S < SMe (*cf.* Table 3) ⟨78AHC(22)71⟩. The quaternization of triazoles, thiadiazoles and tetrazoles requires stronger reagents and conditions; methyl fluorosulfonate is sometimes used ⟨78AHC(22)71⟩. The 1- or 2-substituted 1,2,3-triazoles are difficult to alkylate, but methyl fluorosulfonate succeeds ⟨71ACS2087⟩.

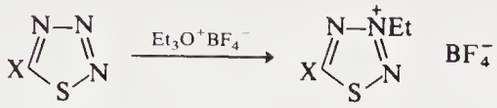
Oxadiazoles are difficult to alkylate, unless the ring contains a strong electron donor group such as an amino substituent.

1,2,3-Thiadiazoles are quaternized to give 3- or mixtures of 2- and 3-alkyl quaternary salts. In 5-amino-1,2,4-thiadiazole, quaternization takes place at the 4-position (**90**) ⟨64AHC(3)1⟩. 1-Substituted 1,2,4-triazoles are quaternized in the 4-position (**91**), and 4-substituted 1,2,4-triazoles are quaternized in the 1- or the 2-position (**92**) ⟨64AHC(3)1⟩



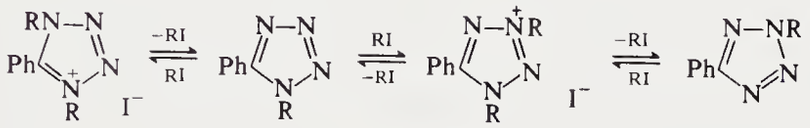
(**90**) (**91**) (**92**)

5-Substituted 1,2,3,4-thiatriazoles (**93**) are alkylated only under very forcing conditions with triethyloxonium fluoroborate, but then give the expected products (**94**) ⟨75JOC431⟩.



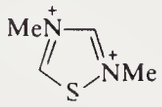
(**93**) X = SEt, SMe, Ph (**94**) X = SEt, SMe, Ph

1-Alkyl-5-phenyltetrazoles are converted into 2-alkyl isomers on heating with alkyl iodide, presumably by quaternary salt formation followed by elimination of alkyl iodide to give the thermodynamically more stable isomer (Scheme 5) ⟨77AHC(21)323⟩.



Scheme 5

1,2,4-Thiadiazole with $Me_3O^+BF_4^-$ gives the diquaternary salt (**95**); diquaternary salts are also known in the 1,2,4-triazole series. 1,3-Disubstituted 1,2,4-triazolium salts can be further alkylated to diquaternary derivatives.

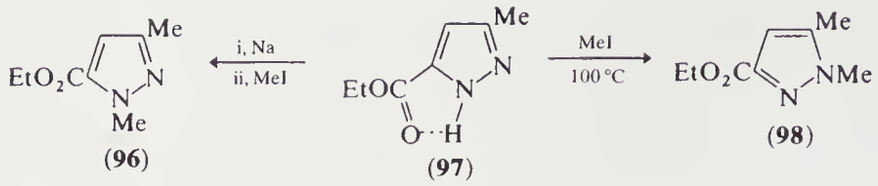


(**95**)

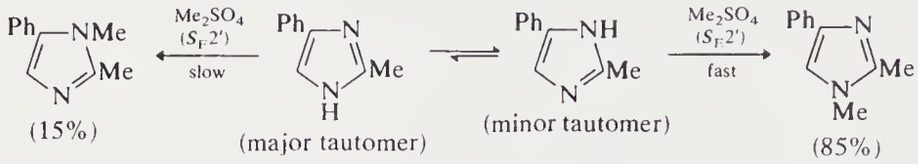
3.4.1.3.9 Alkyl halides and related compounds: compounds with a free NH group

Pyrazoles and imidazoles with free NH groups are readily alkylated, *e.g.* by MeI or Me_2SO_4. A useful procedure is to use the sodium salt of the azole in liquid ammonia ⟨80AHC(27)241⟩. However, alkylation can also occur under neutral conditions, particularly with imidazoles.

Unsymmetrical imidazoles and pyrazoles usually give a mixture of products, the composition of which may depend on the reaction conditions. Thus the ethoxycarbonylpyrazole (**97**) gives predominantly the isomeric *N*-methyl derivatives (**96**) and (**98**) under the conditions indicated. The difference in orientation can be related to the stabilization of the tautomeric structure (**97**) by hydrogen bonding (possibly intramolecular), which means that alkylation of the free base gives (**98**). The isomer (**96**) is formed *via* the anion. Benzylation of (**97**) gives mainly the analogue of (**98**) ⟨80JHC137⟩.



The differential effects of steric hindrance and tautomeric content in the imidazole series are illustrated in Scheme 6 ⟨80AHC(27)241⟩.



Scheme 6

N-Unsubstituted 1,2,3-triazoles are methylated mainly in the 1-position with methyl iodide and silver or thallium salts, but mainly in the 2-position by diazomethane. There is also some steric control. For example, 4-phenyl-1,2,3-triazole with dimethyl sulfate gives the 2-methyl-4-phenyl (38%) and 1-methyl-4-phenyl isomers (62%), but none of the more hindered 1-methyl-5-phenyltriazole ⟨74AHC(16)33⟩. *N*-Unsubstituted 1,2,4-triazoles are generally alkylated at N-1.

Alkylation of tetrazoles as the anions gives mixtures of 1- and 2-alkyl isomers. In general, electron-donating substituents in the 5-position slightly favor alkylation of the 1-position and electron-withdrawing 5-substituents slightly favor the 2-position.

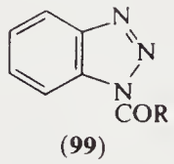
Azolone anions are readily alkylated at nitrogen, *e.g.* 2-triazolone with methyl iodide gives the 1-methyl derivative.

N-Arylation of azoles is achieved either by using arynes, activated halobenzenes (*e.g.* dinitro) or under Ullmann conditions. Thus benzyne reacts with imidazoles to give *N*-arylimidazoles ⟨70AHC(12)103⟩, and these compounds have also been prepared under modified Ullmann conditions.

N-Unsubstituted pyrazoles and imidazoles add to unsaturated compounds in Michael reactions, for example acetylenecarboxylic esters and acrylonitrile readily form the expected addition products. Styrene oxide gives rise, for example, to 1-styrylimidazoles ⟨76JCS(P1)545⟩. Benzimidazole reacts with formaldehyde and secondary amines in the Mannich reaction to give 1-aminomethyl products.

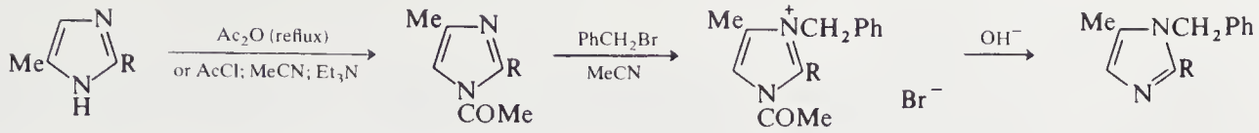
3.4.1.3.10 Acyl halides and related compounds

Azoles containing a free NH group react comparatively readily with acyl halides. *N*-Acyl-pyrazoles, -imidazoles, *etc.* can be prepared by reaction sequences of either type (**66**)→(**67**) or type (**70**)→(**71**) or (**72**). Such reactions have been carried out with benzoyl halides, sulfonyl halides, isocyanates, isothiocyanates and chloroformates. Reactions occur under Schotten–Baumann conditions or in inert solvents. When two isomeric products could result, only the thermodynamically stable one is usually obtained because the acylation reactions are reversible and the products interconvert readily. Thus benzotriazole forms 1-acyl derivatives (**99**) which preserve the 'Kékulé resonance' of the benzene ring and are therefore more stable than the isomeric 2-acyl derivatives. Acylation of pyrazoles also usually gives the more stable isomer as the sole product ⟨66AHC(6)347⟩. The imidazole-catalyzed hydrolysis of esters can be classified as an electrophilic attack on the multiply bonded imidazole nitrogen.



(**99**)

Since *N*-acylation is a reversible process, it has allowed the regiospecific alkylation of, for example, imidazoles to give the sterically less favored derivative. This principle is illustrated in Scheme 7 ⟨80AHC(27)241⟩.



Scheme 7

1,2,3-Triazoles are acylated with acyl halides, usually initially at the 1-position, but the acyl group may migrate to the 2-position on heating or on treatment with base. Thus acetylation with acetyl chloride often gives 1-acetyl derivatives, which rearrange to the 2-isomers above 120 °C ⟨74AHC(16)33⟩.

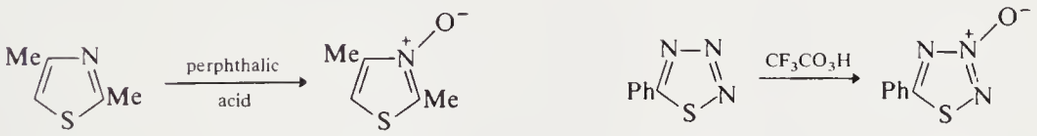
Whether tetrazoles are acylated in the 1- or 2-position depends on the 5-substituent. 2-Acyltetrazoles are unstable (see Section 3.4.3.12.4) ⟨77AHC(21)323⟩; 1-alkylsulfonyltriazoles are also unstable (see Section 3.4.1.2.3).

3.4.1.3.11 Halogens

At room temperature, *N*-unsubstituted azoles react with halogens and interhalogens (*e.g.* ICl) to give *N*-haloazoles, probably *via* unstable adducts. Thus imidazoles with halogens form *N*-halo compounds, which easily rearrange to form *C*-haloimidazoles ⟨70AHC(12)103⟩. *N*-Halopyrazoles are unstable and act as halogenating agents. *N*-Halo-1,2,4-triazoles are more easily isolated, especially when the 3,5-positions are substituted.

3.4.1.3.12 Peracids

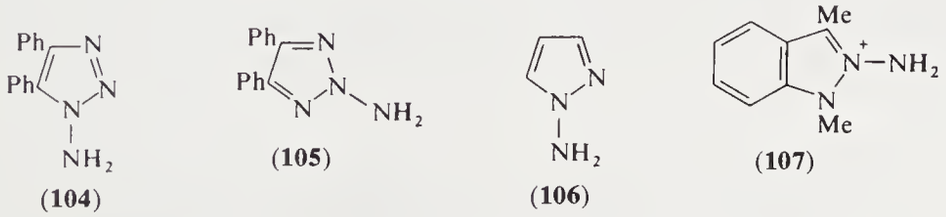
Pyridine 1-oxides are formed in good yield on treatment of pyridines with peracids, although pyridine reacts less readily than aliphatic tertiary amines. Azoles generally react even less readily, and *N*-oxides of azoles can rarely be formed in this way. However, some examples are known. Thus 1-methylpyrazole gives the 2-oxide, 2,4-dimethylthiazole (**100**) the 3-oxide (**101**) ⟨B-71MI40200⟩ and 1,2,3-thiadiazoles the 3-oxides. 5-Phenylthiatriazole (**102**) gives the 3-oxide (**103**) with peroxytrifluoroacetic acid ⟨75T1783⟩. More frequently, attempted *N*-oxide formation affords azolones or ring-cleaved derivatives, probably by nucleophilic attack of a peroxide anion on the azolium ion (*cf.* Section 3.4.1.6.1). Thus attempted conversion of oxazoles into *N*-oxides fails and leads to ring opening ⟨74AHC(17)99⟩, and most thiazoles are extensively degraded.



(**100**) (**101**) (**102**) (**103**)

3.4.1.3.13 Aminating agents

Amination at an azole ring nitrogen is known for *N*-unsubstituted azoles. Thus 4,5-diphenyl-1,2,3-triazole with hydroxylamine-*O*-sulfonic acid gives approximately equal amounts of the 1- (**104**) and 2-amino derivatives (**105**) ⟨74AHC(16)33⟩. Pyrazole affords (**106**) and indazole gives comparable amounts of the 1- and 2-amino derivatives.



(**104**) (**105**) (**106**) (**107**)

Azoles without a free NH group are also aminated, giving *N*-aminoazolium salts, *e.g.* (**107**) ⟨81AHC(29)71⟩.

3.4.1.3.14 Other Lewis acids

Azoles can form stable compounds in which metallic and metalloid atoms are linked to nitrogen. For example, pyrazoles and imidazoles *N*-substituted by B, Si, P and Hg groups are made in this way. Imidazoles with a free NH group can be *N*-trimethylsilylated and *N*-cyanated (with cyanogen bromide). Imidazoles of low basicity can be *N*-nitrated.

3.4.1.4 Electrophilic Attack at Carbon

3.4.1.4.1 Reactivity and orientation

(i) Ease of reaction

Replacing a CH=CH group in benzene with a heteroatom (Z) increases the susceptibility of the ring carbon atoms to electrophilic attack noticeably when Z is S, more when Z is O, and very markedly when Z is NH (*cf.* Chapter 2.4). Replacing one CH group in benzene with a nitrogen atom decreases the ease of electrophilic attack at the remaining carbon atoms (*cf.* Chapter 2.4); replacement of two CH groups with nitrogen atoms decreases it further (*cf.* Chapter 2.4). Such deactivation is very strong in nitration, sulfonation and Friedel–Crafts reactions, which proceed in strongly acidic media, *i.e.* under conditions in which the nitrogen atom is largely protonated (or complexed). The effect of a protonated nitrogen atom is considerably greater than, for example, the two nitro groups in *m*-dinitrobenzene. The deactivating effect is less pronounced in reactions conducted under neutral or weakly acidic conditions, where a large proportion of unprotonated free base exists, *i.e.* as in halogenation and mercuration reactions.

In azole chemistry the total effect of the several heteroatoms in one ring approximates the superposition of their separate effects. It is found that pyrazole, imidazole and isoxazole undergo nitration and sulfonation about as readily as nitrobenzene; thiazole and isothiazole react less readily (*ca.* equal to *m*-dinitrobenzene), and oxadiazoles, thiadiazoles, triazoles, *etc.* with great difficulty. In each case, halogenation is easier than the corresponding nitration or sulfonation. Strong electron-donor substituents help the reaction.

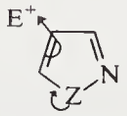
Pyrazoles and imidazoles exist partly as anions (*e.g.* **108** and **109**) in neutral and basic solution. Under these conditions they react with electrophilic reagents almost as readily as phenol, undergoing diazo coupling, nitrosation and Mannich reactions (note the increased reactivity of pyrrole anions over the neutral pyrrole species).

(108)

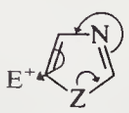
(109)

(ii) Orientation

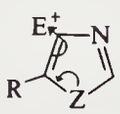
A multiply bonded nitrogen atom deactivates carbon atoms α or γ to it toward electrophilic attack; thus initial substitution in 1,2- and 1,3-dihetero compounds should be as shown in structures (**110**) and (**111**). Pyrazoles (**110**; Z = NH), isoxazoles (**110**; Z = O), isothiazoles (**110**; Z = S), imidazoles (**111**; Z = NH, tautomerism can make the 4- and 5-positions equivalent) and thiazoles (**111**; Z = S) do indeed undergo electrophilic substitution as expected. Little is known of the electrophilic substitution reactions of oxazoles (**111**; Z = O) and compounds containing three or more heteroatoms in one ring. Deactivation of the 4-position in 1,3-dihetero compounds (**111**) is less effective because of considerable double bond fixation (*cf.* Sections 2.4.3.2.1 and 3.4.3.1.7), and if the 5-position of imidazoles or thiazoles is blocked, substitution can occur in the 4-position (**112**).



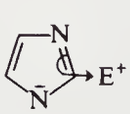
(110)



(111)



(112)



(113)

The above considerations do not necessarily apply to reactions of electrophilic reagents with pyrazole and imidazole anions (**108**, **109**). The imidazole anion is sometimes substituted in the 2-position (**113**) and the indazole anion in the 3-position (*cf.* Section 3.4.1.4.5).

(iii) Effect of substituents

Just as in benzene, substituents can strongly activate (*e.g.* NH_2, NMe_2, OMe), strongly deactivate (*e.g.* NO_2, SO_3H, CO_2Et) or have relatively little effect on (*e.g.* Me, Cl) the ring toward further substitution. Further electrophilic substitution generally will not take place on an azole which carries a strongly deactivating substituent unless the azole ring is also carrying a strong electron-donor group or is strongly activated, as it is in the azolone form. However, these considerations can be affected by basicity considerations: thus a strongly deactivating group can also increase the amount of more reactive neutral molecule compared with a less reactive cation.

When the preferred substitution position (*cf.* **110** and **111**) is occupied, activating substituents can facilitate substitution in other positions (*cf.* examples in Sections 3.4.1.4.2 and 3.4.1.4.5); *ipso* attack can also occur if the substituent is itself easily displaced.

In benz- and phenyl-azolones, electrophilic substitution often occurs in the benzene ring; such reactions are considered as reactions of substituents (see Sections 3.4.3.2.1 and 3.4.3.4.1).

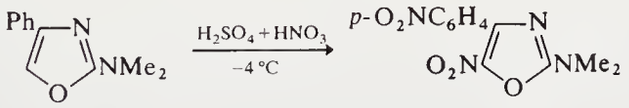
3.4.1.4.2 Nitration

Nitration of monocyclic compounds is summarized in Table 4. Substitution occurs in the expected positions. The reaction conditions required are more vigorous than those needed for benzene, but less than those for pyridine. Ring nitration of oxazoles is rare, but (**114**) has been obtained in this way ⟨74AHC(17)99⟩.

Table 4 Nitration and Sulfonation of Azoles

Heterocycle	*Position substituted*	*Reaction conditions*	
		Sulfonation	*Nitration*
Pyrazole	4	H_2SO_4/SO_3, 100 °C	$HNO_3/H_2SO_4/SO_3$, 100 °C
Imidazole	4 (≡5)	H_2SO_4/SO_3, 160 °C	HNO_3/H_2SO_4, 160 °C
3-Methylisoxazole	4	HSO_3Cl, 100 °C	$HNO_3/H_2SO_4/SO_3$, 70 °C
Isothiazole	4	H_2SO_4/SO_3, 150 °C [a]	HNO_3/H_2SO_4, 230 °C
Thiazole	5	$H_2SO_4/SO_3/Hg$, 250 °C	—
4-Methylthiazole	5	H_2SO_4/SO_3, 200 °C	$HNO_3/H_2SO_4/SO_3$, 160 °C
2,5-Dimethylthiazole	4	H_2SO_4/SO_3, 200 °C	$HNO_3/H_2SO_4/SO_3$, 160 °C

[a] ⟨66GEP1208303⟩.

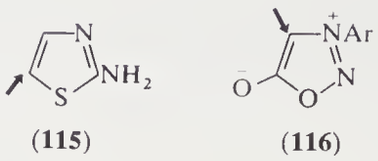


(**114**)

Substituents are sometimes displaced: thus chloroimidazoles are nitrated normally, but iodo analogues suffer nitro-deiodination.

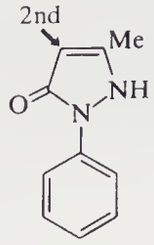
Pyrazoles can undergo nitration at several positions: 4-bromo-1-methylpyrazole yields the 3,5-dinitro product. 1-Methylpyrazole 2-oxide yields the 5-nitro derivative.

As expected, nitration is facilitated by activating groups such as an amino group; for example, nitration of (**115**) occurs at about 20 °C (HNO_3/H_2SO_4). Sydnones (**116**) are nitrated readily. The pyrazolinone (**117**) is nitrated as indicated, and 1,2,4-triazolinones have also been ring nitrated.



(**115**)

(**116**)



(**117**)

3.4.1.4.3 Sulfonation

Sulfonation conditions are given in Table 4. The orientation is as expected. Azolinones react as readily as the corresponding azoles; sulfonation of (**117**) occurs at the positions indicated (H_2SO_4/SO_3 at 100 °C). Imidazoles are readily chlorosulfonated at C-4.

3.4.1.4.4 Acid-catalyzed hydrogen exchange

Acid-catalyzed hydrogen exchange is used as a measure of the comparative reactivity of different aromatic rings (see Table 5). These reactions take place on the neutral molecules or, at high acidities, on the cations. At the preferred positions the neutral isoxazole, isothiazole and pyrazole rings are all considerably more reactive than benzene. Although the 4-position of isothiazole is somewhat less reactive than the 4-position in thiophene, a similar situation does not exist with isoxazole–furan ring systems.

Table 5 Reactivities Toward Acid-catalyzed Deuterodeprotonation ⟨79AHC(25)147⟩

	log (partial rate factor)[a] *Ring positions*			
Heterocycle	*2*	*3*	*4*	*5*
Isoxazole	—	—	4.3	—
Isothiazole	—	—	3.6	—
Furan	8.2	*ca.* 4.5	*ca.* 4.5	8.2
Thiophene	8.6	5.0	5.0	8.6
1-Methylpyrazole	—	5.6	9.8	5.6

[a] Relative to position 1 of benzene = 1.

Imidazoles, because of their high basicity, are very unreactive unless electron-withdrawing substituents are present.

3.4.1.4.5 Halogenation

Imidazoles and pyrazoles containing an unsubstituted NH group are easily chlorinated (Cl_2/H_2O or *N*-chlorosuccinimide/$CHCl_3$), brominated ($Br_2/CHCl_3$; $KOBr/H_2O$), and iodinated (I_2/HIO_3). Substitution generally occurs first at the 4-position, but further reaction at other available nuclear positions takes place readily, especially in the imidazole series. When halogenation of the nucleus involves electrophilic attack on anions of type (**109**), the 4-position of imidazole is again initially substituted (earlier work suggested a different orientation). The benzimidazole anion is iodinated at the 2-position; other halogenation generally occurs in the benzene ring.

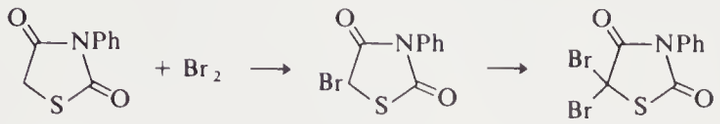
Isoxazoles can be halogenated in the 4-position ⟨63AHC(2)365⟩. Ring bromination of oxazoles with bromine or NBS occurs preferentially at the 5-position and, if this is occupied, at the 4-position ⟨74AHC(17)99⟩. Aminooxazoles are readily halogenated.

Isothiazoles with electron-releasing substituents such as amino, hydroxy, or alkoxy in the 3- or 5-position are brominated in high yield in the 4-position. Alkylisothiazoles give lower yields, but 3-methylisothiazole-5-carboxylic acid has been brominated in 76% yield ⟨72AHC(14)1⟩. Again, thiazoles with an electron-releasing substituent in the 2- or 4-position are brominated at the 5-position ⟨79HC(34-1)5⟩.

1,2,3-Triazoles are brominated at the 4- or 5-positions, but only if there is no *N*-substituent ⟨74AHC(16)33⟩. This also applies to 1,2,4-triazoles. *N*-Halo derivatives are frequently isolated as intermediates ⟨81HC(37)289⟩.

3-Amino-1,2,5-thiadiazole is chlorinated or brominated at the 4-position at 20 °C in acetic acid. 3-Methyl-1,2,5-thiadiazole can also be chlorinated in the 4-position ⟨68AHC(9)107⟩. Bromination of 2-amino-1,3,4-thiadiazole succeeds in the 5-position ⟨65ACS2434⟩.

Azolidinones are very easily halogenated, *e.g.* (**118**) gives (**119**) ⟨79AHC(25)83⟩; similar reactions occur in the isothiazolidinone series.

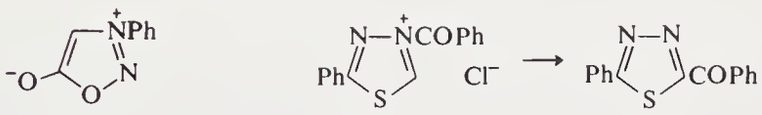


(**118**) (**119**)

3.4.1.4.6 Acylation and alkylation

Although in general azoles do not undergo Friedel–Crafts type alkylation or acylation, several isolated reactions of this general type are known. 3-Phenylsydnone (**120**) undergoes Friedel–Crafts acetylation and Vilsmeier formylation at the 4-position, and the 5-alkylation of thiazoles by carbonium ions is known.

Heating *N*-substituted pyrazoles with benzoyl chloride at 200 °C gives quite high yields of 4-benzoylpyrazoles, even in the absence of catalysts. Benzylation of *N*-substituted pyrazoles proceeds similarly in the 4-position ⟨66AHC(6)347⟩.



(**120**) (**121**) (**122**)

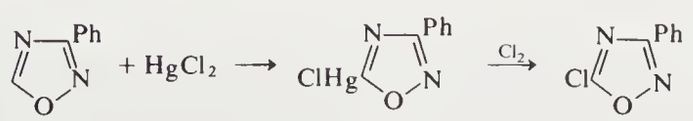
Heating 2-phenyl-4-benzoyl-1,3,4-thiadiazolium chloride (**121**) at 200 °C causes the benzoyl group to move to the 2-position as in (**122**) ⟨68AHC(9)165⟩, probably *via* deprotonation.

For the *C*-acylation of imidazoles *via* deprotonation, see Section 3.4.1.7.4.

4-Aminotriazole is carboxylated at the 5-position by heating with aqueous sodium bicarbonate in a Kolbe-type reaction ⟨71JCS(C)1501⟩. 2-Thiazolinones undergo the Gattermann and Reimer–Tiemann reactions at the 4-position, and 3- and 4-pyrazolinone anions on alkylation give 4-alkyl as well as *O*- and *N*-alkyl derivatives.

3.4.1.4.7 Mercuration

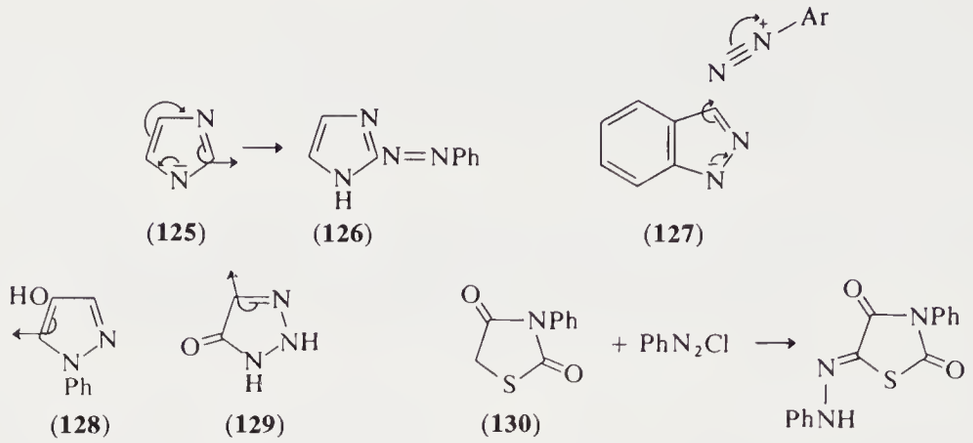
While there appears to have been no general study of the mercuration of azoles, the reaction seems to proceed readily in several systems. Thus pyrazoles are 4-chloromercurated by $HgCl_2$. Oxazoles are mercurated in acetic acid: the ring positions react 5 > 4 > 2 ⟨74AHC(17)99⟩. Thiazoles react under the same conditions and show the same order of ring position reactivities. Isoxazoles can be easily mercurated in the 4-position with mercury(II) acetate ⟨63AHC(2)365⟩. Oxadiazoles have been mercurated, *e.g.* (**123**) gives (**124**) ⟨64HCA838⟩. 1-Phenyltetrazole is mercurated in the 5-position, and 3-arylsydnones at the 4-position.



(**123**) (**124**)

3.4.1.4.8 Diazo coupling

Diazo coupling is expected to occur only with highly reactive systems, and experiment bears this out. Diazonium ions couple with the anions of *N*-unsubstituted imidazoles at the 2-position (*e.g.* **125** yields **126**) and with indazoles (**127**) in the 3-position. In general, other azoles react only when they contain an amino, hydroxy, or potential hydroxy group, *e.g.* the 4-hydroxypyrazole (**128**), the triazolinone (**129**) and the thiazolidinedione (**130**) (all these reactions occur on the corresponding anions).



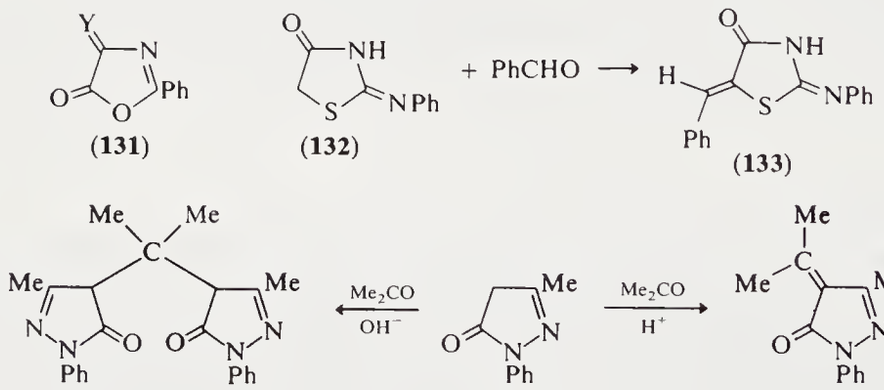
3.4.1.4.9 Nitrosation

Under alkaline conditions, alkyl nitrites nitrosate imidazoles which possess a free NH group in the 4-position ⟨70AHC(12)103⟩. Nitrosation of 3,5-dimethylpyrazoles gives the 4-diazonium salt by further reaction of the nitroso compound with more NO^+. 5-Pyrazolinones are often nitrosated readily at the 4-position. 3-Alkyl-5-acetamidoisothiazoles undergo 4-nitrosation.

3.4.1.4.10 Reactions with aldehydes and ketones

Imidazoles are hydroxymethylated by CH_2O at the 4-position; 1-substituted imidazoles react at the 2-position. Isoxazoles can be chloromethylated in the 4-position ⟨63AHC(2)365⟩.

Aldehydes and ketones react with azolinones. The reaction between aldehydes and 2-phenyl-5-oxazolinone (**131**; $Y = H_2$), formed *in situ* from $PhCONHCH_2CO_2H$ and Ac_2O, gives azlactones (**131**; $Y = RCH$). Similar reactions are given by 4-thiazolidinones, *e.g.* (**132**) gives (**133**) ⟨79AHC(25)83⟩, and 4-imidazolinones. In pyrazolin-5-ones the 4-position is sufficiently activated for condensation to occur with ketones in acidic media (Scheme 8) ⟨66AHC(6)347⟩.



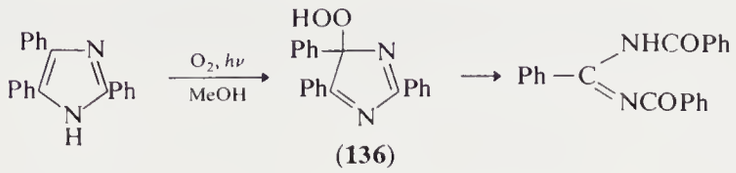
Scheme 8

3.4.1.4.11 Oxidation

The pyrazole ring is generally stable to oxidation and side chains are oxidized to carbonyl groups ⟨66AHC(6)347⟩. 1-Aryl-3-methylpyrazoles (**134**) react with ozone to yield 1,3,4-oxadiazolinones (**135**) ⟨66AHC(7)183⟩.

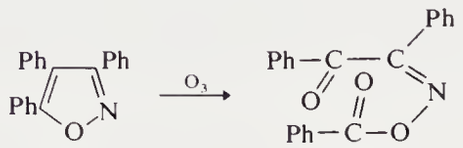
(134) (135)

Imidazole rings also survive most oxidation conditions, but photosensitized oxidation of imidazoles can give diarylbenzamidines through a hydroperoxide (**136**) ⟨70AHC(12)103⟩.



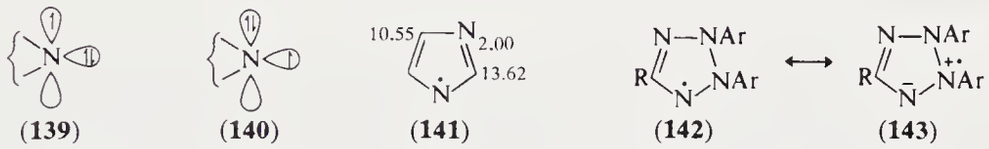
(136)

The thiazole, triazole and tetrazole rings are resistant to oxidation (*e.g.* by $KMnO_4$, CrO_3). Isoxazoles are more susceptible (*e.g.* **137**→**138**, benzil α-monoxime benzoate). The oxazole ring is relatively readily cleaved by oxidizing agents such as permanganate, chromic acid or hydrogen peroxide to give acids or amides. Oxidation of 4,5-diaryloxazoles with chlorine or bromine gives the corresponding benzils in high yield ⟨74AHC(17)99⟩.

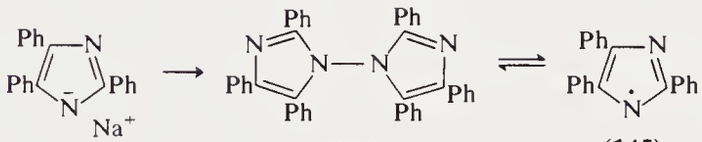


(137) (138)

Oxidation of azole anions can give neutral azole radicals which could, in principle, be π (**139**) or σ (**140**) in nature. ESR spectra indicate structure (**141**; hyperfine splittings in G) for imidazolyl radicals, but both π- and σ-character have been observed for pyrazolyl radicals. Tetrazolyl radicals (**142**↔**143**) are also well known ⟨79AHC(25)205⟩. Oxidation of 2,4,5-triarylimidazole anions with bromine gives 1,1′-diimidazolyls (**144**) which are in equilibrium with the dissociated free radical (**145**) ⟨70AHC(12)103⟩.



(139) (140) (141) (142) (143)

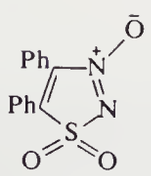


(144) (145)

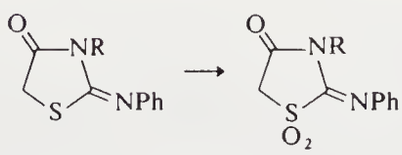
3.4.1.5 Attack at Sulfur

3.4.1.5.1 Electrophilic attack

In contrast to thiazoles, certain isothiazoles and benzisothiazoles have been directly oxidized to sulfoxides and sulfones. 4,5-Diphenyl-1,2,3-thiadiazole is converted by peracid into the trioxide (**146**). Although 1,2,5-thiadiazole 1,1-dioxides are known, they cannot be prepared in good yield by direct oxidation, which usually gives sulfate ion analogous to the results obtained with 1,2,4- and 1,3,4-thiadiazoles ⟨68AHC(9)107⟩.



(146)



Scheme 9

When a hydroxyazole can tautomerize to a non-aromatic structure, oxidation at an annular sulfur atom becomes easy, *e.g.* as in Scheme 9 ⟨79AHC(25)83⟩.

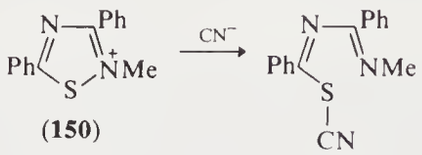
Thiazoles are desulfurized by Raney nickel, a reaction probably initiated by coordination of the sulfur at Ni. The products are generally anions and carbonyl compounds (see Section 3.4.1.8.4).

3.4.1.5.2 Nucleophilic attack

Isothiazoles and isothiazolium cations are attacked by carbanions at sulfur and on recyclization can give thiophenes, illustrated by (**147**)→(**148**). 2-Alkyl-3-isothiazolinones (*e.g.* **149**) are also vulnerable to nucleophilic attack at sulfur ⟨72AHC(14)1⟩.

(**147**) (**148**) (**149**)

Nucleophilic attack at sulfur is implicated in many reactions of 1,2,4-thiadiazoles; generally, 'soft' nucleophiles attack at sulfur, *cf.* (**150**)→(**151**). *n*-Butyllithium with 4,5-diphenyl-1,2,3-thiadiazole yields PhC≡CPh, probably by initial nucleophilic attack at sulfur.

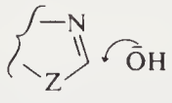


(**150**) (**151**)

3.4.1.6 Nucleophilic Attack at Carbon

Because of the increased importance of inductive electron withdrawal, nucleophilic attack on uncharged azole rings generally occurs under milder conditions than those required for analogous reactions with pyridines or pyridones. Azolium rings are very easily attacked by nucleophilic reagents; reactions similar to those of pyridinium and pyrylium compounds are known; azolium rings open particularly readily.

Nucleophilic attack on the ring carbon atoms of azoles occurs readily with oxazole and aza analogues. Such reactions are generally facilitated by additional ring heteroatoms and by electron-attracting substituents, and hindered by electron-donating substituents. A fused benzene ring aids nucleophilic attack on azoles, azolium ions and azolones; this may be rationalized because the loss of aromaticity involved in the formation of the initial adduct is less than that in monocyclic compounds. The orientation of attack is generally between two heteroatoms, as in (**152**).

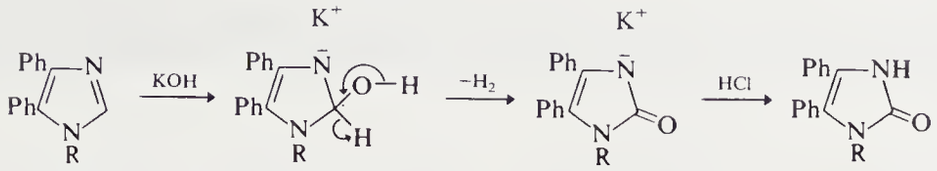


(**152**)

3.4.1.6.1 Hydroxide ion and other O-nucleophiles

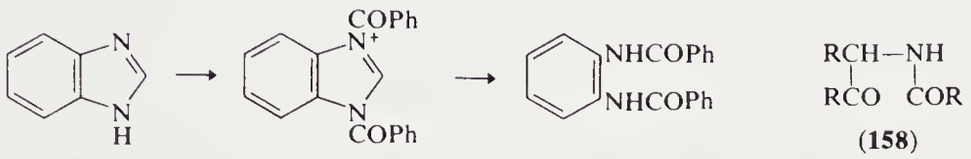
(i) Neutral azoles

Uncharged azoles not containing oxygen or sulfur are often resistant to attack by hydroxide ions at temperatures up to 100 °C and above. However, neutral azoles react with hydroxide ions under extreme conditions, *e.g.* 1-substituted imidazoles such as (**153**) at 300 °C give the corresponding imidazolinone (**154**) ⟨80AHC(27)241⟩.



(153) (154)

Imidazoles and benzimidazoles (**155**) react with acid chloride and alkali to give compounds of type (**157**), but these are reactions of the cation (**156**). 1,2,4-Triazoles and tetrazoles similarly undergo ring opening.



(155) (156) (157) (158)

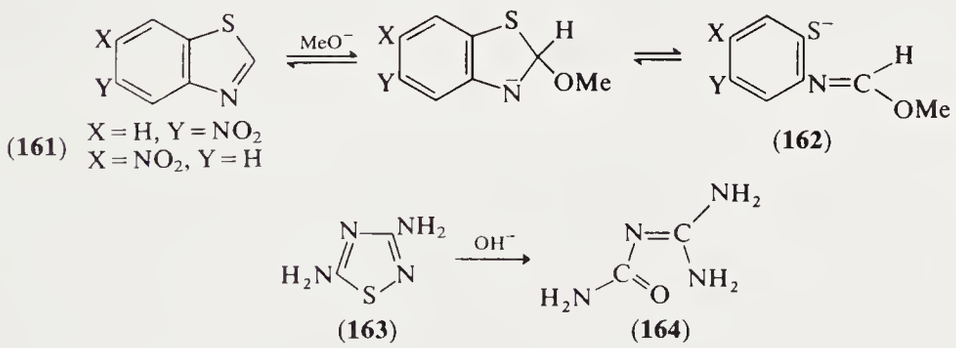
Isoxazoles are also rather stable to nucleophilic attack by OH^- at carbon. For reactions with base at a ring hydrogen atom, leading, for example, to ring opening of isoxazoles, see Section 3.4.1.7.1.

Oxazoles give acylamino ketones (**158**) by acid-catalyzed ring scission, although they are somewhat more stable than furans. The oxazole ring is also moderately stable to alkali ⟨74AHC(17)99⟩; as expected, reaction with hydroxide ions is facilitated by electron-withdrawing substituents and fused benzene rings.

Oxazoles are easily cleaved. 2,5-Dialkyl-1,3,4-oxadiazoles (**159**) in aqueous solution with acid or base give hydrazides (if suitable substituents are present, further reaction can occur; see Section 3.4.3.5.1). 3-Methyl-1,2,4-oxadiazole (**160**) is easily hydrolyzed to acetamidoxime ⟨61CI(L)292⟩.

(159) (160)

Isothiazoles and thiazoles are rather stable toward nucleophilic attack. Both 5- and 6-nitrobenzothiazole (**161**) add methoxide at C–2; the initial adduct undergoes ring opening to give (**162**) ⟨79AHC(25)1⟩. Unsubstituted 1,2,4-thiadiazole is sensitive to alkali. Substituents stabilize the ring somewhat, but ring-opening reactions are still common, *e.g.* (**163**)→(**164**). 5-Alkylamino-1,2,3,4-thiatriazoles are cleaved by alkali to azide ion and an isothiocyanate; in addition, a Dimroth rearrangement occurs to give a mercaptotetrazole ⟨64AHC(3)263⟩.

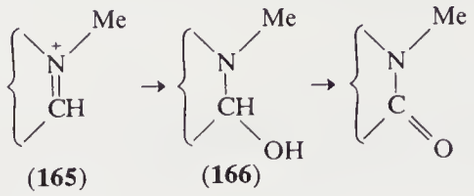


(161) X = H, Y = NO_2; X = NO_2, Y = H (162) (163) (164)

(ii) Azolium ions

Azolium ions (**165**) react reversibly with hydroxide ions to form a small proportion of the pseudo base (**166**). The term 'pseudo' is used to designate bases that react with acids measurably slowly, not instantaneously as is normal for acid–base reactions. Fused benzene rings reduce the loss of resonance energy when the hetero ring loses its aromaticity, and hence pseudo bases are formed even more readily by benzothiazolium cations than by thiazolium ions. Pseudo bases

carrying the hydroxy group in the α-position are usually formed preferentially. As expected, pseudo base formation for S-containing azoliums is easiest with the dithiolylium and least easy with the thiazolium ⟨79AHC(25)1⟩.

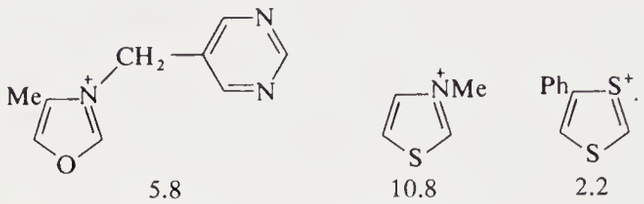


(165) (166)

pK_R^+ values for pseudo base formation are defined by equation (1),

$$K_R^+ = [H^+][QOH]/[Q^+] \quad (1)$$

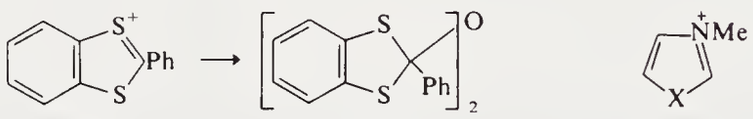
where Q^+ and QOH denote the azolium cation and pseudo base, respectively. Some pK_R^+ values are given in Scheme 10.



5.8 10.8 2.2

Scheme 10 pK_{R^+} values for azolium cations

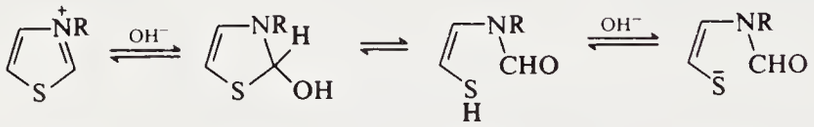
Some pseudo bases are stable. 1,3-Dithiolylium adds alkoxide ions at the 2-position to give stable adducts which regenerate the starting salts with acids ⟨80AHC(27)151⟩. Pseudo bases can also lose water to give an ether (*e.g.* **167**→**168**).



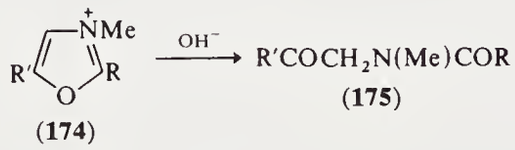
(167) (168) (169)

Oxidation to an azolone is an expected reaction for a pseudo base, but little appears to be known of such reactions. Most commonly, pseudo bases suffer ring fission. Estimated rates of ring opening of (**169**) are in the ratio 10^9: $10^{4.5}$: 1 for X = O, S and NMe, respectively ⟨79AHC(25)1⟩.

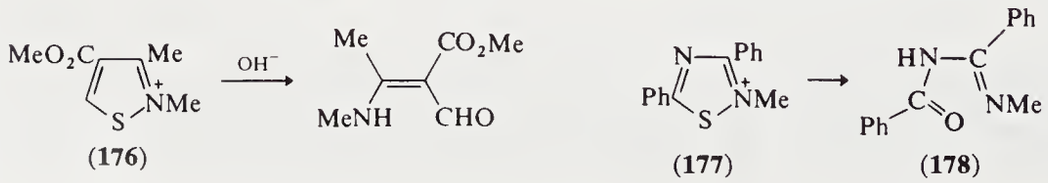
Thus quaternized thiazoles (**170**) consume two equivalents of OH^- on titration because the pseudo bases (**171**) ring open to (**172**), which form anions (**173**). Quaternized oxazoles (**174**) are readily attacked by hydroxide to give open-chain products such as (**175**) ⟨74AHC(17)99⟩, and quaternized 1,3,4-oxadiazoles behave similarly. Quaternary isothiazoles (*e.g.* **176**) are cleaved by hydroxide ⟨72AHC(14)1⟩, as are 1,2,4-thiadiazolium salts (**177**→**178**).



(170) (171) (172) (173)

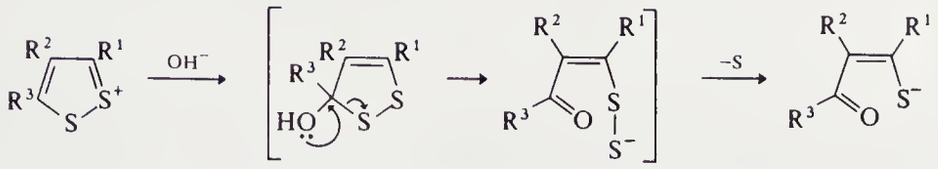


(174) (175)



(176) (177) (178)

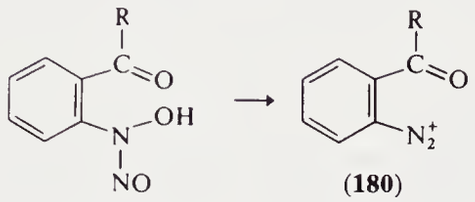
1,2-Dithiolylium ions undergo ring opening and degradation with hydroxide (Scheme 11) ⟨66AHC(7)39, 80AHC(27)151⟩. 1,2-Dimethylpyrazolium is degraded to MeNHNHMe.



Scheme 11

Reclosure to form a new heterocyclic or homocyclic ring can occur in azolium ions carrying suitable substituents; these reactions are considered under the appropriate substituents.

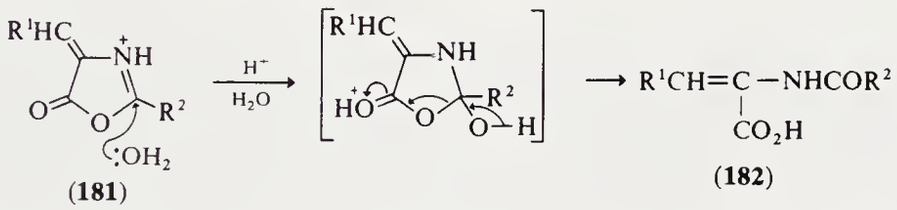
Anthranils are readily cleaved by nitrous acid, presumably by attack of water on *N*-nitroso cations. The first product that can be observed is the nitrosohydroxylamino compound (**179**), which becomes reduced to the diazonium salt (**180**) ⟨67AHC(8)277⟩.



(**179**) (**180**)

(iii) Azolinones

Although imidazolinones are usually resistant to hydrolysis, oxazolinone rings are often easily opened. In acid-catalyzed reactions of this type, water converts azlactones (**181**) into α-acylamino-α,β-unsaturated acids (**182**) ⟨77AHC(21)175⟩. 1,3,4-Oxadiazolinones are readily opened by hot water to give hydrazine carboxylic acids which undergo decarboxylation.

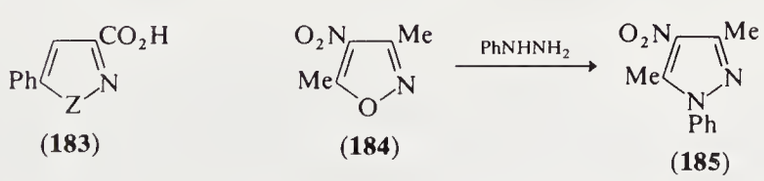


(**181**) (**182**)

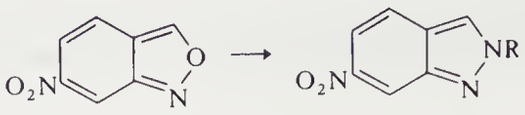
3.4.1.6.2 Amines and amide ions

(i) Azoles

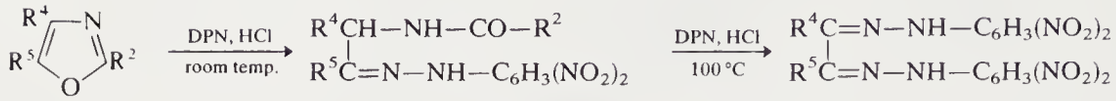
Oxygen-containing rings can be opened by amines; frequently this is followed by reclosure of the intermediate to form a new heterocycle. Thus isoxazoles containing electron-withdrawing substituents give pyrazoles with hydrazine, *e.g.* (**183**; Z = O)→(**183**; Z = NH), and (**184**)→(**185**) ⟨66AHC(6)347⟩. In the benzo series a rather different reaction can occur: 6-nitroanthranil (**186**) is converted by amines into 2-indazoles (**187**) ⟨61JOC3714⟩. Oxazoles heated at 180 °C with formamide are transformed into imidazoles ⟨74AHC(17)99⟩. With 2,4-dinitrophenylhydrazine in HCl, oxazoles form hydrazones by ring fission (Scheme 12) ⟨74AHC(17)99⟩. Benzoxazole with hydroxylamine gives 2-aminobenzoxazole by elimination of water from the initial adduct. 1,3,4-Oxadiazoles react readily with ammonia and primary amines to give 1,2,4-triazoles.



(**183**) (**184**) (**185**)



(186) **(187)**



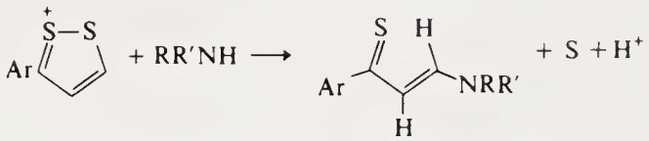
Scheme 12

Amines are insufficiently nucleophilic to react with most azoles which do not contain a ring oxygen, and the stronger nucleophile NH_2^- is required. When treated with amide ions, thiazoles can be aminated in the 2-position by $NaNH_2$ at 150 °C. Only *N*-substituted condensed imidazoles such as 1-alkylbenzimidazole react in such Chichibabin reactions. Imidazoles are aminated by alkaline NH_2OH.

(ii) Azolium ions

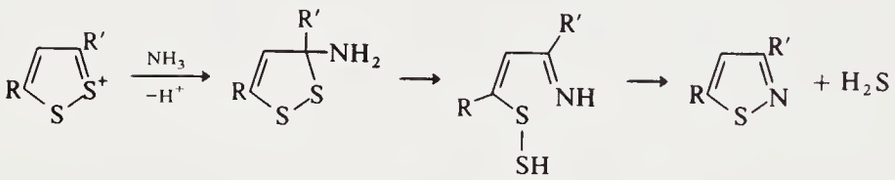
Most azolium ions are sufficiently reactive to be attacked by amines. Sometimes the initial adducts are stable: ammonia and primary and secondary amines add to 1,3-dithiolylium salts at the 2-position to give compounds of the types NT_3, RNT_2 and R_2NT, respectively, where T = the 1,3-thiol-2-yl group ⟨80AHC(27)151⟩.

Some azoliums give open-chain products: primary and secondary amines with 1,2-dithiolyliums generally give **(188)** ⟨80AHC(27)151⟩.

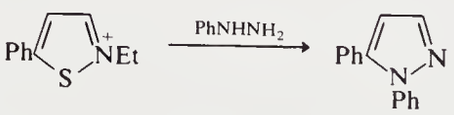


(188)

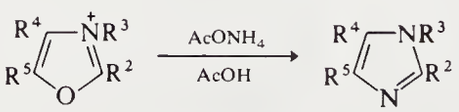
In other cases, reclosure to a new ring occurs: 1,2-dithiolylium ions with ammonia give isothiazoles according to the mechanism shown in Scheme 13 ⟨80AHC(27)151⟩. Treatment of quaternary isothiazoles with hydrazine or phenylhydrazine gives pyrazoles (Scheme 14) ⟨72AHC(14)1⟩, and 1,2,4-thiadiazoliums similarly yield 1,2,4-thiazoles. Oxazolium ions react with ammonium acetate in acetic acid to give the corresponding imidazoles (Scheme 15) ⟨74AHC(17)99⟩.



Scheme 13



Scheme 14



Scheme 15

Where an *N*-methoxy group is present, as in 1-methyl-3-methoxybenzimidazole, elimination of MeOH can give an aromatic product.

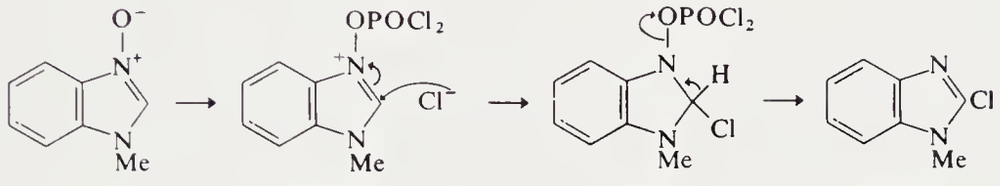
3.4.1.6.3 S-Nucleophiles

Data on reactions of sulfur nucleophiles with azoles are sparse. Oxazoles are transformed in low yield into the corresponding thiazoles over alumina with H_2S at 350 °C ⟨74AHC(17)99⟩. Sulfur nucleophiles such as SH^- or RS^- add to 1,3-dithiolylium salts at the 2-position ⟨80AHC(27)151⟩.

3.4.1.6.4 Halide ions

Chloride ions are comparatively weak nucleophiles and do not react with azoles. In general, there is also no interaction of halide ions with azolium compounds.

Benzimidazole 3-oxides, *e.g.* (**189**), react with phosphorus oxychloride or sulfuryl chloride to form the corresponding 2-chlorobenzimidazoles. The reaction sequence involves first formation of a nucleophilic complex (**190**), then attack of chloride ions on the complex, followed by re-aromatization involving loss of the *N*-oxide oxygen (**191**→**192**).

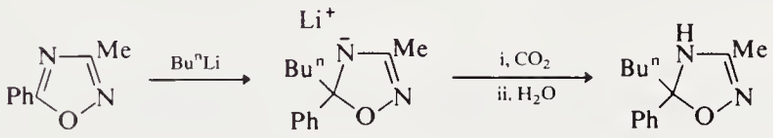


(**189**) (**190**) (**191**) (**192**)

3.4.1.6.5 Carbanions

(i) Organometallic compounds

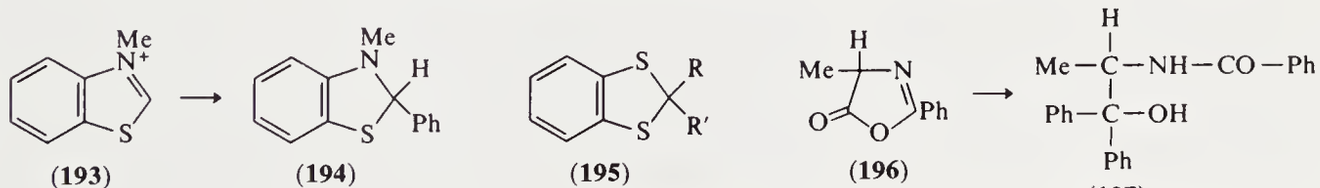
In contrast to pyridine chemistry, the range of nucleophilic alkylations that can be effected on neutral azoles is quite limited. Lithium reagents can add at the 5-position of 1,2,4-oxadiazoles (Scheme 16) ⟨70CJC2006⟩. Benzazoles are attacked by organometallic compounds at the C=N α-position unless it is blocked.



Scheme 16

Azolium rings react readily with organometallic compounds. With a Grignard reagent, conversion (**193**)→(**194**) is known in the benzothiazolium series, and 1,3-benzodithiolyliums give products of type (**195**).

4-Methyl-2-phenyl-5-oxazolinone (**196**) with phenylmagnesium bromide gives (**197**) ⟨65AHC(4)75⟩.

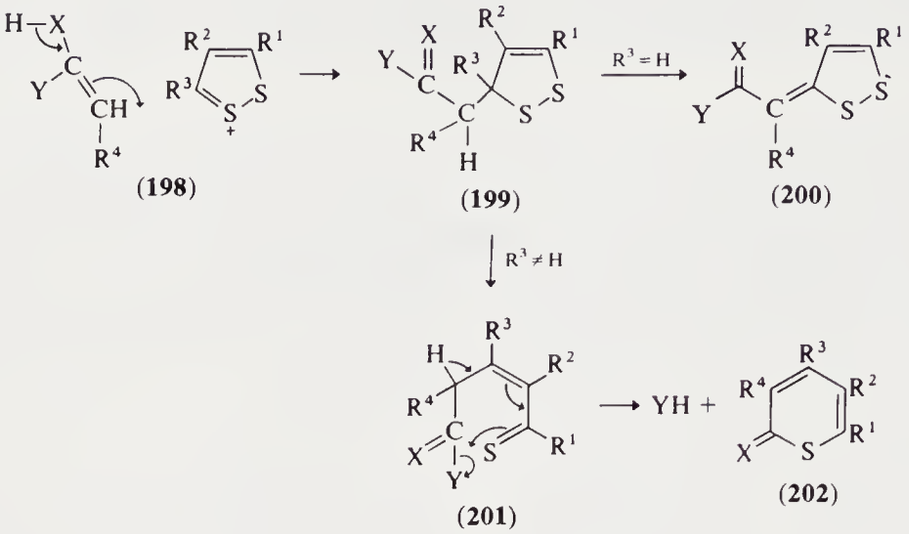


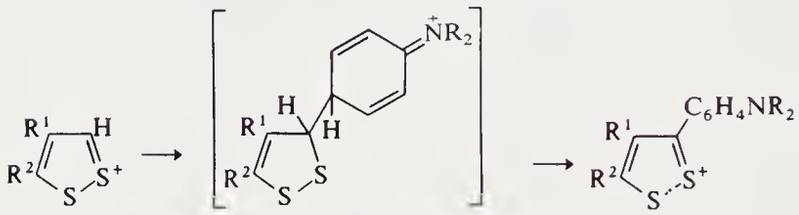
(**193**) (**194**) (**195**) (**196**) (**197**)

(ii) Activated methyl and methylene carbanions

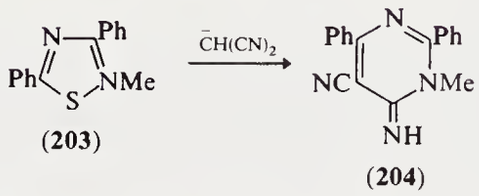
The mesomeric anions of activated methyl and methylene compounds react with azolium ions. Thus 1,2-dithiolylium ions with a free 3- or 5-position react with various carbon nucleophiles to

give products which are oxidized *in situ* to mesomeric anhydro-bases (**198**→**199**→**200**). Dimethylaniline gives an intermediate which is oxidized to a new dithiolylium salt (Scheme 17) ⟨66AHC(7)39⟩. However, in 3,5-disubstituted 1,2-dithiolylium cations an alternative ring scission can occur (**199**→**201**→**202**) ⟨80AHC(27)151⟩. In this sequence, (**198**) can be $ArCOCH_2CS_2Me$, $NCCH_2CSNH$ or $NCCH_2CO_2Et$. The conversion in the 1,2,4-thiadiazole series of (**203**) into (**204**) is analogous.

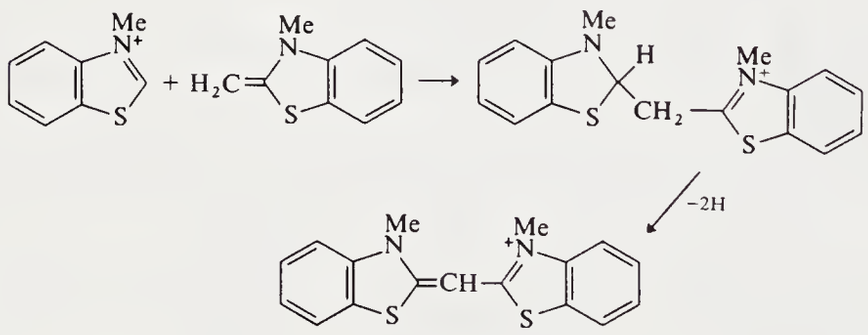




Scheme 17

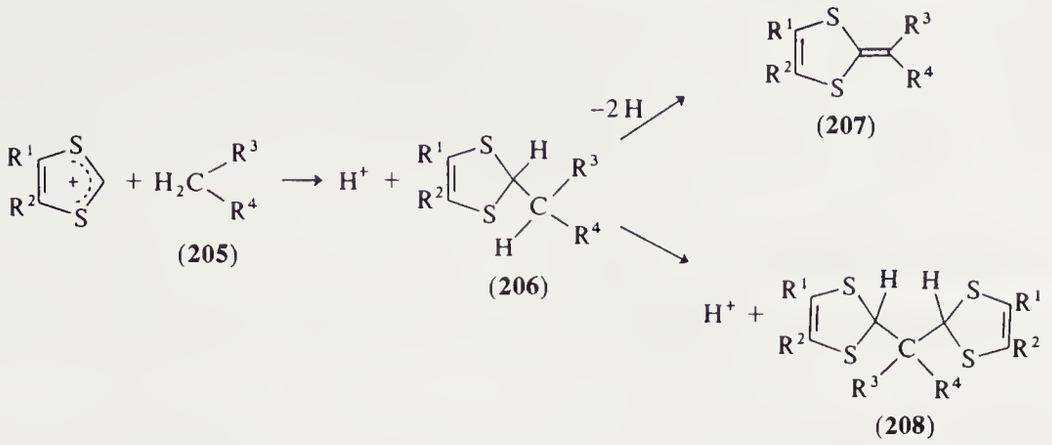


Anhydro bases can attack the α-position, *e.g.* of thiazolium cations, with the formation of adducts capable of oxidation to cyanine dyes, *e.g.* Scheme 18 (see Section 3.4.3.3.4).



Scheme 18

Active methylene compounds can add to 1,3-dithiolylium ions to give 2-substituted 1,2-dihydro-1,3-dithioles (**206**). Again, addition is often followed by oxidation (to **207**). Alternatively, further addition can occur (to **208**) ⟨80AHC(27)151⟩. In this reaction, (**205**) can be $CH_2(CN)_2$, $CH_2(COMe)_2$ or even MeCOMe. Somewhat similar reactions are shown by 1,3-diarylimidazolium ions.



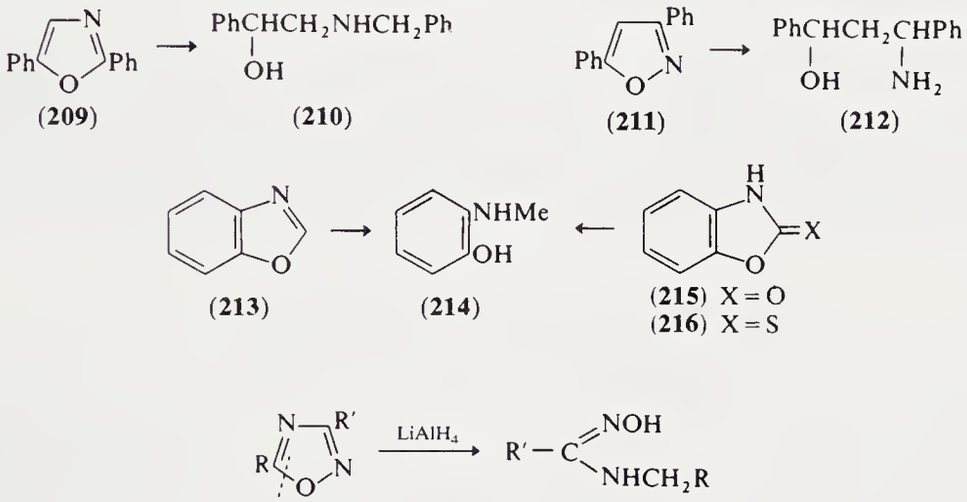
(205) (206) (207) (208)

(iii) Cyanide ions

Cyanopyrazoles are formed by irradiation of pyrazoles in the presence of cyanide ions in photosubstitution reactions.

3.4.1.6.6 Reduction by complex hydrides

Oxygen-containing azoles are readily reduced, usually with ring scission. Only acyclic products have been reported from the reductions with complex metal hydrides of oxazoles (*e.g.* **209**→**210**), isoxazoles (*e.g.* **211**→**212**), benzoxazoles (*e.g.* **213**→**214**) and benzoxazolinones (*e.g.* **215**, **216**→**214**). Reductions of 1,2,4-oxadiazoles always involve ring scission. Lithium aluminum hydride breaks the C—O bond in the ring (Scheme 19) ⟨76AHC(20)65⟩.



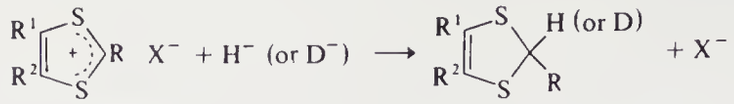
(209) (210) (211) (212) (213) (214) (215) X = O (216) X = S

Scheme 19

Nitrogen azoles are less easily reduced: benzimidazole with lithium aluminum hydride gives dihydrobenzimidazole ⟨52CB390⟩.

Cationic rings are readily reduced by complex hydrides under relatively mild conditions. Thus isoxazolium salts with sodium borohydride give the 2,5-dihydro derivatives (**217**) in ethanol, but yield the 2,3-dihydro compound (**218**) in $MeCN/H_2O$ ⟨74CPB70⟩. Pyrazolyl anions are reduced by borohydride to pyrazolines and pyrazolidines. Thiazolyl ions are reduced to 1,2-dihydrothiazoles by lithium aluminum hydride and to tetrahydrothiazoles by sodium borohydride. The tetrahydro compound is probably formed *via* (**219**), which results from proton addition to the dihydro derivative (**220**) containing an enamine function. 1,3-Dithiolylium salts easily add hydride ion from sodium borohydride (Scheme 20) ⟨80AHC(27)151⟩.

(217) (218) (219) (220)

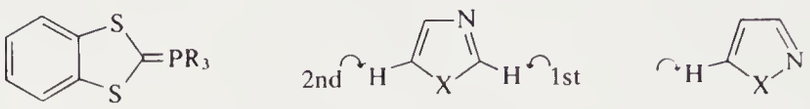


R = H, SMe, NR_2, aryl, cyclohexyl

Scheme 20

3.4.1.6.7 Phosphorus nucleophiles

Trialkyl- and triaryl-phosphines react with 1,3-benzodithiolylium ions to give a phosphonium salt which is deprotonated by *n*-butyllithium to give (**221**) ⟨76TL3695⟩.



(**221**) (**222**) (**223**)

3.4.1.7 Nucleophilic Attack at Hydrogen Attached to Ring Carbon or Ring Nitrogen

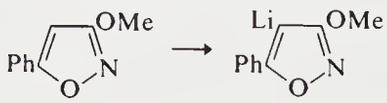
Hydrogens attached to ring carbon atoms of neutral azoles, and especially azolium ions, are acidic and can be removed as protons by bases. Reaction follows the orientations shown in (**222**) and (**223**). The anions from neutral azoles can be stabilized as lithium derivatives, except in isoxazoles where ring cleavage occurs. Typically, the anion adds a proton again and hydrogen isotope exchange can result. The zwitterions from azolium rings can react as carbenes.

3.4.1.7.1 Metallation at a ring carbon atom

Neutral azoles are readily *C*-lithiated by *n*-butyllithium provided they do not contain a free NH group (Table 6). Derivatives with two heteroatoms in the 1,3-orientation undergo lithiation preferentially at the 2-position; other compounds are lithiated at the 5-position. Attempted metallation of isoxazoles usually causes ring opening *via* proton loss at the 3- or 5-position (Section 3.4.1.7.5); however, if both of these positions are substituted, normal lithiation occurs at the 4-position (Scheme 21).

Table 6 Lithiation of Azoles by *n*-Butyllithium

Heterocycle	*Position lithiated*	*Temperature* (°C)	*Ref.*
3-Methyl-1-phenylpyrazole	5	—	66AHC(6)347, 52JA3242
3,5-Disubstituted isoxazoles	4	−70 to −65	79AHC(25)147, 70CJC1371
3,5-Disubstituted isothiazoles	5	−70	65AHC(4)75, 72AHC(14)1
1-Substituted imidazoles	2	—	—
1-Substituted oxazoles	2	'low'	74AHC(17)99
1-Substituted thiazoles	2	−60	—
2-Substituted thiazoles	5	−100	—
1-Phenyl-1,2,3-triazoles	5	−60 to −20	74AHC(16)33, 71CJC1792
1-Butyltetrazole	5	−60	77AHC(21)323

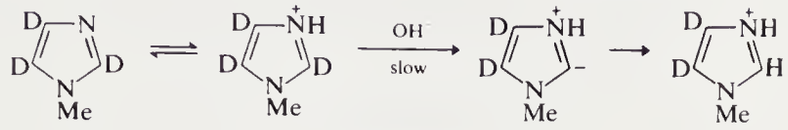


Scheme 21

3.4.1.7.2 Hydrogen exchange at ring carbon in neutral azoles

Base-catalyzed hydrogen exchange has been summarized for five-membered rings ⟨74AHC(16)1⟩. In many reactions of this type the protonated azole is attacked by hydroxide ion to form an ylide in

the rate-determining step, *e.g.* for imidazole (Scheme 22) ⟨74AHC(16)1⟩. Deuteration of imidazole is fast at the 2-position and much slower at the 4- and 5-positions. Rates fall off for *N*-unsubstituted imidazoles at high pH values because of the formation of unreactive anions. In the case of 1-methylbenzimidazole the rate of hydrogen exchange in the 2-position is independent of the acidity over a wide range, in agreement with the mechanism shown in Scheme 22 ⟨80AHC(27)241⟩.



Scheme 22

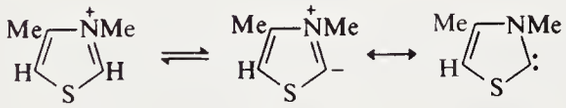
Under strongly basic conditions oxazoles undergo fast 2-deuteration and slower 5-deuteration ⟨74AHC(17)99⟩. The hydrogen in the 5-position of isothiazoles exchanges rapidly under basic conditions ⟨69JHC199⟩. Neutral thiazoles exchange by two competitive mechanisms: at pD 0–11 the conjugate acid exchanges the 2-H *via* the ylide (**224**), whereas at higher pD exchange is at the 2- and 5-positions *via* the carbanions (**225**) and (**226**). The 1,2,4- (**227**), 1,3,4- (**228**) and 1,2,3-thiadiazoles (**229**) all undergo rapid exchange at the 5-, 2- and 5-positions, respectively ⟨74AHC(16)1⟩.

(**224**) (**225**) (**226**) (**227**) (**228**) (**229**)

1-Substituted tetrazoles readily exchange the 5-hydrogen for deuterium in aqueous solution. A major rate-enhancing effect is observed with copper(II) or zinc ions due to σ-complexation with the heterocycle. The rate of base-induced proton–deuterium exchange of 1-methyltetrazole is 10^5 times faster than 2-methyltetrazole ⟨77AHC(21)323⟩.

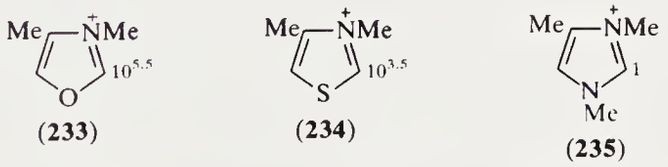
3.4.1.7.3 Hydrogen exchange at ring carbon in azolium ions and dimerization

Hydrogen atoms in azolium ions can be removed easily as protons (*e.g.* **230**→**232**); exchange with deuterium occurs in heavy water. The intermediate zwitterion (*e.g.* **231**) can also be written as a carbene, and in some cases this carbenoid form can be trapped or isolated as a dimer.



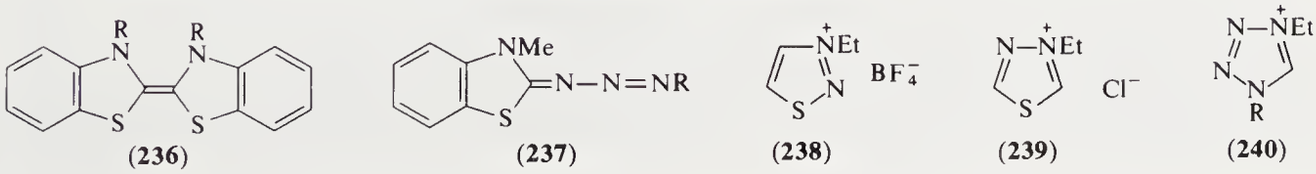
(**230**) (**231**) (**232**)

The relative rates of H-isotope exchange in D_2O/OD^- for oxazolium, thiazolium and imidazolium are shown in formulae (**233**)–(**235**), respectively ⟨71PMH(4)55⟩. The intermediate carbene, *e.g.* (**232**), can form a dimer (**236**) or be trapped with azides (**237**) ⟨74AHC(16)1⟩. Hydrogen atoms in positions 3 and 5 of 1,2-dithiolylium ions undergo deprotonation and can be replaced by deuterium ⟨80AHC(27)151⟩. Thiadiazolium salts (**238**) and (**239**) ⟨74AHC(16)1⟩, and especially tetrazolium salts (*e.g.* **240**) ⟨74AHC(16)1⟩, exchange particularly quickly.



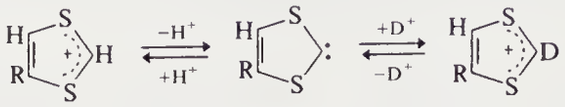
(**233**) (**234**) (**235**)

Relative rates of H-isotope exchange in D_2O/OD^-



(**236**) (**237**) (**238**) (**239**) (**240**)

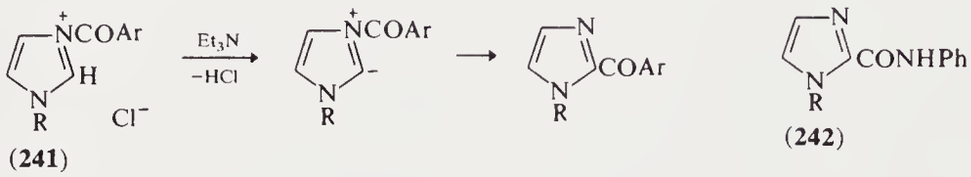
Base-catalyzed hydrogen exchange occurs at the 3- and 5-positions of 1,2-dimethylpyrazolium salts. 2-Unsubstituted 1,3-dithiolylium salts are easily deprotonated by nucleophilic attack of hydrogen. The intermediate carbene easily undergoes dimerization. Hydrogen exchange can also occur (Scheme 23) ⟨80AHC(27)151⟩.



Scheme 23

3.4.1.7.4 C-*Acylation* via *deprotonation*

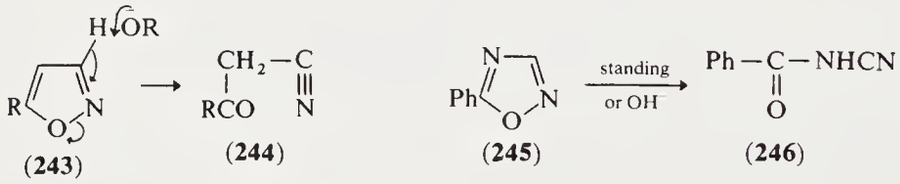
1-Substituted imidazoles can be acylated at the 2-position by acid chlorides in the presence of triethylamine. This reaction proceeds by proton loss on the *N*-acylated intermediate (**241**). An analogous reaction with phenyl isocyanate gives (**242**), probably *via* a similar mechanism. Benzimidazoles react similarly, but pyrazoles do not ⟨80AHC(27)241⟩ (*cf.* Section 3.4.1.4.6).



(**241**) (**242**)

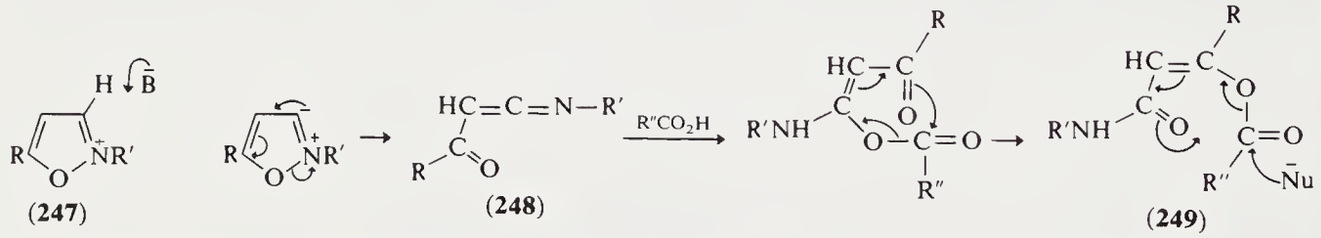
3.4.1.7.5 *Ring cleavage* via C-*deprotonation*

Isoxazoles unsubstituted in the 3-position react with hydroxide or ethoxide ions to give β-keto nitriles (**243**)→(**244**). This reaction involves nucleophilic attack at the 3-CH group. 1,2-Benzisoxazoles unsubstituted in the 3-position similarly readily give salicylyl nitriles ⟨67AHC(8)277⟩, and 5-phenyl-1,3,4-oxadiazole (**245**) is rapidly converted in alkaline solution into benzoylcyanamide (**246**) ⟨61CI(L)292⟩. A similar cleavage is known for 3-unsubstituted pyrazoles and indazoles; the latter yield *o*-cyanoanilines.



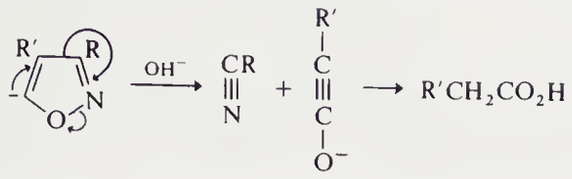
(**243**) (**244**) (**245**) (**246**)

3-Unsubstituted isoxazolium salts (**247**) lose the 3-proton under very mild conditions, *e.g.* at pH 7 in aqueous solution, to give intermediate acylketenimines (**248**) which convert carboxylic acids into efficient acylating agents (**249**) ⟨79AHC(25)147⟩.

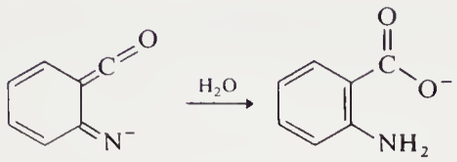


(**247**) (**248**) (**249**)

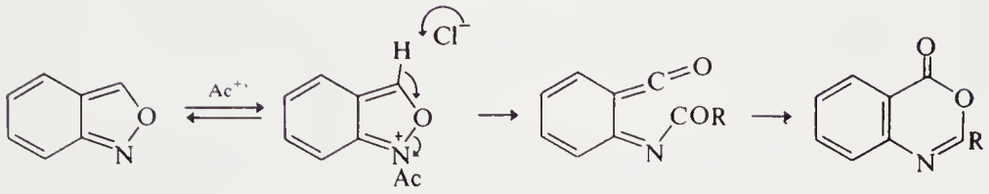
Isoxazoles substituted in the 3-position, but unsubstituted in the 5-position, react under more vigorous conditions to give acids and nitriles (Scheme 24). Anthranils unsubstituted in the 3-position are similarly converted into anthranilic acids by bases (Scheme 25) ⟨67AHC(8)277⟩. Attempted acylation of anthranils gives benzoxazine derivatives *via* a similar ring opening (Scheme 26) ⟨67AHC(8)277⟩.



Scheme 24



Scheme 25



Scheme 26

For ring-opening reactions of *C*-metallated azoles, see Section 3.4.3.8.

3.4.1.7.6 Proton loss from a ring nitrogen atom

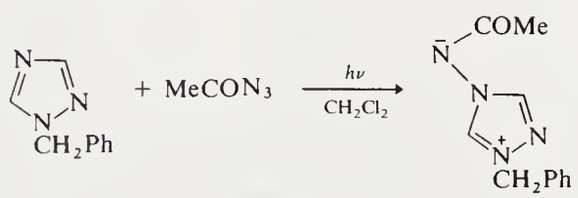
Pyrazoles, imidazoles, triazoles and tetrazoles are weak acids. They form metallic salts (*e.g.* with $NaNH_2$, RMgBr) which are extensively hydrolyzed by water. The anions react very readily with electrophilic reagents on either ring nitrogen or carbon atoms, as discussed in Sections 3.4.1.3 and 3.4.1.4. For example, proton loss from a ring nitrogen atom gives the highly nucleophilic imidazole anion. This anion can be formed with sodium hydroxide or sodium alkoxide; good results are obtained with sodamide in liquid ammonia ⟨70AHC(12)103⟩.

Azolinones are weak to medium strong acids of pK_a 4–11. They form mesomeric anions which react very readily with electrophilic reagents at the nitrogen, oxygen or carbon atoms, depending on the conditions; see Section 3.4.1.1.4.

3.4.1.8 Reactions with Radicals and Electron-deficient Species; Reactions at Surfaces

3.4.1.8.1 Carbenes and nitrenes

Few reactions of azoles with these reagents have been reported. 2-Methylimidazole reacts with $:CCl_2$ to give 5-chloro-2-methylpyrimidine in poor yield. Pyrazoles react with $HCCl_3$ at 550°C (with $:CCl_2$ formation) to give 2-chloropyrimidines in good yields. 1-Alkyl-1,2,4-triazoles react with nitrenes formed by the irradiation of azides to give *N*-imines (Scheme 27) ⟨74AHC(17)213⟩.



Scheme 27

3.4.1.8.2 Free radical attack at the ring carbon atoms

Despite some recent discoveries, free radical reactions are still very much less common in azole chemistry than those involving electrophilic or nucleophilic reagents. In some reactions involving free radicals, substituents have little orienting effect; however, rather selective radical reactions are now known.

(i) Aryl radicals

Phenyl radicals attack azoles unselectively to form a mixture of phenylated products. Relative rates and partial rate factors are given in Table 7. The phenyl radicals may be prepared from the usual precursors: PhN(NO)COMe, $Pb(OCOPh)_4$, $(PhCO_2)_2$ or $PhI(OCOPh)_2$. Substituted phenyl radicals react similarly.

Table 7 Relative Rates and Partial Rate Factors for the Homolytic Phenylation[a] of Five-membered Heterocycles ⟨74AHC(16)123⟩

Heterocycle	*Relative rates*	*Partial rate factors* 2	3	4	5
Thiazole	1.6	6.2	—	1.0	2.8
2-Methylthiazole	0.6	—	—	1.0	2.4
4-Methylthiazole	1.2	2.9	—	—	4.3
5-Methylthiazole	0.8	3.8	—	1.0	—
Isothiazole	0.95	—	2.7	0.5	2.5
1-Methylpyrazole	0.6	—	0.18	0.03	3.4
1-Methylimidazole	1.2	—	2.7	0.5	2.5

[a] Benzoyl peroxide is the source of the phenyl radicals, except for the first entry, where it is nitrosoacetanilide.

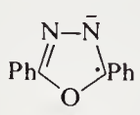
(ii) Alkyl radicals

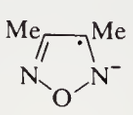
Alkyl radicals produced by oxidative decarboxylation of carboxylic acids are nucleophilic and attack protonated azoles at the most electron-deficient sites. Thus imidazole and 1-alkylimidazoles are alkylated exclusively at the 2-position ⟨80AHC(27)241⟩. Similarly, thiazoles are attacked in acidic media by methyl and propyl radicals to give 2-substituted derivatives in moderate yields, with smaller amounts of 5-substitution. These reactions have been reviewed ⟨74AHC(16)123⟩; the mechanism involves an intermediate σ-complex.

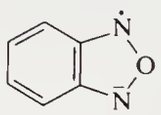
Similar reactions occur with acyl radicals, for example with the $CONH_2$ radical from formamide ⟨74AHC(16)123⟩.

3.4.1.8.3 Electrochemical reactions and reactions with free electrons

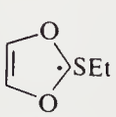
Neutral rings are reduced by the uptake of an electron to form anion radicals ⟨80AHC(27)31⟩. In isoxazole and oxazole this can be achieved in an argon matrix, but normally ring fission occurs; reduction of 1,2,4-thiadiazoles also usually results in ring cleavage. Thiazoles containing electron-withdrawing groups, 1,3,4-oxadiazoles, 1,2,5-oxadiazoles and 1,2,5-thiadiazoles on electrochemical reduction yield transient anion radicals which can be characterized by ESR, *e.g.* (**250**) and (**251**). Anion radicals from benzazoles can be more stable, *e.g.* (**252**).

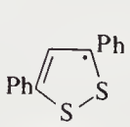

(**250**)

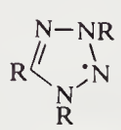

(**251**)

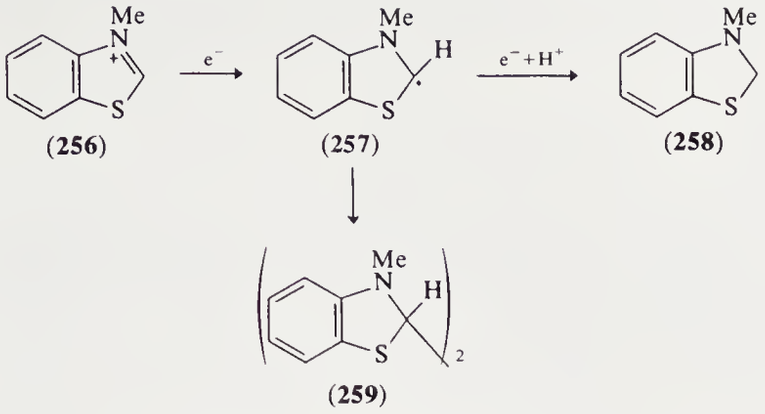

(**252**)

Cationic rings are reduced with the uptake of one electron (*e.g.* electrochemically) to give neutral radicals ⟨80AHC(27)31⟩. Examples of radicals which have been detected by ESR are (**253**) and (**254**). Such radicals, *e.g.* those from benzothiazolium ions, can dimerize (to **259**) or undergo further reduction (to **258**). 3-Methylbenzothiazolium (**256**) is reduced in a two-electron wave. The preparative reduction gives a mixture of the dihydro derivative (**258**) and the dimer (**259**) ⟨70AHC(12)213⟩. Benzofurazan is reduced polarographically in a six-electron reaction to *o*-phenylenediamine ⟨59MI40200⟩.


(**253**)


(**254**)

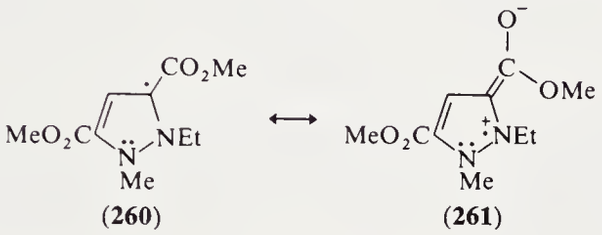

(**255**)



(256) (257) (258) (259)

Calculations indicate that 1,2-dithiolyl radicals have large spin densities at the 3,5-positions and that 1,3-dithiolyl radicals have large spin densities at the 2-position. In agreement, radicals of these types unsubstituted at such positions dimerize very readily; when the position is substituted, the radical is more stable (**253** and **254**). Reduction of tetrazolium salts gives tetrazolyl radicals (**255**) which show appreciable spin density on all four ring nitrogen atoms ⟨77AHC(21)323⟩.

Electron-withdrawing substituents stabilize such neutral radicals considerably. Merostabilization is found, for example, in the pyrazolyl derivative (**260**)↔(**261**) ⟨74JCS(P1)1422⟩.



(260) (261)

3.4.1.8.4 Other reactions at surfaces (heterogeneous catalysis and reduction reactions)

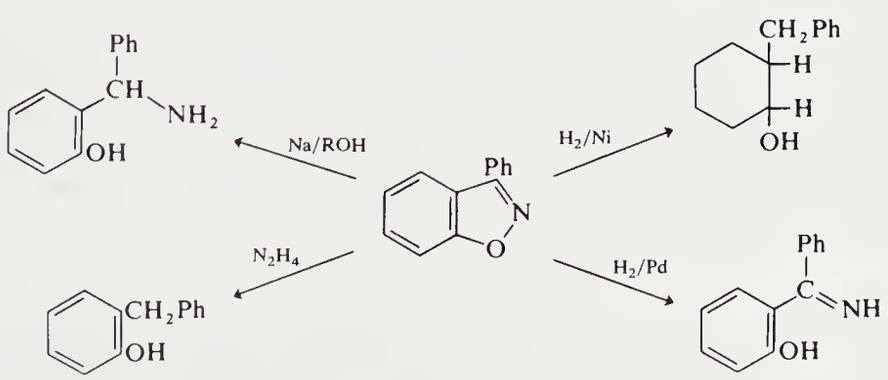
(i) Catalytic hydrogenation and reduction by dissolving metals

In general, azoles containing a cyclic oxygen atom are readily reduced, those with cyclic sulfur with more difficulty, and wholly nitrogenous azoles not at all.

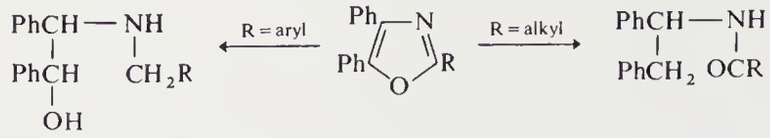
Pyrazoles are very resistant to catalytic reduction, resisting hydrogenation over nickel at 150 °C and 100 atm ⟨66AHC(6)347⟩. Imidazoles are generally resistant to reduction.

Isoxazoles are readily reduced, usually with concomitant ring fission (*e.g.* **262**→**263**). They behave as masked 1,3-diketones ⟨79AHC(25)147⟩. 1,2-Benzisoxazoles are easily reduced to various products (Scheme 28) ⟨67AHC(8)277⟩. Chemical or catalytic reduction of oxazoles invariably cleaves the heterocyclic ring (Scheme 29) ⟨74AHC(17)99⟩. For similar reactions of thiazoles, see Section 3.4.1.5.1.

(262) (263)

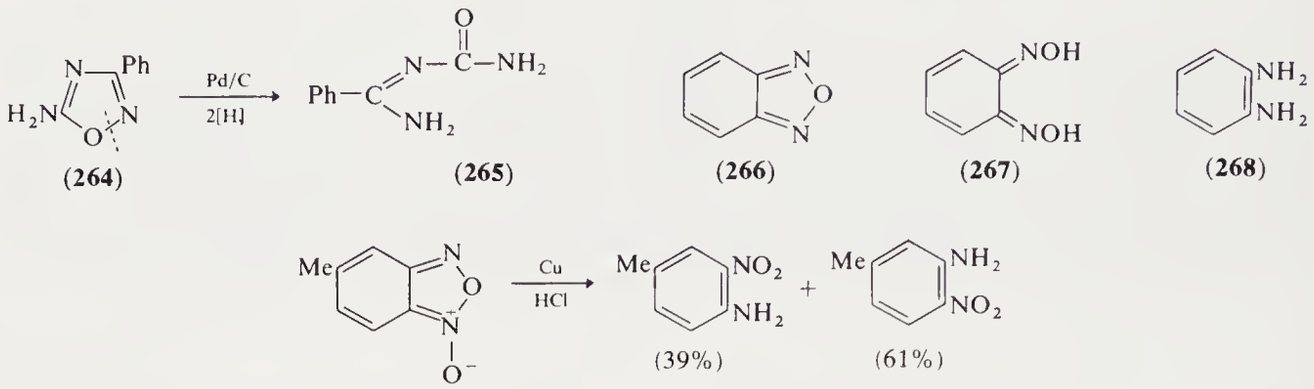


Scheme 28



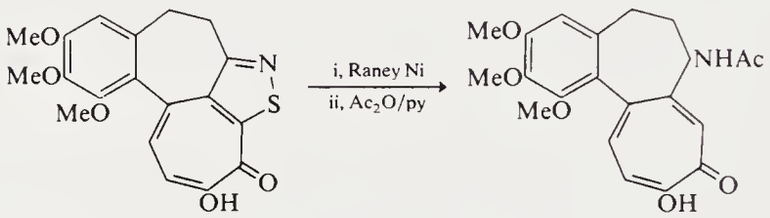
Scheme 29

Catalytic reduction of 1,2,4-oxadiazoles also breaks the N—O bond; *e.g.* (**264**) gives (**265**). Benzofuroxan can be reduced under various conditions to benzofurazan (**266**), the dioxime (**267**) or *o*-phenylenediamine (**268**) ⟨69AHC(10)1⟩. Reduction by copper and hydrochloric acid produced *o*-nitroanilines (Scheme 30) ⟨69AHC(10)1⟩.

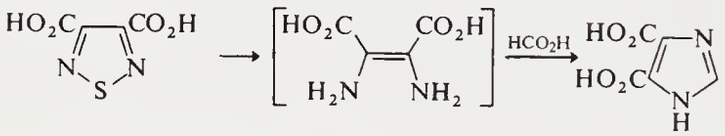


Scheme 30

Isothiazoles are reductively desulfurized by Raney nickel, *e.g.* as in Scheme 31 ⟨72AHC(14)1⟩. 1,2,5-Thiadiazoles are subject to reductive cleavage by zinc in acid, sodium in alcohol, or Raney nickel, *e.g.* Scheme 32 ⟨68AHC(9)107⟩.



Scheme 31

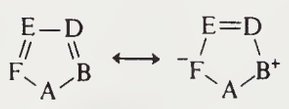


Scheme 32

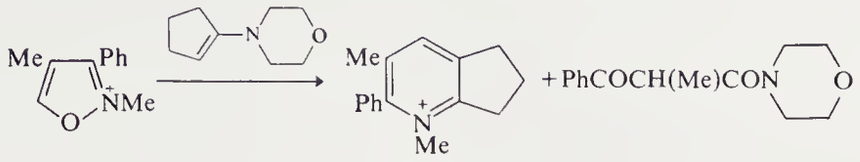
3.4.1.9 Reactions with Cyclic Transition States

3.4.1.9.1 Diels–Alder reactions and 1,3-dipolar cycloadditions

The distinction between these two classes of reactions is semantic for the five-membered rings: Diels–Alder reaction at the F/B positions in (**269**) (four atom fragment) is equivalent to 1,3-dipolar cycloaddition in (**270**) across the three-atom fragment, both providing the four-π-electron component of the cycloaddition. Oxazoles and isoxazoles and their polyaza analogues show reduced aromatic character and will undergo many cycloadditions, whereas fully nitrogenous azoles such as pyrazoles and imidazoles do not, except in certain isolated cases.

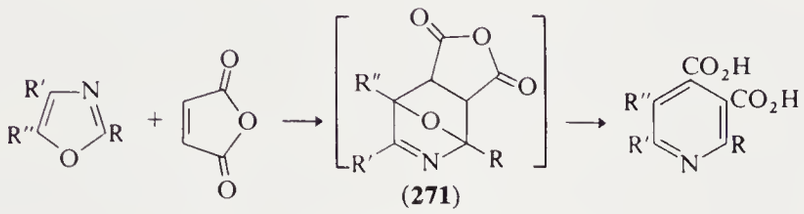


Isoxazolium salts react with enamines to give pyridinium salts (Scheme 33) ⟨69CPB2209⟩.



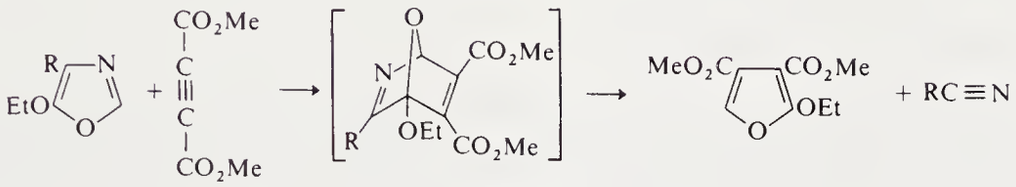
Scheme 33

Diels–Alder reactions of oxazoles afford useful syntheses of pyridines (Scheme 34) ⟨74AHC(17)99⟩. A study of the effect of substituents on the Diels–Alder reactivity of oxazoles has indicated that rates decrease with the following substituents: alkoxy > alkyl > acyl ≫ phenyl. The failure of 2- and 5-phenyl-substituted oxazoles to react with heterodienes is probably due to steric crowding. In certain cases, bicyclic adducts of type (**271**) have been isolated and characterized ⟨74AHC(17)99⟩; they can also decompose to yield furans (Scheme 35). Oxazoles react with singlet oxygen to give bicyclic adducts of type (**272**) which subsequently decompose (*e.g.* to **273**) ⟨74AHC(17)99⟩.

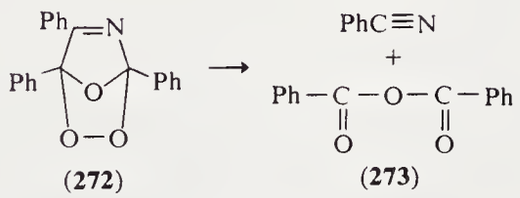


(**271**)

Scheme 34

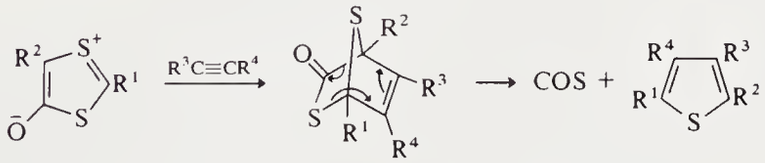


Scheme 35

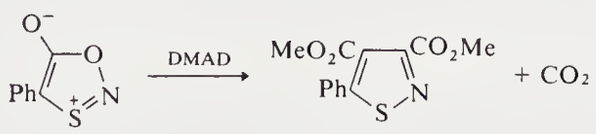


(**272**) (**273**)

1,2,3,4-Thiatriazolin-5-imines undergo a variety of cycloaddition reactions with the elimination of N_2. 1,3-Dithiolylium-4-olates undergo cycloaddition reactions, *e.g.* as in Scheme 36 ⟨80AHC(27)151⟩. Scheme 37 gives an example of cycloaddition in the oxathiazole series.



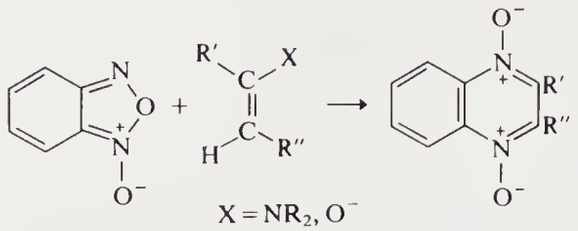
Scheme 36



Scheme 37

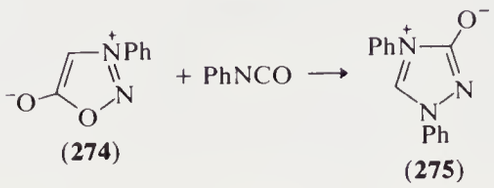
Enamines and enolate anions react with benzofuroxan to give quinoxaline di-*N*-oxides (Scheme 38) ⟨69AHC(10)1⟩. Sydnones (**274**) with phenyl isocyanate give 1,2,4-triazoles (**275**) ⟨76AHC(19)1⟩, and from (**276**) the intermediate adduct (**277**) can be isolated ⟨73JA8452⟩. This is one of the few

instances in which such primary cycloadducts have been isolated in the oxazole series of mesoionic compounds.

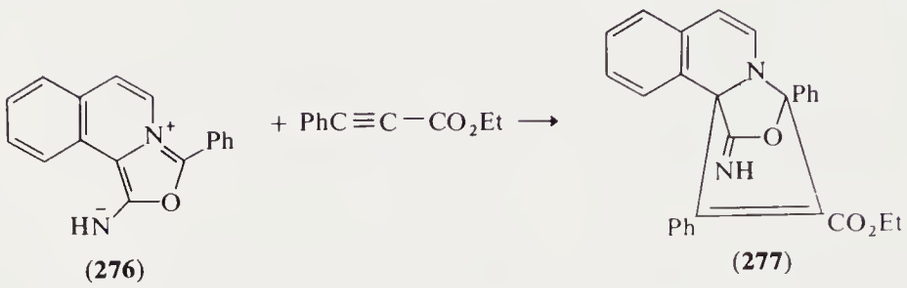


$X = NR_2, O^-$

Scheme 38



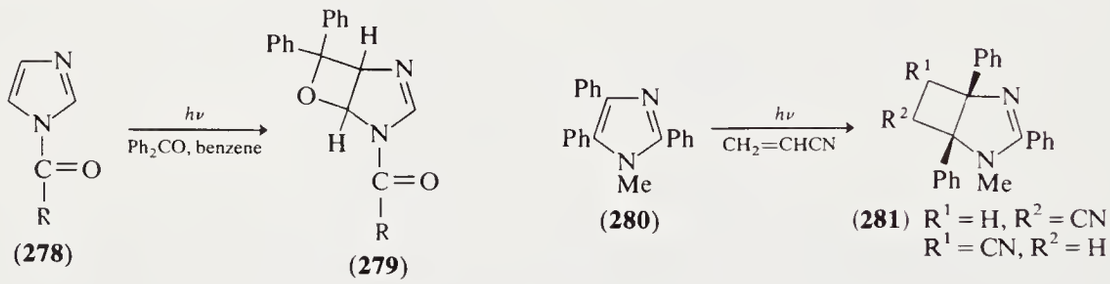
(274) **(275)**



(276) **(277)**

3.4.1.9.2 Photochemical cycloadditions

Photochemical additions to give four-membered rings are known. Thus the reactions of imidazoles across the 4,5-bond with benzophenone and acrylonitrile are illustrated by (**278**)→(**279**) and (**280**)→(**281**), respectively ⟨80AHC(27)241⟩. Oxazolin-2-one undergoes acetone-photosensitized photochemical addition to ethylene ⟨80CB1884⟩.



(278) **(279)** **(280)** **(281)** $R^1 = H, R^2 = CN$; $R^1 = CN, R^2 = H$

3.4.2 REACTIONS OF NON-AROMATIC COMPOUNDS

Discussion of these compounds is divided into isomers of aromatic compounds, and dihydro and tetrahydro derivatives. The isomers of aromatic azoles are a relatively little-studied class of compounds. Dihydro and tetrahydro derivatives with two heteroatoms are quite well studied, but such compounds become more obscure and elusive as the number of heteroatoms increases. Thus dihydrotriazoles are rare; dihydrotetrazoles and tetrahydro-triazoles and -tetrazoles are unknown unless they contain doubly bonded exocyclic substituents.

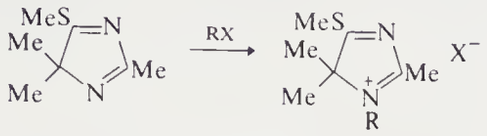
S-Oxides of sulfur-containing azoles comprise another class of non-aromatic azoles.

3.4.2.1 Isomers of Aromatic Derivatives

3.4.2.1.1 Compounds not in tautomeric equilibrium with aromatic derivatives

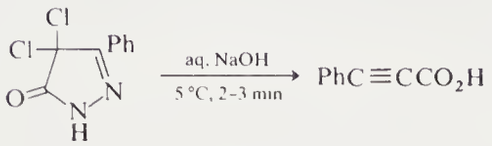
The 3*H*- and 4*H*-pyrazoles and 2*H*- and 4*H*-imidazoles ⟨83UP40200⟩ contain two double bonds in the heterocyclic ring, but in each case the conjugation does not include all the ring atoms; hence the compounds are not aromatic.

The quaternization of 5*H*-imidazoles occurs at the 1-position (Scheme 39) ⟨64AHC(3)1⟩. 4*H*-Pyrazoles are also readily monoquaternized.



Scheme 39

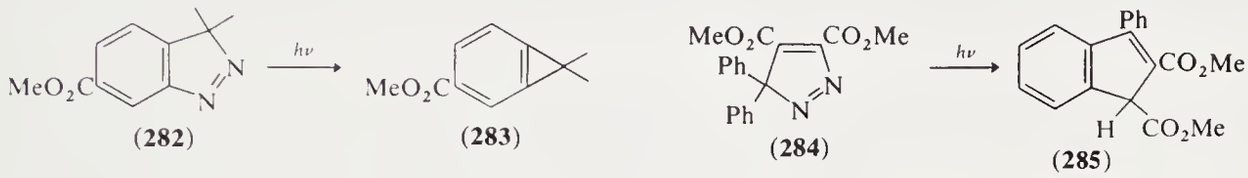
Dichloropyrazolinones with alkali give alkynoic acids (Scheme 40) ⟨58JA599⟩.



Scheme 40

Migrations of *C*-linked substituents around the ring, on to carbon or nitrogen atoms, are common amongst these compounds. This is the van Alphen–Huttel rearrangement and by it 3*H*-pyrazoles are converted into 1*H*-pyrazoles, and 2*H*-imidazoles are thermally isomerized into 1*H*-imidazoles.

3*H*-Pyrazoles are photochemically converted into cyclopropenes, and 3*H*-indazoles react similarly, *e.g.* **(282)**→**(283)** ⟨70AHC(11)1⟩. If a 3-aryl group is present, an indene can be formed, *e.g.* **(284)**→**(285)** ⟨83UP40200⟩.



(282) **(283)** **(284)** **(285)**

Addition of nucleophiles to C=N bonds is common in these compounds.

3.4.2.1.2 Compounds in tautomeric equilibria with aromatic derivatives

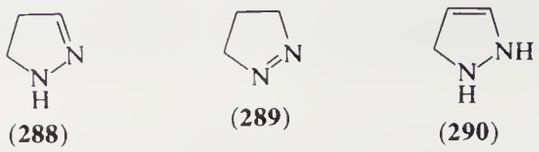
Compounds of types **(286)** and **(287)** are in tautomeric equilibria with 4- or 5-hydroxyazoles. However, the non-aromatic form is sometimes by far the more stable. Thus oxazolinone derivatives of type **(287)** have been obtained as optically active forms; they undergo racemization at measurable rates with nucleophiles ⟨77AHC(21)175⟩. Reactions of these derivatives are considered under the aromatic tautomer.

(286) **(287)**

3.4.2.2 Dihydro Compounds

3.4.2.2.1 Tautomerism

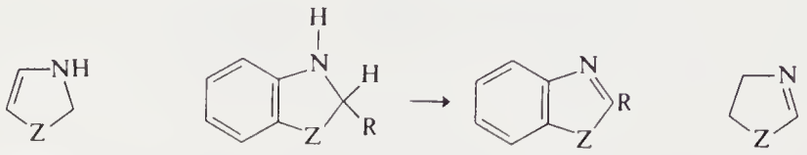
Dihydroazoles can exist in at least three forms (*cf.* Section 2.4.1.3), which in the absence of substituents are tautomeric with each other. The forms in which there is no hydrogen on at least one ring nitrogen normally predominate because imines are generally more stable than vinylamines in aliphatic chemistry. Thus for dihydropyrazoles the stability order is Δ^2 (hydrazone) **(288)** > Δ^1 (azo) **(289)** > Δ^3 (enehydrazine) **(290)**.



(288) (289) (290)

3.4.2.2.2 *Aromatization*

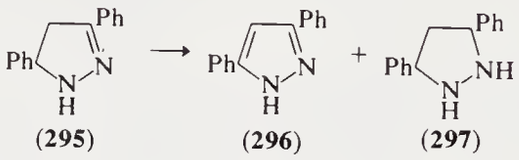
Δ^4-Imidazolines, -oxazolines and -thiazolines (**291**), and their benzo derivatives (**292**), are very easily aromatized (**292**→**293**), and syntheses which might be expected to yield such dihydro compounds often afford the corresponding aromatic products.



(291) (292) (293) (294)

Dehydrogenation of Δ^2-imidazolines (**294**; Z = NR) gives imidazoles, but requires quite high temperatures and a catalyst such as nickel or platinum. Alternatively, hydrogen acceptors such as sulfur or selenium can be used ⟨70AHC(12)103⟩.

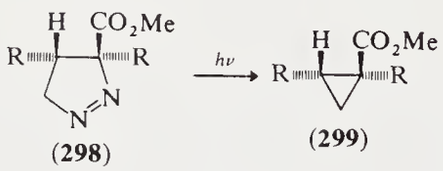
Δ^2-Pyrazolines are converted into pyrazoles by oxidation with bromine or $Pb(OAc)_4$ and they can also be dehydrogenated with sulfur. 3,5-Diphenylpyrazoline (**295**) on heating with platinum disproportionates to the pyrazole (**296**) and the pyrazolidine (**297**) ⟨66AHC(6)347⟩.



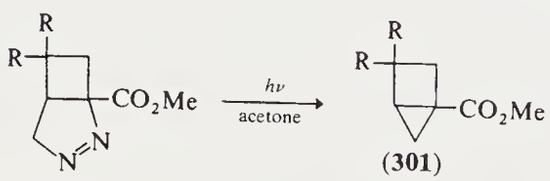
(295) (296) (297)

3.4.2.2.3 *Ring contraction*

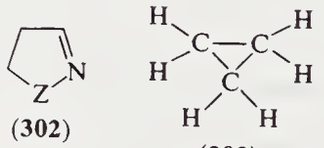
1-Pyrazolines undergo photochemically induced nitrogen elimination and ring contraction to cyclopropanes, *e.g.* (**298**)→(**299**). This is particularly useful for the preparation of strained rings, *e.g.* (**300**)→(**301**) ⟨70AHC(11)1⟩. Δ^2-Pyrazolines unsubstituted in the 1-position lose nitrogen on pyrolysis to give cyclopropanes (*e.g.* **302**; Z = NH→**303**), probably *via* Δ^1-pyrazolines.



(298) (299)

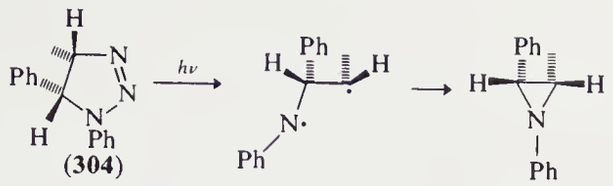


(300) (301)



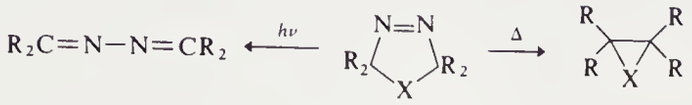
(302) (303)

Photodecomposition of Δ^2-1,2,3-triazolines gives aziridines. In cyclohexane the *cis* derivative (**304**) gives the *cis* product (**305**), whereas photolysis in benzene in the presence of benzophenone as sensitizer gives the same ratio of *cis*- and *trans*-aziridines from both triazolines and is accounted for in terms of a triplet excited state ⟨70AHC(11)1⟩. Δ^2-Tetrazolines are photolyzed to diaziridines.



(304) (305)

Fragmentation of Δ^3-1,3,5-thiadiazoline derivatives is summarized in Scheme 41.



$X = S, SO, SO_2$

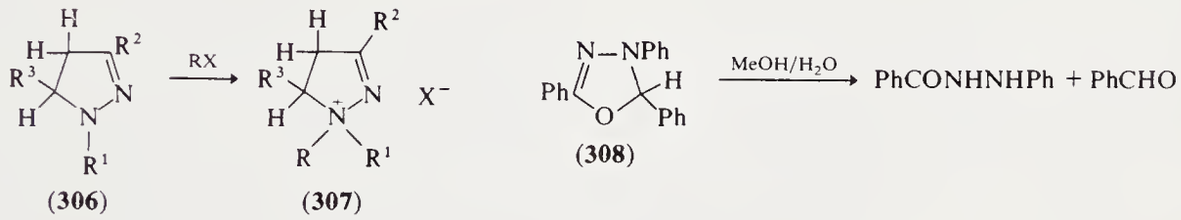
Scheme 41

3.4.2.2.4 Other reactions

Dihydro compounds show reactions which parallel those of their aliphatic analogues provided that the aromatization reactions just discussed do not interfere.

Δ^2-Imidazolines (**294**; Z = NH) are cyclic amidines and exhibit the characteristic resonance stabilization and high basicity. Δ^2-Oxazolines (**294**; Z = O) are cyclic imino ethers, and Δ^2-thiazolines (**294**; Z = S) are imino thioethers; both are consequently easily hydrolyzed by dilute acid.

Δ^2-Pyrazolines and Δ^2-isoxazolines (**302**; Z = NH, O) are cyclic hydrazones and oximes, respectively. 2-Pyrazolines are quaternized at the 2-position (**306**→**307**) ⟨64AHC(3)1⟩. 1,3,4-Oxadiazolines (*e.g.* **308**) are very easily ring-opened ⟨66AHC(7)183⟩.



(306) (307) (308)

Reduction of dihydro compounds to the tetrahydro derivatives is sometimes possible. For example, thiazolines are reduced to thiazolidines by aluminum amalgam.

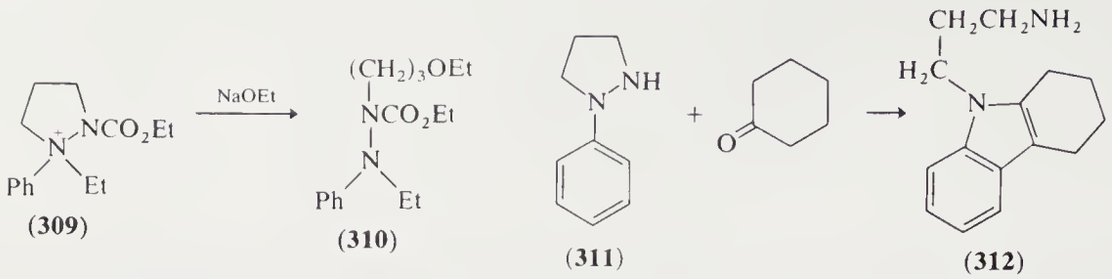
3.4.2.3 Tetrahydro Compounds

3.4.2.3.1 Aromatization

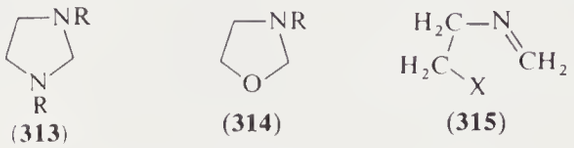
Some tetrahydro azoles can be aromatized, but this is more difficult than in the corresponding dihydro series. Thus the conversion of pyrazolidines into pyrazoles is accomplished with chloranil. Imidazolidines are aromatized with great difficulty.

3.4.2.3.2 Ring fission

Cleavage of the heterocyclic ring is usually accomplished using degradative procedures which are also applicable in the aliphatic series. Thus a nitrogen-containing ring can be opened by Hofmann exhaustive methylation (*e.g.* **309**→**310**). Pyrazolidines also undergo reactions of the Fischer indole synthesis type (**311**→**312**). The sulfur-containing ring of thiazolidines can be opened by Raney nickel desulfurization.



Compounds of types (**313**; R = H) and (**314**; R = H) are in equilibrium with open-chain forms (**315**); such tetrahydro compounds are readily hydrolyzed by dilute acid (R ≠ H).

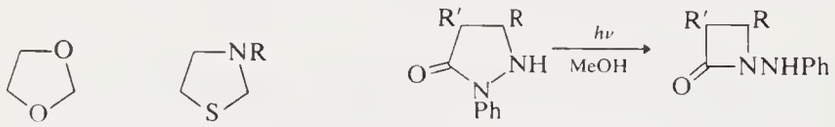


Isoxazolidines sometimes undergo retro 1,3-dipolar cycloaddition to give back alkenes and nitrones ⟨77AHC(21)207⟩.

3.4.2.3.3 Other reactions

These compounds usually show the typical reactions of their aliphatic analogues. 1,3-Dioxolanes (**316**), tetrahydroimidazoles (**313**), tetrahydrooxazoles (**314**) and tetrahydrothiazoles (**317**) are somewhat less easily ring-cleaved than their acyclic analogues (*cf.* previous section), but their properties are otherwise similar.

1-Aryl-5-pyrazolidinones (**318**) are photochemically ring-contracted to β-lactams ⟨70AHC(11)1⟩.



3.4.2.3.4 Stereochemistry

Whereas the aromatic systems are planar, fully reduced five-membered rings have non-planar envelope conformations, as is discussed in Section 2.4.4.3.

3.4.3 REACTIONS OF SUBSTITUENTS

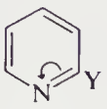
Substituents attached to carbon are considered by classes; substituents linked to ring nitrogen are considered separately because of their differing character.

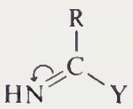
3.4.3.1 General Survey of Substituents on Carbon

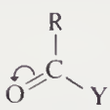
If the reactions of the same substituents on heteroaromatic azoles and on benzene rings are compared, the differences in the reactivities are a measure of the heteroatoms' influence. Such influence by the mesomeric effect is smaller when the substituent is β to a heteroatom than when it is α or γ. The influence by the inductive effect is largest when the substituent is α to a heteroatom.

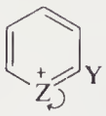
3.4.3.1.1 Substituent environment

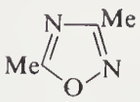
The electronic environment of an α-substituent on pyridine (**319**) approaches that of a substituent on the corresponding imino compound (**320**) and is intermediate between those of substituents on benzene and substituents attached to carbonyl groups (**321, 322**) (*cf.* discussion in Chapter 3.2). Substituents attached to certain positions in azole rings show similar properties to those of α- and γ-substituents on pyridine. However, the azoles also possess one heteroatom which behaves as an electron source and which tends to oppose the effect of other heteroatom(s).


(**319**)


(**320**)


(**321**)


(**322**)


(**323**)

Substituents cannot directly conjugate with β-pyridine-like nitrogen atoms. Azole substituents which are not α or γ to a pyridine-like nitrogen react as they would on a benzene ring. Conjugation with an α-pyridine-like nitrogen is much more effective through formal double bonds; thus the 5-methyl group in 3,5-dimethyl-1,2,4-oxadiazole (**323**) is by far the more reactive as it is so activated by both nitrogen atoms.

In azolium cations, the electron-pull of the positively charged heteroatom is strong, and substituents attached α or γ to positive poles in azolium rings show correspondingly enhanced reactivity.

Azolinones and azole *N*-oxides possess systems which can act either as an electron source or as an electron sink, depending on the requirements of the reaction.

3.4.3.1.2 The carbonyl analogy

In aliphatic compounds, reactions of functional groups are often modified very significantly by an adjacent carbonyl group. As would be expected from the discussion in the preceding section, the reactions of certain substituents α and γ to pyridine-like nitrogen atoms in azole rings are similarly influenced. Such effects on substituents can be classified into six groups.

(i) Substituents which can leave as anions are displaced by nucleophilic reagents (**324**).

(ii) α′-Hydrogen atoms are easily lost as protons (**325**) .

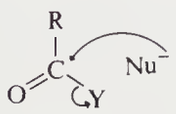
(iii) As a consequence of (ii), tautomerism is possible (**326**⇌**327**).

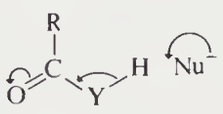
(iv) Carbon dioxide is readily lost from carboxymethyl (**328**) and carboxyl groups (**329**).

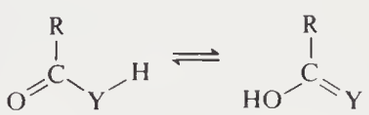
(v) These effects are transferred through a vinyl group, and nucleophilic reagents will add to vinyl and ethynyl groups (**330**) (Michael reaction).

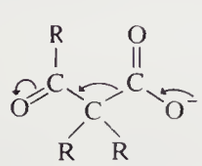
(vi) Electrons are withdrawn from aryl groups (**331**).

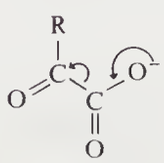
Examples of these for both carbonyl and heterocyclic compounds are listed in Table 8.

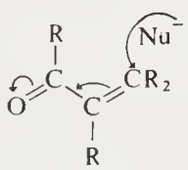

(**324**)


(**325**)


(**326**) (**327**)


(**328**)


(**329**)


(**330**)

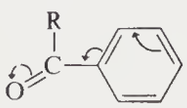
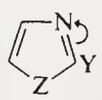

(**331**)

Table 8 Reactivity of Substituents: The Carbonyl Analogy ⟨B-68MI40200⟩

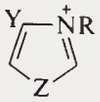
Reaction type	*Group*	*α- or γ-Groups*	*Compare with*
Nucleophilic displacement	Nitro	Are displaced readily	—
	Halogen	Are displaced	Acid chloride
	Alkoxyl, Amino	Are displaced when additionally activated	Ester, Amide
Proton loss	Hydroxyl	Are acidic	Carboxylic acid
	Amino	Are less basic	Amide
	Alkyl	Become 'active'	Ketone
Tautomerism	Hydroxyl	Exist largely in the oxo form	Carboxylic acid (two equivalent structures)
	Amino	Exist to a small extent only in the imine form	Amide
	Mercapto	Exist largely in the thione form	Thiocarboxylic acid
Decarboxylation	Carboxyl	Decarboxylate at *ca.* 200 °C	α-Keto acids
	Carboxymethyl	Decarboxylate at *ca.* 50 °C	β-Keto acids
Michael reactions	Vinyl, Ethynyl	Undergo Michael additions readily	α,β-Unsaturated ketones
	β-Hydroxyethyl	Undergo reverse Michael reaction readily (lose H_2O)	β-Hydroxy ketones
Electrophilic attack on phenyl groups	Phenyl	Undergo electrophilic substitution in the *meta* and *para* positions (*ca.* 1:1)	Phenyl ketones

3.4.3.1.3 Two heteroatoms in the 1,3-positions

The 2-position in imidazoles, thiazoles and oxazoles is electron deficient, and substituents in the 2-position (**332**) generally show the same reactivity as α- or γ-substituents on pyridines. 2-Substituents in azoliums of this type, including 1,3-dithiolyliums, are highly activated.



(**332**)

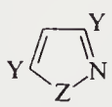


(**333**)

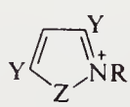
Substituents in the 4-position of these compounds are also α to a multiply bonded nitrogen atom, but because of bond fixation they are relatively little influenced by this nitrogen atom even when it is quaternized (**333**). This is similar to the situation for 3-substituents in isoquinolines, *cf.* Chapter 3.2. In general, substituents in the 4- and 5-positions of imidazoles, thiazoles and oxazoles show much the same reactivity of the same substituents on benzenoid compounds (but see Section 3.4.3.9.1).

3.4.3.1.4 Two heteroatoms in the 1,2-positions

Substituents on pyrazoles and isoxazoles, regardless of their positions, generally show reactivity closer to that of the same substituent on a benzene ring rather than to that of α- or γ-substituents on pyridine. The (electron-releasing) mesomeric effect of the 'pyrrole-type' NH group and 'furan-type' oxygen atom appears to be more important than their (electron-withdrawing) inductive effect in pyrazole and isoxazole (**334**). However, some reactions of these types are known (see *e.g.* Section 3.4.3.3.3) and halogen atoms and methyl groups in the 3- and 5-positions of pyrazoles and isoxazoles (**334**) become 'active' if the ring is quaternized (**335**).



(**334**)



(**335**)

Substituents on the isothiazole ring are a little more reactive, especially in the 5-position. In cationic rings reactivity is much higher, *e.g.* for substituents in 1,2-dithiolylium salts.

3.4.3.1.5 Three heteroatoms

In the 1,2,4-thiadiazole ring the electron density at the 5-position is markedly lower than at the 3-position, and this affects substituent reactions. 5-Halo derivatives, for example, approach the reactivity of 4-halopyrimidines. The 1,2,4-oxadiazole ring shows a similar difference between the 3- and 5-positions.

Substituents in 1,3,4-thiadiazoles are quite strongly activated, as in the 2-position of pyridine.

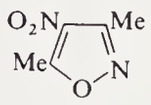
In contrast, substituents in 1,2,4-triazoles are usually rather similar in reactivity to those in benzene; although nucleophilic substitution of halogen is somewhat easier, forcing conditions are required.

3.4.3.1.6 Four heteroatoms

Alkyl groups and halogen atoms in tetrazoles are not highly activated unless the ring is quaternized.

3.4.3.1.7 The effect of one substituent on the reactivity of another

The effect of one substituent on the reactivity of another is generally similar to that observed in the corresponding polysubstituted benzenes. However, the partial bond fixation in an azole can lead to differential effects in the mutual interactions of substituents, similar to those found in naphthalene where the benzene ring fusion induces bond fixation. A good example is in the comparison of methyl group reactivity in (**336**); the 5-methyl group condenses with aldehydes easily, the 3-methyl group does not. However, quaternization at nitrogen renders the 3-methyl group reactive.



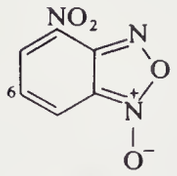
(**336**)

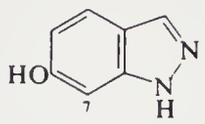
3.4.3.1.8 Reactions of substituents not directly attached to the heterocyclic ring

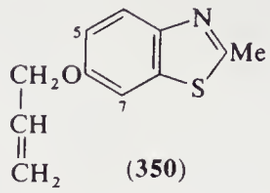
In general, substituents removed from the ring by two or more saturated carbon atoms undergo normal aliphatic reactions, and substituents attached directly to fused benzene rings or aryl groups undergo the same reactions as those on normal benzenoid rings.

3.4.3.1.9 Reactions of substituents involving ring transformations

Several classes are known. Dimroth-type rearrangements occur by ring opening and reclosure so that one ring atom changes places with an exocyclic atom. The rearrangement of 5-phenylaminothiatriazole to 1-phenyl-5-mercaptotetrazole in basic solution is reversible (Scheme 42). As the anion it is the tetrazole system which is the stable one, whereas the neutral species is the thiatriazole ⟨76AHC(20)145⟩.


(348)

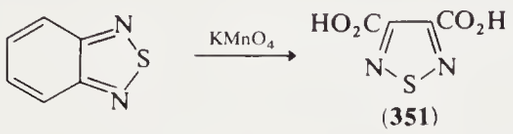

(349)

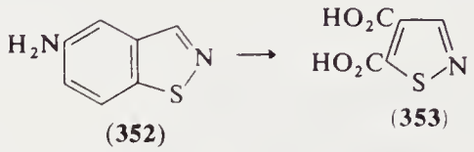

(350)

A heterocyclic ring induces partial double-bond fixation in a fused benzene ring. Hence, for example, diazo coupling occurs at the 7-position of 6-hydroxyindazole (**349**), and Claisen rearrangement of 6-allyloxy-2-methylbenzothiazole (**350**) gives the 7- and 5-allyl products in a ratio of 20:1.

3.4.3.2.2 Oxidative degradation

Vigorous oxidation (*e.g.* with $KMnO_4$) usually degrades fused benzene rings in preference to many azole rings, especially under acidic conditions. Thus benzimidazoles are oxidized by chromic acid or 30% hydrogen peroxide to imidazole-4,5-dicarboxylic acid ⟨70AHC(12)103⟩, and 2,1,3-benzothiadiazole is oxidized by ozone or potassium permanganate to the dicarboxylic acid (**351**) ⟨68AHC(9)107⟩.

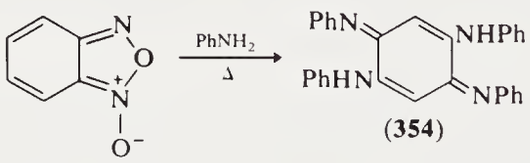

(351)


(352) (353)

As expected, oxidative degradation of a fused benzene ring is facilitated when it carries electron-donating groups and is hindered by electron-withdrawing substituents. 5-Aminobenzisothiazole (**352**) with potassium permanganate gives the carboxylic acid (**353**) ⟨59JCS3061⟩.

3.4.3.2.3 Nucleophilic attack

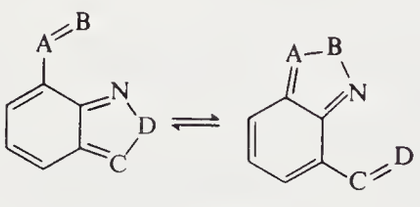
Most fused benzene rings are stable toward nucleophilic attack but exceptions are known for highly electron-deficient benzazoles. Thus aniline and benzofuroxan at 150 °C give the anil (**354**) ⟨45HCA850⟩.

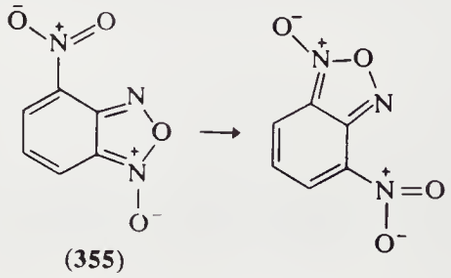

(354)

Halogen atoms on benzazole rings can be activated toward nucleophilic displacement by electron-withdrawing groups. Thus azide ion displaces chlorine from 5-chloro-4-nitro- and 4-chloro-7-nitro-benzofuroxan ⟨65JCS5958⟩.

3.4.3.2.4 Rearrangements

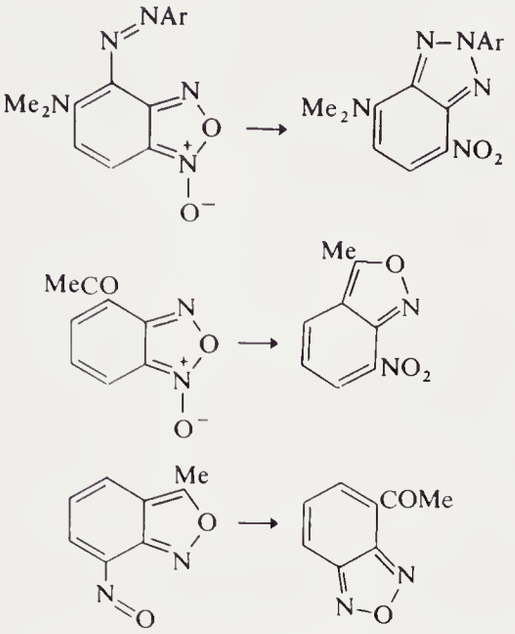
In the benzazole series, reactions of the type discussed for monocyclic derivatives in Section 3.4.3.1.9 are generalized by Scheme 45 and examples are given in Table 9 (p. 338).


Scheme 45

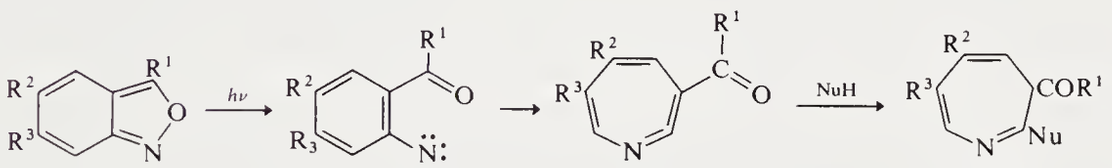

(355)

4-Nitrobenzofuroxan (**355**) undergoes a rearrangement (recognizable as an isomerization in unsymmetrically substituted derivatives) which is an example of this general rearrangement (Scheme 45) ⟨64AG(E)693⟩; see Table 10.

Table 10 Benzazole Rearrangements ⟨71JCS(C)1193⟩

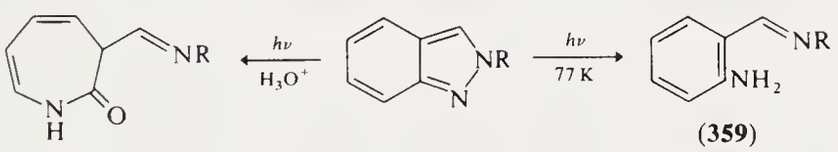
Examples of involvement of two-atom side chains


Photolysis of anthranils (**356**) in methanol or amines gives 2-methoxy- or 2-amino-3*H*-azepines (**357**) by ring expansion of intermediate nitrenes ⟨81AHC(28)231⟩. Photolysis of 2-alkylindazoles probably also goes through a nitrene intermediate, which either abstracts hydrogen from the solvent to give (**359**) ⟨81AHC(28)231⟩ or ring expands to yield (**358**).



(**356**) (**357**)

R^1 = Ph or Me; R^2, R^3 = H or Cl; NuH = MeOH, Et_2NH or $PhNH_2$



(**358**) (**359**)

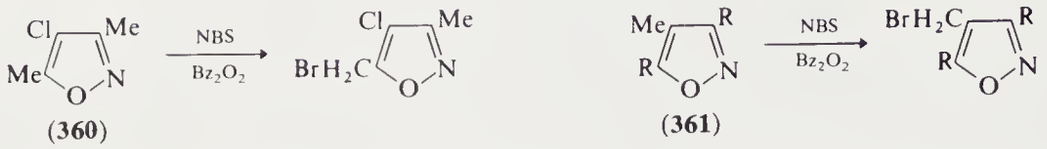
3.4.3.3 Alkyl Groups

3.4.3.3.1 Reactions similar to those of toluene

Alkyl groups attached to heterocyclic systems undergo many of the same reactions as those on benzenoid rings.

(i) Oxidation in solution ($KMnO_4$, CrO_3, *etc.*) gives the corresponding carboxylic acid or ketone; for example, alkyl groups on pyrazoles are oxidized with permanganate to carboxylic acids ⟨66AHC(6)347⟩, 3-methylisothiazoles are converted by chromium trioxide into the 3-carboxylic acids ⟨72AHC(14)1⟩, and methylthiazoles with SeO_2 give thiazolecarbaldehydes.

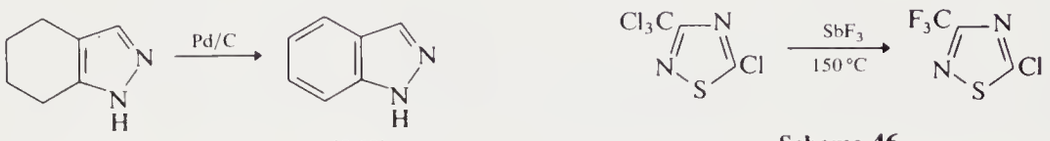
(ii) Free radical bromination with *N*-bromosuccinimide often succeeds. Thus 2,5-disubstituted 4-methyloxazoles on bromination give the 4-bromomethyl compounds ⟨74AHC(17)99⟩, and methyl groups in the 4- and 5-positions of isoxazole (**360**) and (**361**) have been brominated with NBS ⟨63AHC(2)365⟩.



(360) (361)

(iii) A fused cyclohexeno ring can be converted into a fused benzene ring, *e.g.* (**362**)→(**363**).

(iv) A trichloromethyl group has been converted by antimony trifluoride into a trifluoromethyl group in the 1,2,4-thiadiazole series (Scheme 46).



(362) (363)

Scheme 46

3.4.3.3.2 Alkylazoles: reactions involving essentially complete anion formation

In addition to the reactions described in the preceding section, alkyl groups in the 2-positions of imidazole, oxazole and thiazole rings show reactions which result from the easy loss of a proton from the carbon atoms of the alkyl group which is adjacent to the ring (see Section 3.4.3.1.2).

Additional nitrogen atoms facilitate such reactions, particularly if they are α or γ to the alkyl group, and, if α, act across a formal double bond. Thus, the 5-methyl group in 3,5-dimethyl-1,2,4-oxadiazole is much more reactive than the 3-methyl group in this compound or the methyl groups in 2,5-dimethyl-1,3,4-oxadiazole ⟨76AHC(20)65⟩.

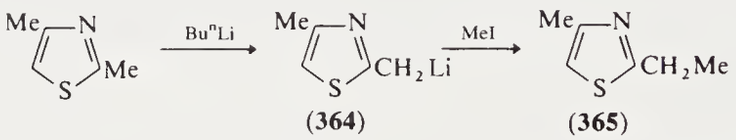
The strongest bases, such as sodamide ($NaNH_2/NH_3$, 40 °C) or organometallic compounds ($BuLi/Et_2O$, 40°C), convert, for example, 2-methyl-oxazole and -thiazole and 1,2-dimethyl-imidazole essentially completely into the corresponding anions (*e.g.* **364**), although some ring metallation also occurs (*cf.* Section 3.4.1.7.1). These anions all react readily even with mild electrophilic reagents; thus the original alkyl groups can be substituted in the following ways.

(i) Alkylation, *e.g.* MeI→CH_2Me for the formation of (**365**).

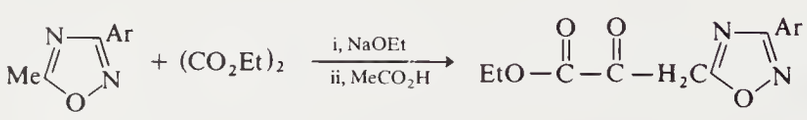
(ii) Acylation, *e.g.* the oxadiazole (**366**) undergoes Claisen condensation with ethyl oxalate ⟨76AHC(20)65⟩.

(iii) Carboxylation, *e.g.* CO_2→CH_2CO_2H in the tetrazole series.

(iv) Reactions with aldehydes, *e.g.* MeCHO → ·CH_2CH(OH)Me in the 1,2-dimethyl-imidazole series.



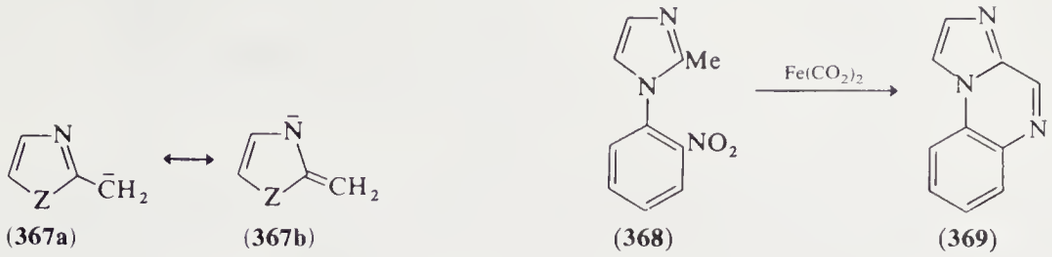
(364) (365)



(366)

3.4.3.3.3 Reactions of alkylazoles involving traces of reactive anions

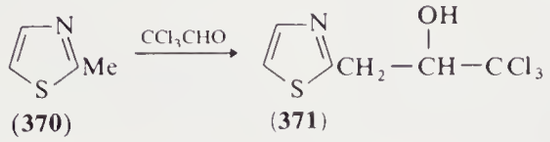
In aqueous or alcoholic solution, certain alkylazoles react with bases to give traces of anions of type (**367**). With suitable electrophilic reagents, these anions undergo reasonably rapid and essentially non-reversible reaction.



(367a) (367b) (368) (369)

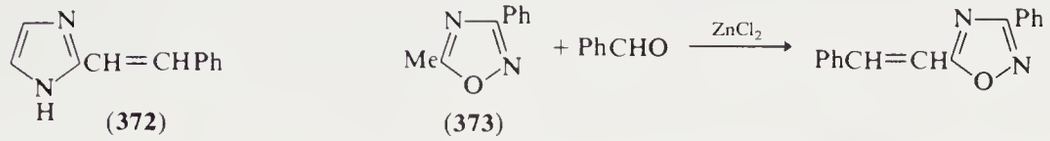
(i) A nitroso group gives an imine, as in the probable mechanism of the conversion of (**368**) into (**369**).

(ii) Aliphatic aldehydes can form monoalcohols, *e.g.* (**370**) gives (**371**) ⟨79HC(34-1)5⟩.



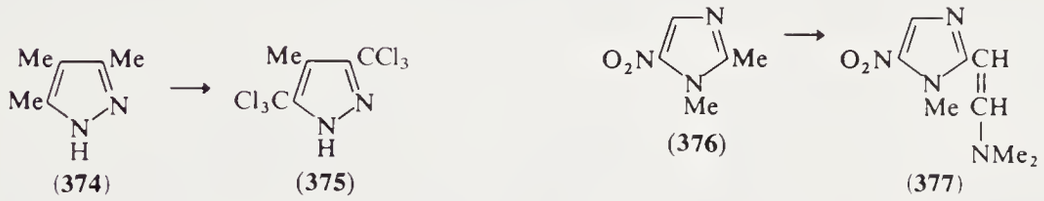
(370) (371)

(iii) Aromatic aldehydes give styryl derivatives (*e.g.* **372**) by spontaneous dehydration of the intermediate alcohol (*cf.* Section 3.4.3.1.2). 5-Methyl-3-phenyl-1,2,4-oxadiazole (**373**) reacts thus with benzaldehyde in the presence of zinc chloride ⟨76HC(20)65⟩. Benzaldehyde has not been condensed with any of the methylisothiazoles, but 3-nitrobenzaldehyde reacts with the 5-methyl derivative ⟨65AHC(4)75⟩. The 4- and 5-methylthiazoles are unreactive.



(372) (373)

(iv) Halogens displace hydrogen atoms, *e.g.* 3,4,5-trimethylpyrazole (**374**) is converted into (**375**) ⟨56LA(598)186⟩.

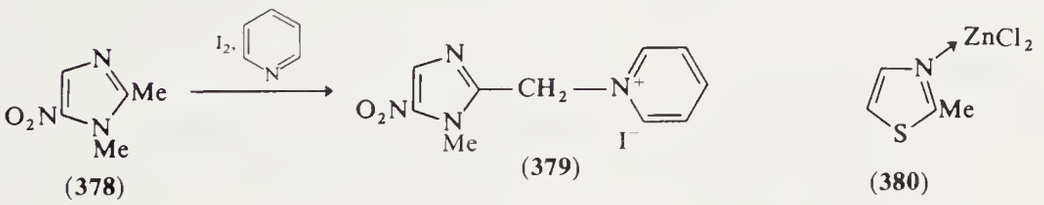


(374) (375) (376) (377)

(v) Formamide acetal gives dimethylaminovinyl derivatives, as in (**376**)→(**377**).

(vi) Pyridine and iodine give pyridylmethyl compounds, *e.g.* (**378**) yields (**379**) ⟨80AHC(27)241⟩.

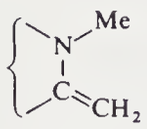
Reactions of types (i)–(vi) can be catalyzed by alkoxide or hydroxide ions, or amines. Alternatively, an acid catalyst forms a complex of type (**380**) from which proton loss is facilitated.



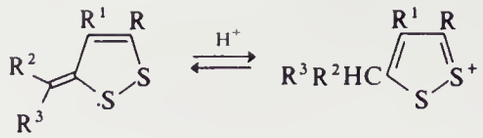
(378) (379) (380)

3.4.3.3.4 C-*Alkyl-azoliums, -dithiolyliums,* etc.

Proton loss from alkyl groups α or γ to a cationic center in an azolium ring is often easy. The resulting neutral anhydro bases or methides (*cf.* **381**) can sometimes be isolated; they react readily with electrophilic reagents to give products which can often lose another proton to give new resonance-stabilized anhydro bases. Thus the trithione methides are anhydro bases derived from 3-alkyl-1,2-dithiolylium salts (**382**⇌**383**) ⟨66AHC(7)39⟩. These methides are stabilized by electron-acceptor substituents such as CN or CO_2R ⟨66AHC(7)39⟩.

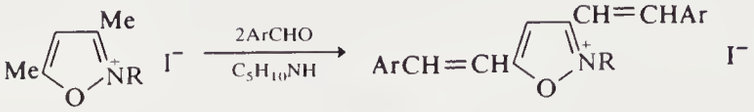


(381)



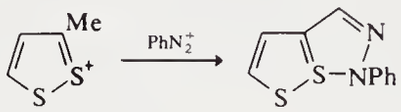
(382) (383)

Both α- and γ-alkylazolium ions, analogously to the 2- and 4-alkylazoles themselves, can also react with electrophilic reagents without initial complete deprotonation. They undergo the same types of reactions as the alkylazoles but under milder conditions, and these reactions are often catalyzed by piperidine. Thus in quaternized pyrazoles, 5-methyl groups react with benzaldehyde to give styryl derivatives and can be chlorinated ⟨66AHC(6)347⟩. The methyl groups in quaternized isoxazoles are also reactive, and here piperidine is sufficient as catalyst (Scheme 47) ⟨63AHC(2)365⟩.

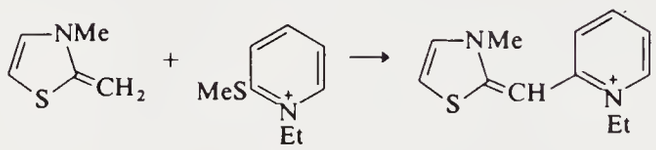


Scheme 47

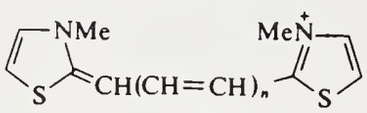
Some weak electrophilic reagents, which are usually inert toward azoles, also react with quaternized azoles. Diazonium salts yield phenylhydrazones (Scheme 48) in a reaction analogous to the Japp–Klingemann transformation of β-keto esters into phenylhydrazones; in the dithiolylium series illustrated the product has bicyclic character. Cyanine dye preparations fall under this heading (see also Section 3.4.1.6.5). Monomethine cyanines are formed by reaction with an iodo quaternary salt, *eg.* Scheme 49. Tri- and penta-methinecarbocyanines (**384**; $n = 1$ and 2, respectively) are obtained by the reaction of two molecules of a quaternary salt with one molecule of ethyl orthoformate (**384**; $n = 1$) or β-ethoxyacrolein acetal (**384**; $n = 2$), respectively.



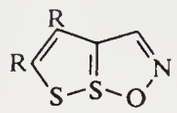
Scheme 48



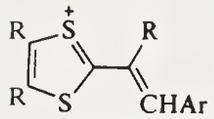
Scheme 49



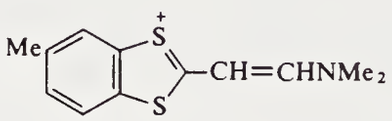
(384)



(385)



(386)

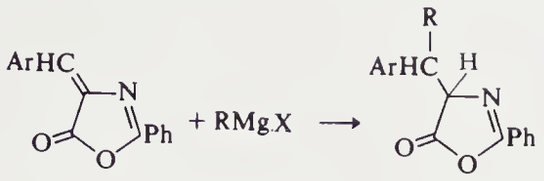


(387)

3-Methyl-1,2-dithiolyliums react with aldehydes to give styryl derivatives, with DMF to give Vilsmeier salts, and on nitrosation form the bicyclic products (**385**) ⟨80AHC(27)151⟩. 2-Alkyl groups in 1,3-dithiolylium ions also react with aromatic aldehydes to give (**386**), with DMF to give (**387**), and with other electrophiles ⟨80AHC(27)151⟩.

In general, methyl groups in the 4- and 5-positions of imidazole, oxazole and thiazole do not undergo such deprotonation-mediated reactions, even when the ring is cationic.

Compounds which can formally be considered as anhydro bases can sometimes react with nucleophiles. Thus unsaturated azlactones with Grignard reagents give saturated azlactones (Scheme 50) ⟨65AHC(4)75⟩.



Scheme 50

3.4.3.4 Other *C*-Linked Substituents

3.4.3.4.1 Aryl groups: electrophilic substitution

Electrophilic substitution occurs readily in *C*-aryl groups, often predominantly at the *para* position. Thus nitrations of phenyl-thiazoles, -oxazoles and -imidazoles (HNO_3/H_2SO_4 at 100 °C) all yield the corresponding *p*-nitrophenyl derivatives. This is to be contrasted with the situation for α-phenylpyridine, where a mixture of mainly *m*- and *p*-nitrophenyl derivatives is formed. Although in strongly acidic media a *C*-linked aryl group is generally more readily substituted than the ring, the orientation often changes when *C*-phenylazole derivatives are nitrated under less acidic conditions. Thus 3- and 5-phenylpyrazoles can give under such conditions the 4-nitro derivatives. Such orientation changes have been demonstrated to result from changes in the species undergoing reaction from the azolium ion to the neutral azole.

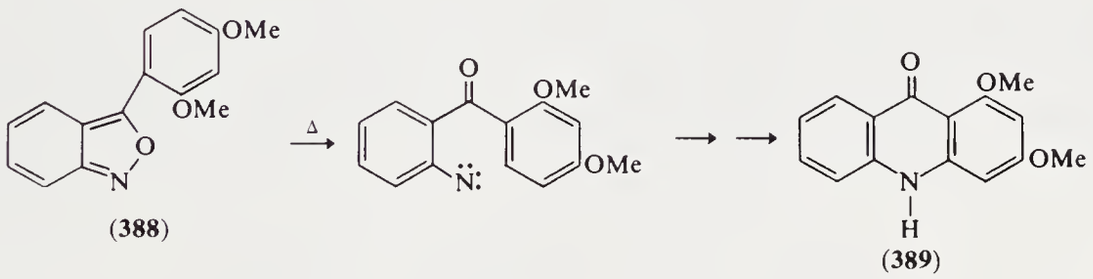
3-Phenylisothiazole is nitrated predominantly in the *meta* position of the phenyl group, whereas phenyl groups. 5-Methyl-3-phenylisoxazole is nitrated as a conjugate acid at the *meta* position but as the free base at the *para* position of the phenyl group ⟨79AHC(25)147⟩. Phenyl groups attached to oxazole rings are nitrated or sulfonated in the *para* position, with relative reactivities of the phenyl groups in the order 5 > 4 > 2 ⟨74AHC(17)99⟩.

3-Phenylisothiazole is nitrated predominantly in the *meta* position of the phenyl group, whereas 4-phenylisothiazole is nitrated *ortho* and *para* in the phenyl group ⟨72AHC(14)1⟩. Nitration of 3-phenyl-1,2,4-oxadiazole gives a mixture of *m*- and *p*-nitrophenyl derivatives ⟨63G1196⟩.

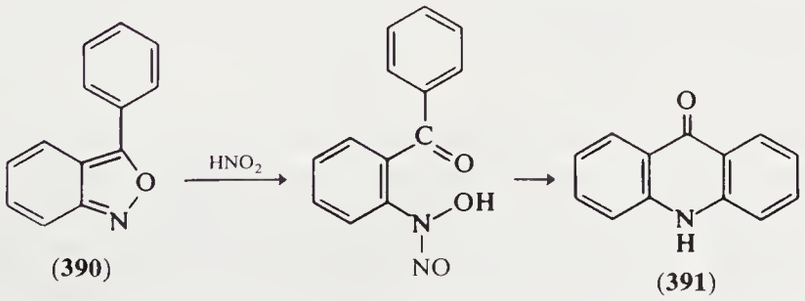
In the 1,2-dithiolylium ion system, 3- and 5-phenyl groups on nitration give mixtures of *para* and *meta* orientation, whereas nitration of a 4-phenyl group gives *para* substitution only ⟨61JA2934⟩.

3.4.3.4.2 Aryl groups: other reactions

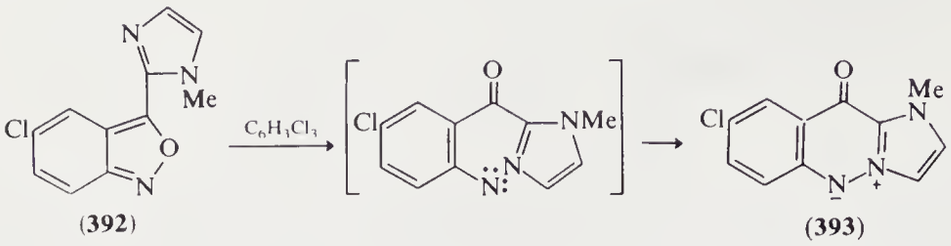
3-Arylanthranils (**388**) on thermolysis give acridones (**389**) ⟨81AHC(28)231⟩. 3-Phenylanthranils (**390**) also form acridones (**391**) on treatment with nitrous acid ⟨67AHC(8)277⟩. Related rearrangements are found with 3-heteroarylanthranils (*e.g.* **392**→**393**) ⟨81AHC(28)231⟩.



(**388**) (**389**)

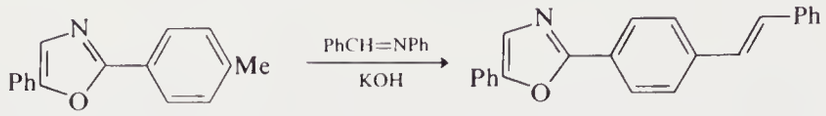


(**390**) (**391**)



(392) (393)

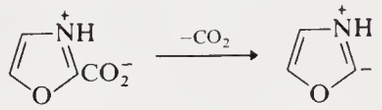
Methyl groups on *C*-linked phenyl attached to oxazoles, isoxazoles and oxadiazoles react with benzylidineaniline to give stilbene derivatives (Scheme 51) ⟨78AHC(23)171⟩.



Scheme 51

3.4.3.4.3 Carboxylic acids

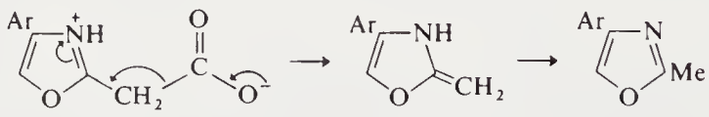
Azolecarboxylic acids can be quite strongly acidic. Thus 1,2,5-thiadiazole-3,4-dicarboxylic acid has first and second pK_a values of 1.6 and 4.1, respectively ⟨68AHC(9)107⟩. The acidic strengths of the oxazolecarboxylic acids are in the order 2 > 5 > 4, in agreement with the electron distribution within the oxazole ring ⟨74AHC(17)99⟩. Azolecarboxylic acids are amino acids and can exist partly in the zwitterionic, or betaine, form (*e.g.* **394**).



(394) (395)

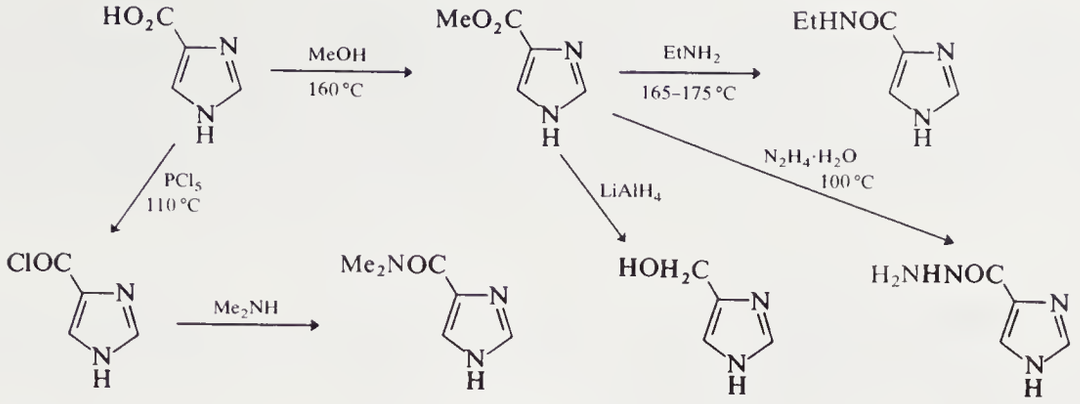
The relatively easy decarboxylation of many azolecarboxylic acids is a result of inductive stabilization of intermediate zwitterions of type (**395**) (*cf.* Section 3.4.1.7.1). Kinetic studies have shown that oxazole-2- and -5-carboxylic acids both decarboxylate through the zwitterionic tautomers ⟨71JA7045⟩. Thiazole-2-carboxylic acids, and to a lesser extent -5-carboxylic acids, decarboxylate readily; thiazole-4-carboxylic acids are relatively stable, Isothiazole-5-carboxylic acids decarboxylate readily, the 3-isomers less so while the 4-isomers require high temperatures. The 1,2,4-, 1,2,5- and 1,3,4-thiadiazolecarboxylic acids are also easily decarboxylated; their stability is increased by electron-donating substituents ⟨68AHC(9)165⟩. Most 1,2,3-triazole-carboxylic acids lose carbon dioxide when heated above their melting points ⟨74AHC(16)33⟩.

Azoleacetic acids with a carboxymethyl group also decarboxylate readily, *e.g.* all three thiazole isomers, by a mechanism similar to that for the decarboxylation of β-keto acids; *cf.* Section 3.4.3.1.2. The mechanism has been investigated in the oxazole case, (**396**)→(**397**)→(**398**) ⟨72JCS(P2)1077⟩.

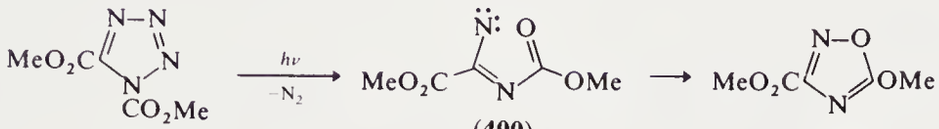


(396) (397) (398)

In most other reactions the azolecarboxylic acids and their derivatives behave as expected (*cf.* Scheme 52) ⟨37CB2309⟩, although some acid chlorides can be obtained only as hydrochlorides. Thus imidazolecarboxylic acids show the normal reactions: they can be converted into hydrazides, acid halides, amides and esters, and reduced by lithium aluminum hydride to alcohols ⟨70AHC(12)103⟩. Again, thiazole- and isothiazole-carboxylic acid derivatives show the normal range of reactions.



Scheme 52

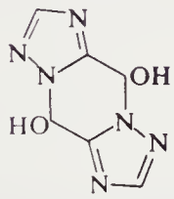


(**399**) (**400**) (**401**)

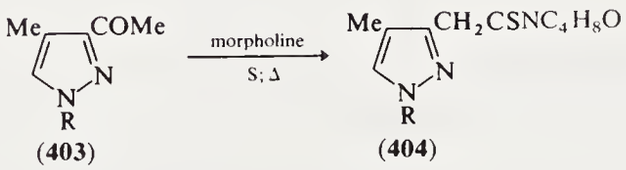
However, in some cases carboxylic acid-derived groups can participate in ring fission–reclosure reactions. Thus photolysis of 1,5-disubstituted tetrazole (**399**) gives nitrogen and appears to involve the nitrene intermediate (**400**), which reacts further to give (**401**) ⟨77AHC(21)323⟩.

3.4.3.4.4 Aldehydes and ketones

In general, the properties of these compounds and those of their benzenoid analogues are similar. Thus isothiazole aldehydes and ketones behave normally and form the usual derivatives ⟨72AHC(14)1⟩. Imidazole-2-carbaldehyde exists as a hydrate in aqueous solution. 4-Acetyloxazoles are oxidized to the corresponding acids with sodium hypobromite ⟨74AHC(17)99⟩. Thiazole aldehydes undergo the benzoin and Cannizzaro reactions. However, compounds with aldehyde groups α to an NH group sometimes form dimers, *e.g.* as in the 1,2,4-triazole series (**402**) ⟨70TL943⟩.



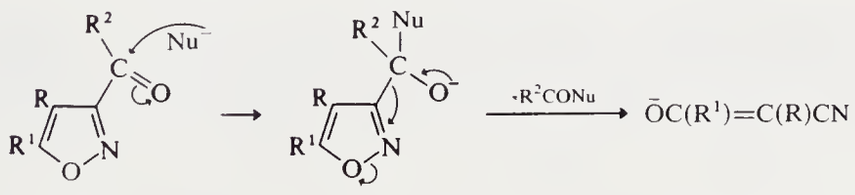
(**402**)



(**403**) (**404**)

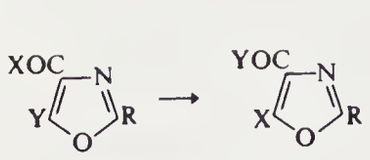
The Willgerodt reaction can proceed normally. Thus the 3-acetylpyrazole (**403**) is converted into the morpholide (**404**) ⟨57JCS2356⟩.

Deacylations are known. *C*-Acyl groups in 1,3,4-thiadiazoles are cleaved by sodium ethoxide in ethanol ⟨68AHC(9)165⟩. Imidazole-2-carbaldehyde behaves similarly, yielding imidazole and ethyl formate; this reaction involves an ylide intermediate. 3-Acylisoxazoles (**405**) are attacked by nucleophiles in a reaction which involves ring opening ⟨79AHC(25)147⟩.

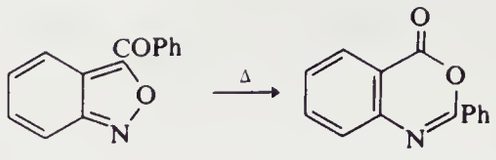


(**405**)

Sometimes ring opening and reclosure can occur with participation of a *C*-acyl group. Thus oxazole derivatives of type (**406**; X = H, Cl or NH_2; Y = OH or OEt) rearrange on heating to 255 °C by ring opening and recyclization ⟨74AHC(17)99⟩. 3-Acylanthranils (**407**) rearrange to benzoxazinones (**408**) on heating ⟨67AHC(8)277⟩.



(406) R = alkyl or aryl



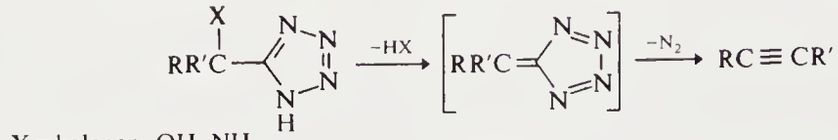
(407) (408)

3.4.3.4.5 *Vinyl and ethynyl groups*

Such groups α to a pyridine-like nitrogen atom are expected to undergo Michael additions. Examples are known in the imidazole series.

3.4.3.4.6 *Ring fission*

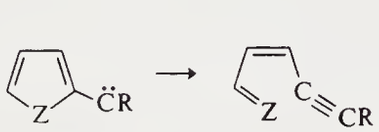
Certain α-substituted alkyltetrazoles on pyrolysis yield nitrogen and an alkyne by the mechanism shown in Scheme 53 ⟨77AHC(21)323⟩.



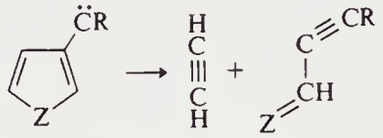
X = halogen, OH, NH_2

Scheme 53

When an azole carbene is formed, spontaneous ring fission can occur. The prototypes for these reactions are shown: (**409**)→(**410**), (**411**)→(**412**); *cf.* corresponding nitrene reactions (Section 3.4.3.6.2).



(409) (410)

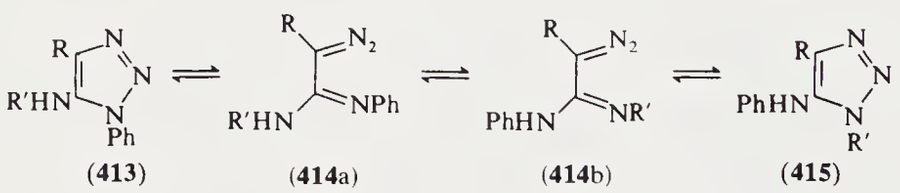


(411) (412)

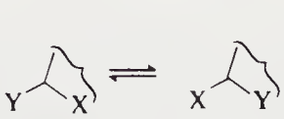
3.4.3.5 Aminoazoles

3.4.3.5.1 *Dimroth rearrangement*

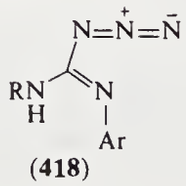
The thermal acid- or base-catalyzed interconversion of 5-amino-1-phenyltriazoles (**413**) and 5-anilinotriazoles (**415**) was discovered by Dimroth. It is an example of a general class of heterocyclic rearrangements (**416**⇌**417**) now known by the name Dimroth rearrangements ⟨74AHC(16)33⟩. The original Dimroth rearrangement probably involves a tautomeric diazoimine intermediate (**414**) ⟨74AHC(16)33⟩. Electron-attracting and large groups tend to favor the tautomer in which they are on the exocyclic nitrogen. Alkyl groups tend to prefer to reside on the cyclic nitrogen ⟨74AHC(16)33⟩. 5-Aminotetrazoles similarly rearrange *via* azidoamidines (**418**).



(413) (414a) (414b) (415)

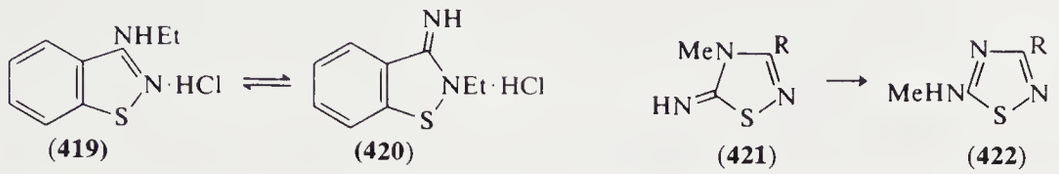


(416) (417)



(418)

There are many related examples which are now known as the general Dimroth rearrangement. For example, 3-ethylamino-1,2-benzisothiazole (**419**) is in equilibrium in aqueous solution with the 2-ethyl-3-imino isomer (**420**) ⟨72AHC(14)43⟩. Dimroth rearrangements are known in the 1,2,4-thiadiazole series (**421**→**422**), and in the 1,3,4-thiadiazole series as products of reactions of halo-1,3,4-thiadiazoles; see Section 3.4.3.9.1 ⟨68AHC(9)165⟩. For a similar example in the 1,2,3,4-thiatriazole series, see Section 3.4.3.1.9.



(**419**) (**420**) (**421**) (**422**)

2-Amino-1,3,4-oxadiazoles (**423**) ring-open and the products immediately recyclize to triazolinones (**424**) ⟨66AHC(7)183⟩.

(**423**) (**424**)

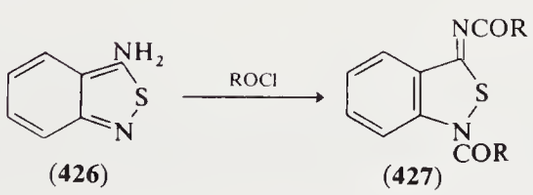
3.4.3.5.2 Reactions with electrophiles (except nitrous acid)

In aminoazoles with the amino group α or γ to C=N, canonical forms of type (**425b**) increase the reactivity of the pyridine-like nitrogen atom toward electrophilic reagents, but decrease that of the amino group. Even when the amino group is β to C=N there is still a small electron flow in the same sense. Consequently, protons, alkylating agents and metal ions usually react with aminoazoles at the annular nitrogen atom (*cf.* Section 3.4.1.3). There are exceptions to this generalization, *e.g.* 4-aminoisothiazole is methylated to the 4-trimethylammonioisothiazole and both 3- and 4-dimethylaminopyrazoles are alkylated at the NMe_2 group.

(**425a**) (**425b**)

Other electrophilic reagents form products of reaction at the amino group. This occurs when initial attack at the pyridine-like nitrogen atom forms an unstable product which either dissociates to regenerate the reactants or undergoes rearrangement inter- or intra-molecularly. In reactions of this type, carboxylic and sulfonic acid chlorides and anhydrides give acylamino- and sulfonamidoazoles, respectively. Thus 3-, 4- and 5-aminothiazoles form acetyl derivatives, sulfonamides and ureas. The 3- and 5-amino-1,2,4-thiadiazoles ⟨65AHC(5)119⟩ can be acylated and sulfonylated; 3-amino-1,2,5- ⟨68AHC(9)107⟩ and 2-amino-1,3,4-thiadiazoles ⟨68AHC(9)165⟩ also behave normally on acylation.

3-Amino-2,1-benzisothiazole (**426**) is acylated both at the cyclic and exocyclic nitrogen atoms to give (**427**) ⟨71AJC2405⟩. 5-Aminotetrazoles with nitric acid give nitramines. Sulfonation of the 5-aminopyrazole (**428**) gives first the expected product, (**429**), then a disulfonyl derivative (**430**), which rearranges on heating to the more stable (**431**). Aminothiazoles react with aldehydes to give Schiff bases.

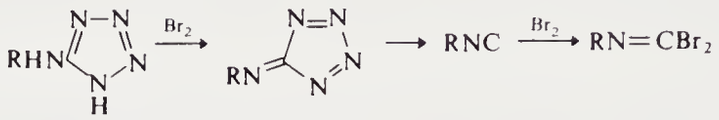


(**426**) (**427**)

(428) (429) (430) (431)

In still other cases, the product of reaction of an electrophile with an aminoazole is from electrophilic attack at a ring carbon. This is electrophilic substitution and is the general result of nitration and halogenation (see Section 3.4.1.4). In such cases, reactions at both cyclic nitrogen and at an amino group are reversible.

In a rather different reaction, aminotetrazoles treated with bromine lose nitrogen and give isocyanide dibromides ⟨77AHC(21)323⟩; probably the mechanism is as shown in Scheme 54.



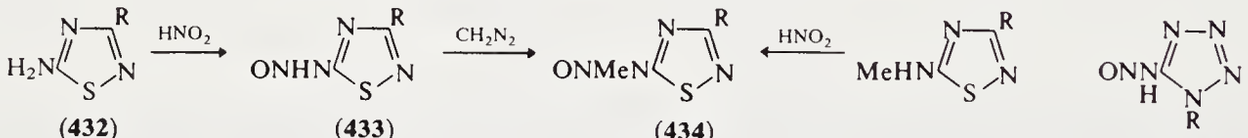
Scheme 54

3.4.3.5.3 Reaction with nitrous acid: diazotization

Primary amino groups attached to azole rings react normally with nitrous acid to give diazonium compounds *via* primary nitroso compounds. However, the azole series shows two special characteristics: the primary nitroso compounds can be stable enough to be isolated, and diazo anhydrides are formed easily from azoles containing ring NH groups.

(i) Primary nitroso compounds

Attempted diazotization in dilute acid sometimes yields primary nitroso compounds. Reactions of 3- and 5-amino-1,2,4-thiadiazoles with sodium nitrite and acid give primary nitrosamines (*e.g.* **432**→**433**) ⟨65AHC(5)119⟩ which can be related to the secondary nitrosamines (**434**) prepared in the normal way. 1-Substituted 5-aminotetrazoles with nitrous acid give stable primary nitrosamines (**435**). Primary nitrosamines have been isolated in the imidazole series.

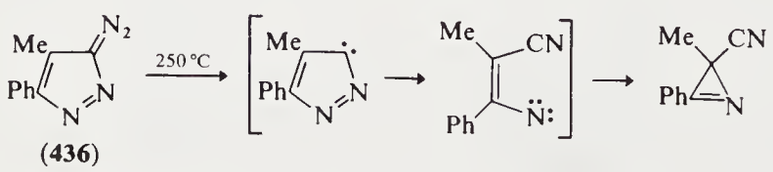


(432) (433) (434) (435)

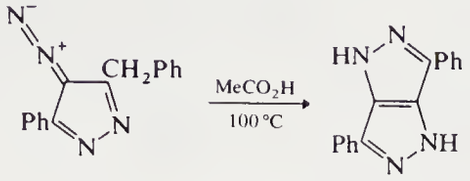
(ii) Diazo anhydrides

Diazotization of aminoazoles with free cyclic NH groups can give diazo anhydrides which show many of the normal reactions of diazoniums ⟨67AHC(8)1⟩. In the pyrazole series these diazo anhydrides are particularly stable.

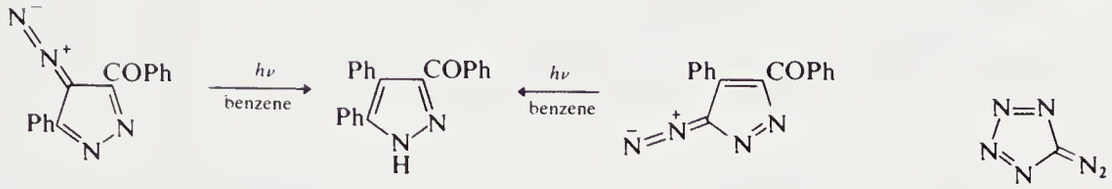
3-Diazopyrazole (**436**) undergoes gas-phase thermal extrusion to form an azirine, probably by the mechanism shown ⟨81AHC(28)231⟩; 4-diazopyrazoles show normal diazonium-type reactions (Schemes 55 and 56) ⟨67AHC(8)1⟩. Analogous diazoimidazoles and diazopurines are known ⟨67AHC(8)1⟩.



(436)



Scheme 55



Scheme 56

(437)

Diazotetrazole (**437**) has been prepared; on pyrolysis it yields carbon atoms and nitrogen ⟨79JA1303⟩.

(iii) Diazonium salts

Pyridine-2- and -4-diazonium ions are far less stable than benzenediazonium ions. Azolediazonium salts generally show intermediate stability; provided diazotization is carried out in concentrated acid, many of the usual diazonium reactions succeed. Indeed, azolediazonium salts are often very reactive in coupling reactions.

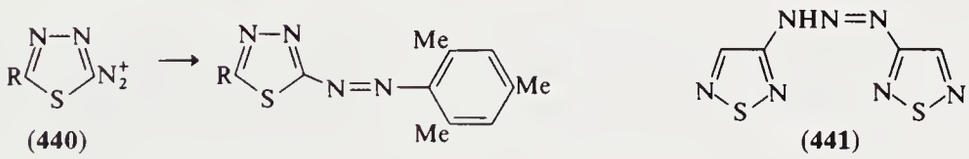
2-Nitroimidazoles and 2-azidoimidazoles are available *via* the diazonium fluoroborates, and photolytic decomposition of the fluoroborates gives 2-fluoroimidazoles ⟨80AHC(27)241⟩.

3-Amino-2,1-benzisothiazole is readily diazotized to (**438**), which gives coupling products and the cyanide (**439**) ⟨72AHC(14)43⟩. Diazonium salts from 3-, 4- and 5-aminothiazoles undergo Sandmeyer reactions (to give haloisothiazoles), reductive deaminations and Gomberg–Hey reactions ⟨72AHC(14)1⟩. 5-Aminooxazoles can be satisfactorily diazotized, but the 2-amino compounds cannot ⟨74AHC(17)99⟩.

(438) **(439)**

The 4- and 5-amino-1,2,3-triazoles are diazotizable, *e.g.* the diazonium salt from 4-aminotriazole-5-carboxamide with potassium iodide gives the 4-iodo derivative, and that from 4-amino-1,5-diphenyltriazole gives 1,5-diphenyltriazole in ethanol ⟨74AHC(16)33⟩.

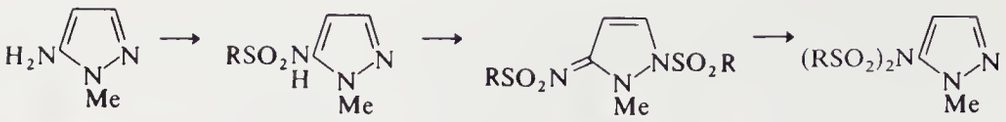
In strong acid the 1,2,4-thiadiazole-3- and -5-diazonium salts have been prepared; the 5-derivatives are very reactive in coupling reactions and undergo Sandmeyer reactions. Diazonium salts from 3-amino-1,2,4-thiadiazoles are less reactive with coupling reagents ⟨65AHC(5)119⟩. Amino-1,3,4-thiadiazoles undergo diazotization smoothly provided the solution is sufficiently acidic. The diazonium salts (**440**) show remarkably strong coupling activity and will even couple with mesitylene ⟨68AHC(9)165⟩. 3-Amino-1,2,5-thiadiazole on attempted diazotization forms only the diazoamino compound (**441**) ⟨68AHC(9)107⟩



(440) **(441)**

3.4.3.5.4 Deprotonation of aminoazoles

Canonical forms of type (**442b**) facilitate proton loss from the amino groups; the anions formed react easily with electrophilic reagents, usually preferentially at the exocyclic nitrogen atom (*e.g.* **443**→**444**) ⟨79HC(34-2)9⟩.



(428) (429) (430) (431)

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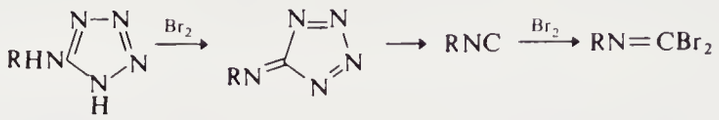

Scheme 54

3.4.3.5.3 Reaction with nitrous acid: diazotization

Primary amino groups attached to azole rings react normally with nitrous acid to give diazonium compounds *via* primary nitroso compounds. However, the azole series shows two special characteristics: the primary nitroso compounds can be stable enough to be isolated, and diazo anhydrides are formed easily from azoles containing ring NH groups.

(i) Primary nitroso compounds

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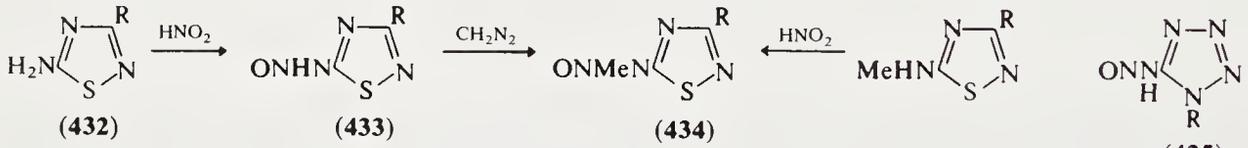

(432) (433) (434) (435)

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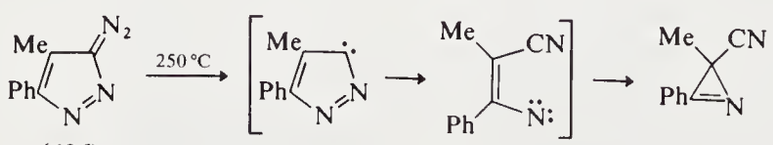
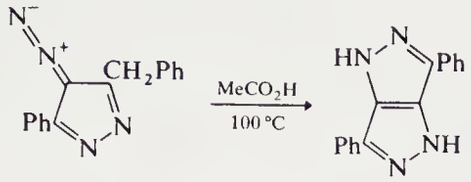
Diazotization of aminoazoles with free cyclic NH groups can give diazo anhydrides which show many of the normal reactions of diazoniums ⟨67AHC(8)1⟩. In the pyrazole series these diazo anhydrides are particularly stable.

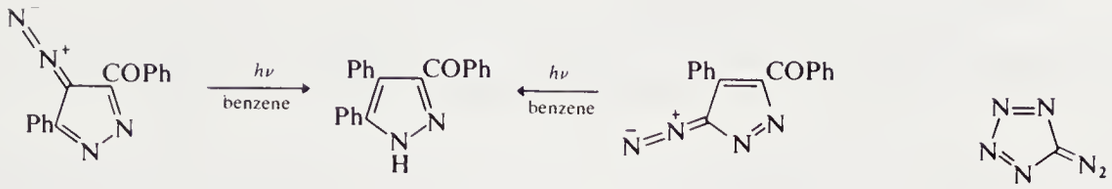
3-Diazopyrazole (**436**) undergoes gas-phase thermal extrusion to form an azirine, probably by the mechanism shown ⟨81AHC(28)231⟩; 4-diazopyrazoles show normal diazonium-type reactions (Schemes 55 and 56) ⟨67AHC(8)1⟩. Analogous diazoimidazoles and diazopurines are known ⟨67AHC(8)1⟩.



(436)



Scheme 55



Scheme 56

(437)

Diazotetrazole (**437**) has been prepared; on pyrolysis it yields carbon atoms and nitrogen ⟨79JA1303⟩.

(iii) Diazonium salts

Pyridine-2- and -4-diazonium ions are far less stable than benzenediazonium ions. Azolediazonium salts generally show intermediate stability; provided diazotization is carried out in concentrated acid, many of the usual diazonium reactions succeed. Indeed, azolediazonium salts are often very reactive in coupling reactions.

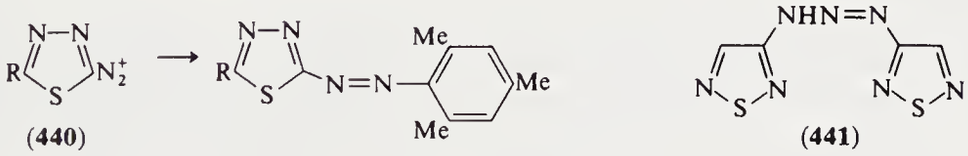
2-Nitroimidazoles and 2-azidoimidazoles are available *via* the diazonium fluoroborates, and photolytic decomposition of the fluoroborates gives 2-fluoroimidazoles ⟨80AHC(27)241⟩.

3-Amino-2,1-benzisothiazole is readily diazotized to (**438**), which gives coupling products and the cyanide (**439**) ⟨72AHC(14)43⟩. Diazonium salts from 3-, 4- and 5-aminothiazoles undergo Sandmeyer reactions (to give haloisothiazoles), reductive deaminations and Gomberg–Hey reactions ⟨72AHC(14)1⟩. 5-Aminooxazoles can be satisfactorily diazotized, but the 2-amino compounds cannot ⟨74AHC(17)99⟩.

(438) **(439)**

The 4- and 5-amino-1,2,3-triazoles are diazotizable, *e.g.* the diazonium salt from 4-aminotriazole-5-carboxamide with potassium iodide gives the 4-iodo derivative, and that from 4-amino-1,5-diphenyltriazole gives 1,5-diphenyltriazole in ethanol ⟨74AHC(16)33⟩.

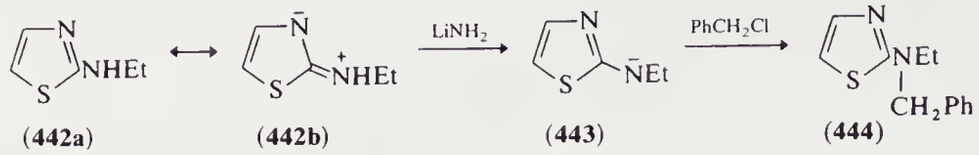
In strong acid the 1,2,4-thiadiazole-3- and -5-diazonium salts have been prepared; the 5-derivatives are very reactive in coupling reactions and undergo Sandmeyer reactions. Diazonium salts from 3-amino-1,2,4-thiadiazoles are less reactive with coupling reagents ⟨65AHC(5)119⟩. Amino-1,3,4-thiadiazoles undergo diazotization smoothly provided the solution is sufficiently acidic. The diazonium salts (**440**) show remarkably strong coupling activity and will even couple with mesitylene ⟨68AHC(9)165⟩. 3-Amino-1,2,5-thiadiazole on attempted diazotization forms only the diazoamino compound (**441**) ⟨68AHC(9)107⟩



(440) **(441)**

3.4.3.5.4 Deprotonation of aminoazoles

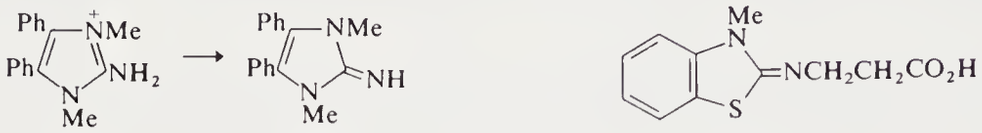
Canonical forms of type (**442b**) facilitate proton loss from the amino groups; the anions formed react easily with electrophilic reagents, usually preferentially at the exocyclic nitrogen atom (*e.g.* **443**→**444**) ⟨79HC(34-2)9⟩.



(442a) (442b) (443) (444)

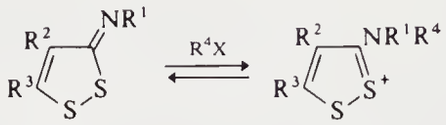
3.4.3.5.5 *Aminoazolium ions/neutral imines*

Amino groups on azolium rings can lose a proton to form strongly basic azolinimines, *e.g.* (**445**) yields (**446**). 2-Iminobenzothiazoline with acrylic acid yields (**447**).



(445) (446) (447)

In the 1,2-dithiole series such imines are readily isolated; they can be alkylated or protonated, *e.g.* (**448**)⇌(**449**) ⟨66AHC(7)39⟩.

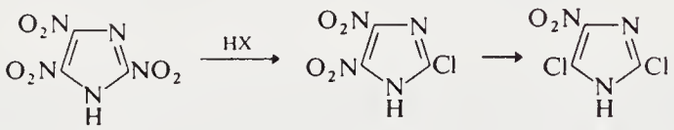


(448) (449)

3.4.3.6 Other *N*-Linked Substituents

3.4.3.6.1 *Nitro groups*

Nitro groups on azole rings are often smoothly displaced by nucleophiles even more readily than are halogen atoms in the corresponding position. Thus 2,4,5-trinitroimidazole (**450**) is converted by HCl successively into (**451**) and (**452**) ⟨80AHC(27)241⟩.

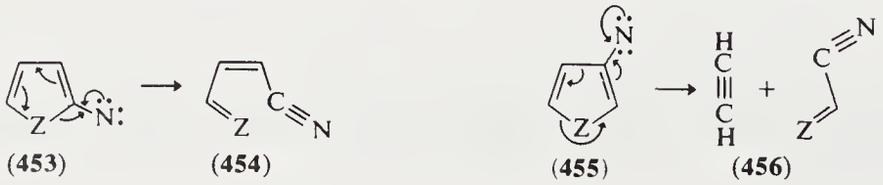


(450) (451) (452)

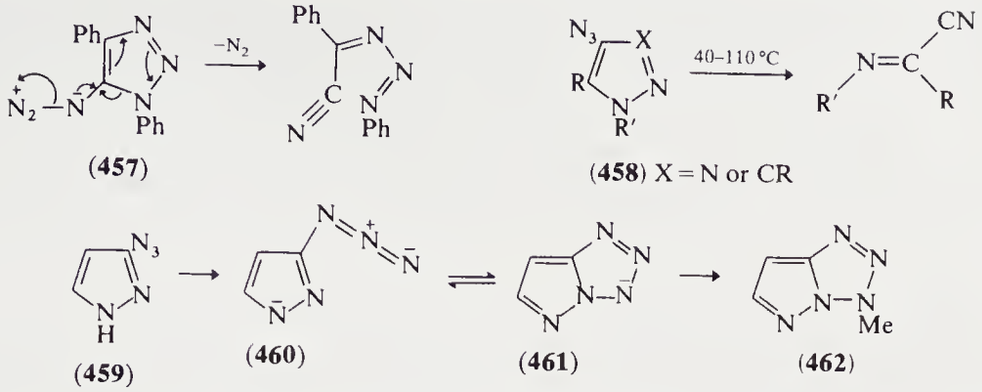
Nitro groups are easily reduced, catalytically or chemically, to give amino compounds, *e.g.* 4-nitroisothiazoles give the corresponding 4-amino derivatives ⟨72AHC(14)1⟩. In the pyrazole series, intermediate nitroso compounds can be isolated. Nitrosoimidazoles are also relatively stable.

3.4.3.6.2 *Azidoazoles*

The most important chemistry of azidoazoles is the fragmentation of derived nitrenes of which the prototypes are (**453**)→(**454**) and (**455**)→(**456**). Thus 5-azido-1,4-diphenyltriazole (**457**) evolves nitrogen at 50 °C ⟨70JOC2215⟩. 4-Azido-pyrazoles and -1,2,3-triazoles (**458**) undergo fragmentation with formation of unsaturated nitriles ⟨81AHC(28)231⟩; *cf.* corresponding carbene reactions (Section 3.4.3.4.6).



(453) (454) (455) (456)



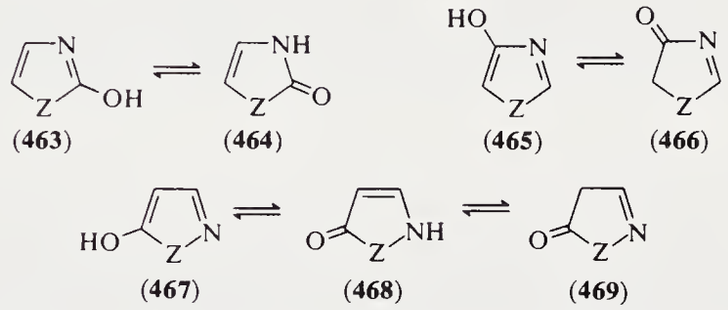
(457) (458) X = N or CR (459) (460) (461) (462)

3-Azidopyrazoles exist as such (**459**), but their anions (**460**) are in equilibrium with tetrazole anions (**461**) which can be trapped as (**462**).

3.4.3.7 *O*-Linked Substituents

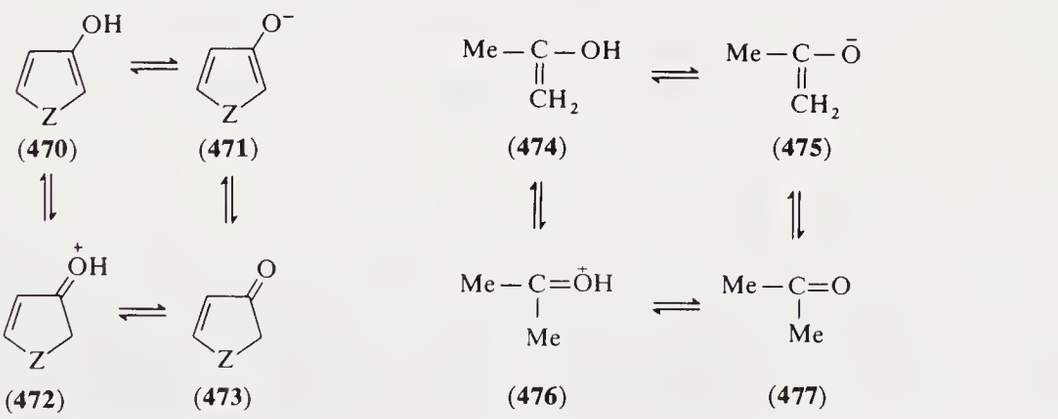
3.4.3.7.1 Tautomeric forms: interconversion and modes of reaction

As discussed in Section 2.4.5.2, hydroxy derivatives of azoles (*e.g.* **463**, **465**, **467**) are tautomeric with either or both of (i) aromatic carbonyl forms (*e.g.* **464**, **468**) (as in pyridones), and (ii) alternative non-aromatic carbonyl forms (*e.g.* **466**, **469**). In the hydroxy 'enolic' form (*e.g.* **463**, **465**, **467**) the reactivity of these compounds toward electrophilic reagents is greater than that of the parent heterocycles; these are analogues of phenol.

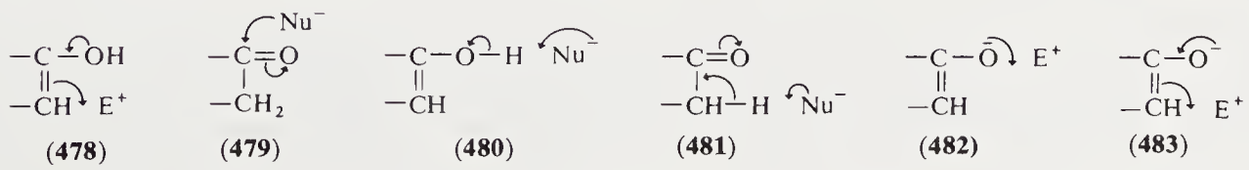


(463) (464) (465) (466) (467) (468) (469)

Interconversion of the hydroxy and carbonyl forms of these heterocycles proceeds through an anion (as **471**) or a cation (as **472**), just as the enol (**474**) and keto forms (**477**) of acetone are interconverted through the ions (**475**) or (**476**). Reactions of the various species derived from the heterocyclic compounds are analogous to those of the corresponding species from acetone: hydroxy forms react with electrophilic reagents (**478**) and carbonyl forms with nucleophilic reagents (**479**). In addition, either form can lose a proton (**480**, **481**) to give an anion which reacts very readily with electrophilic reagents on either oxygen (**482**) or carbon (**483**).



(470) (471) (472) (473) (474) (475) (476) (477)

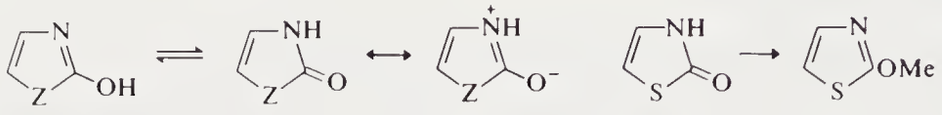


(478) (479) (480) (481) (482) (483)

The completely conjugated carbonyl forms are usually quite stable and highly aromatic in that after reaction they revert to type (Section 3.4.1.1.4). An overall treatment of their reactivity is given in Section 3.4.1.1.4. Electrophilic attack on the oxygen atom of the carbonyl groups, and nucleophilic attack at the carbonyl carbon atom, in reactions which lead to substitution rather than ring opening are discussed in this section. Electrophilic attack at ring carbon (Section 3.4.1.4) and ring nitrogen (Section 3.4.1.3) and nucleophilic attack at ring carbon (Section 3.4.1.6) (other than C=O replacement) are discussed in the sections indicated.

3.4.3.7.2 2-Hydroxy, heteroatoms-1,3

2-Hydroxy-imidazoles, -oxazoles and -thiazoles (**484**; Z = NR, O, S) can isomerize to 2-azolinones (**485a**). These compounds all exist predominantly in the azolinone form and show many reactions similar to those of the pyridones. They are mesomeric with zwitterionic and carbonyl canonical forms (*e.g.* **485a**↔**485b**; Z = NR, O, S).



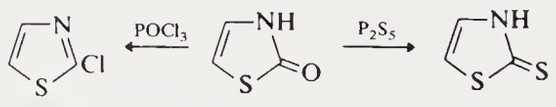
(**484**) (**485**a) (**485**b) (**486**) (**487**)

(i) Electrophilic attack on oxygen

2-Azolinones are protonated on oxygen in strongly acidic media. *O*-Alkylation of 2-azolinones can be effected with diazomethane; thiazolinone (**486**) forms (**487**). Frequently *O*- and *N*-alkylation occur together, especially in basic media where proton loss gives an ambident anion.

(ii) Nucleophilic displacements

2-Imidazolinones, 2-oxazolinones and 2-thiazolinones behave as cyclic ureas, thiocarbamates and carbamates, and predictably do not normally react with nucleophilic 'ketonic reagents' such as HCN, RNH_2, $NaHSO_3$, NH_2OH, N_2H_4, PhN_2H_3 or $NH_2CON_2H_3$. Stronger nucleophilic reagents, *i.e.* those of the type that attack amides, generally also react with azolinones. Thus they can be converted into chloroazoles with $POCl_3$ or PCl_5, *e.g.* (**489**)→(**488**). Similarly, bromoazoles may be prepared using PBr_5. Alkyl substituents on the azole nitrogen atom are usually lost in reactions of this type. Phosphorus pentasulfide converts carbonyl groups into thiocarbonyl groups (*e.g.* **489**→**490**).



(**488**) (**489**) (**490**)

3.4.3.7.3 3-Hydroxy, heteroatoms-1,2

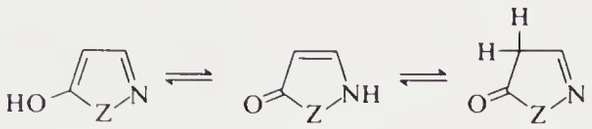
Pyrazoles, isoxazoles and isothiazoles with a hydroxy group in the 3-position (**491**; Z = NR, O, S) could isomerize to 3-azolinones (**492**). However, these compounds behave as true hydroxy derivatives and show phenolic properties. They give an intense violet color with iron(III) chloride and form a salt (**493**) with sodium hydroxide which can be *O*-alkylated by alkyl halides (to give **494**; R = alkyl) and acylated by acid chlorides (to give **494**; R = acyl).

(**491**) (**492**) (**493**) (**494**)

Sometimes compounds which exist predominantly in the hydroxy form give products of *N*-methylation with diazomethane, for example 3-hydroxy-5-phenylisothiazole ⟨63AHC(2)245⟩; of course, the ambident anion (**493**) is an intermediate. 3-Hydroxypyrazoles, under rather severe conditions, can be converted into 3-chloropyrazoles with $POCl_3$ ⟨66AHC(6)347⟩.

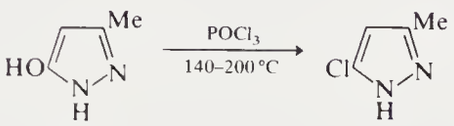
3.4.3.7.4 5-Hydroxy, heteroatoms-1,2

5-Hydroxy-isoxazoles and -pyrazoles can tautomerize in both of the ways discussed in Sections 3.4.3.7.3 and 3.4.3.7.5 (**495**⇌**496**⇌**497**). The hydroxy form is generally the least stable; the alternative azolinone forms coexist in proportions depending on the substituents and the solvent, with non-polar media favoring the CH form (**497**) and polar media the NH form (**496**). The derived ambident anion can react with electrophiles at N, C or O depending on the reagent and conditions.



(**495**) (**496**) (**497**)

The hydroxy groups of 5-hydroxypyrazoles (**498**) are readily replaced by halogens by the action of phosphorus halides.

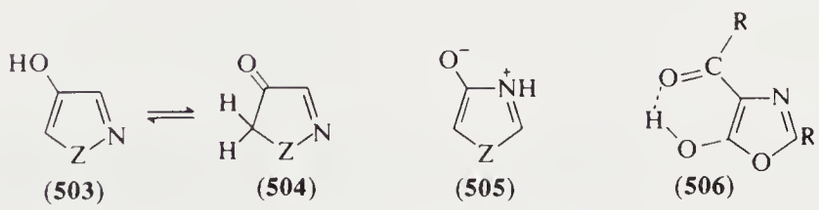


(**498**)

3.4.3.7.5 4- and 5-Hydroxy, heteroatoms-1,3 and 4-hydroxy, heteroatoms-1,2

The 4- and 5-hydroxy-imidazoles, -oxazoles and -thiazoles (**499, 501**) and 4-hydroxy-pyrazoles, -isoxazoles and -isothiazoles (**503**) cannot tautomerize to an aromatic carbonyl form. However, tautomerism similar to that which occurs in hydroxy-furans, -thiophenes and -pyrroles is possible (**499**⇌**500**; **503**⇌**504**; **501**⇌**502**), as well as a zwitterionic NH form (*e.g.* **505**). Most 4- and 5-hydroxy compounds of types (**500**) and (**502**) exist largely in these non-aromatic azolinone forms, although the hydroxy form can be stabilized by chelation (*e.g.* **506**). The derived ambident anions react with electrophilies at O or C. Replacement of the hydroxy group is sometimes possible provided electron-withdrawing groups are present as, for example, in 5-substituted 4-hydroxypyrazoles.

(**499**) (**500**) (**501**) (**502**)

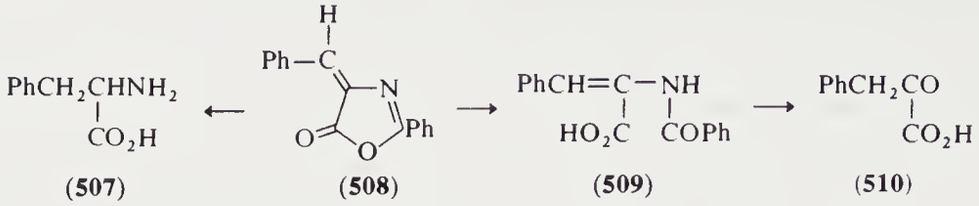


(**503**) (**504**) (**505**) (**506**)

4-Hydroxy derivatives of type (**503**) show more phenolic character; thus 4-hydroxyisothiazoles are normally *O*-methylated and *O*-acylated ⟨72AHC(14)1⟩.

Ring fission occurs readily in many of these compounds. For example, azlactones, *i.e.* 4*H*-oxazolin-5-ones containing an exocyclic C =C bond at the 4-position (**508**), are hydrolyzed to α-

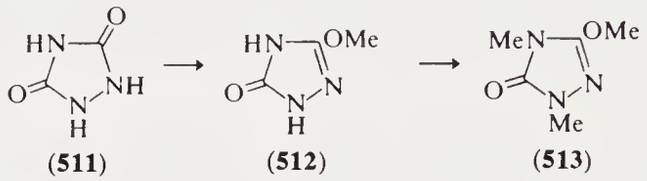
benzamido-α,β-unsaturated acids (**509**), further hydrolysis of which gives α-keto acids (**510**). Reduction and subsequent hydrolysis *in situ* of azlactones is used in the synthesis of α-amino acids (*e.g.* **508**→**507**).



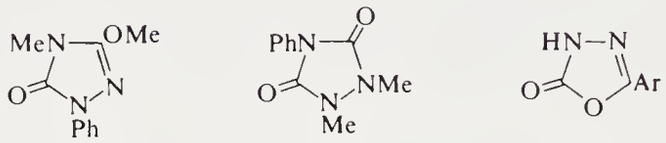
(**507**) (**508**) (**509**) (**510**)

3.4.3.7.6 Hydroxy derivatives with three heteroatoms

These compounds generally exist in carbonyl forms. The oxygen function can be converted into halogen by phosphorus halides. Reactions with electrophiles are quite complex. Thus urazole (**511**) reacts with diazomethane quickly to yield (**512**), which is more slowly converted into (**513**). 1-Phenylurazole gives (**514**); however, 4-phenylurazole yields (**515**). Oxadiazolinones of type (**516**) can be alkylated at both O- and N-atoms.



(**511**) (**512**) (**513**)

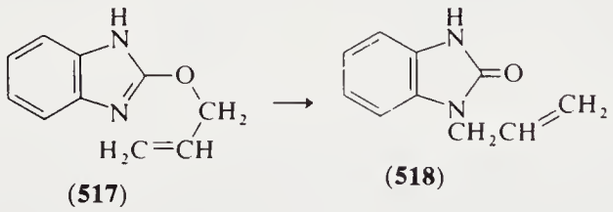


(**514**) (**515**) (**516**)

3.4.3.7.7 Alkoxy groups

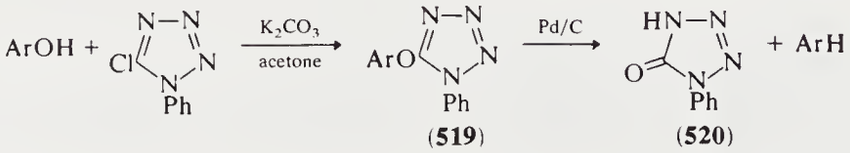
The alkoxy groups in alkoxyazoles undergo easy dealkylation to the corresponding hydroxyazoleazolinone when several nitrogen atoms are present or when they are additionally activated by another substituent. Thus pyrazolyl ethers are cleaved under vigorous conditions, or more easily if a nitroso group is present. Nucleophilic displacement of alkoxy groups on cationic rings occurs readily, *e.g.* in quaternary 1,2,3-triazole ethers.

Azoles with alkoxy groups α to nitrogen can rearrange to *N*-alkylazolinones on heating; thus 2-alkoxy-1-methylimidazoles give 3-alkylimidazolin-2-ones and 2-methoxythiazoles behave similarly. *O*-Allyl groups rearrange considerably more readily, *e.g.* 2-allyloxybenzimidazole (**517**) gives 1-allyl-2-benzimidazolinone (**518**) at 180°C ⟨67AHC(8)143⟩. 5-Allyloxypyrazoles undergo Claisen rearrangement of the allyl group to the 4-position.



(**517**) (**518**)

Aryl tetrazolyl ethers (**519**) are reduced by palladium on charcoal to give the arene and the tetrazolinone (**520**) ⟨77AHC(21)323⟩; this reaction is used for the removal of phenolic functionality.

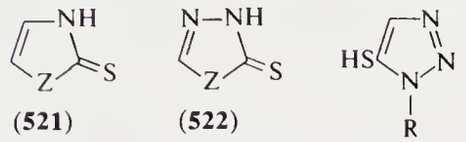


(**519**) (**520**)

3.4.3.8 *S*-Linked Substituents

3.4.3.8.1 Mercapto compounds: tautomerism

Many mercaptoazoles exist predominantly as thiones. This behavior is analogous to that of the corresponding hydroxyazoles (*cf.* Section 3.4.3.7). Thus oxazoline-, thiazoline- and imidazoline-2-thiones (**521**) all exist as such, as do compounds of type (**522**). However, again analogously to the corresponding hydroxy derivatives, other mercaptoazoles exist as such. 5-Mercaptothiazoles and 5-mercapto-1,2,3-triazoles (**523**), for example, are true SH compounds.



(**521**) (**522**) (**523**)

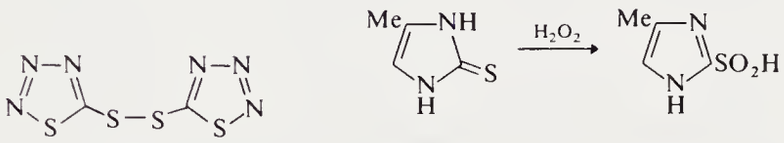
The pattern of reactivity is similar to that discussed for the azolinones in Sections 3.4.1.1.4 and 3.4.3.7.1. A difference is the greater nucleophilicity of sulfur, and thus more reactions of the ambident anion with electrophiles occur at sulfur.

3.4.3.8.2 Thiones

Many azolinethiones show reactions typical of thioamides; in particular, they react with electrophiles at the sulfur atom.

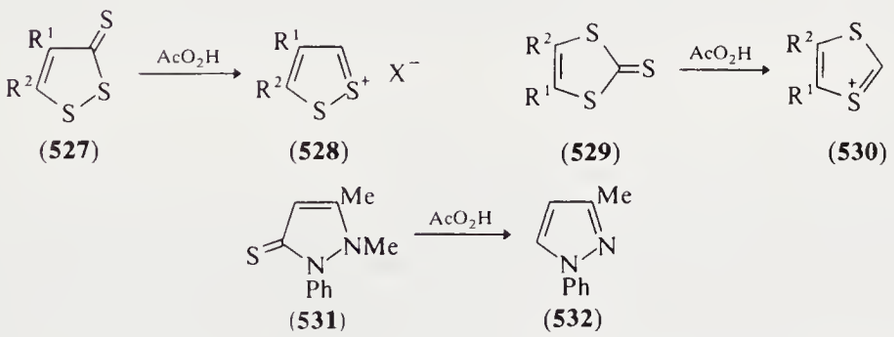
(i) Alkyl halides give alkylthio derivatives, *e.g.* in the imidazoline-2-thione, thiazoline-2-thione and 1-arylpyrazoline-5-thione series.

(ii) Thiones are oxidized, *e.g.* by iodine, into disulfides. Thus 5-mercapto-1,2,3,4-thiatriazole is converted into the disulfide (**524**) ⟨64AHC(3)263⟩; similar behavior is known in the tetrazole series.



(**524**) (**525**) (**526**)

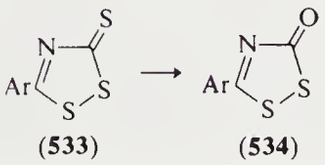
(iii) Thione groups can often be eliminated by oxidation; probably the sulfinic acid is the intermediate. Sometimes the sulfinic acid can be isolated (*e.g.* **525**→**526**), but more usually it spontaneously loses SO_2. In this way, thiazoline-2-thiones give thiazoles, 1,2-dithiole-3-thiones (**527**) are converted into 1,2-dithiolylium salts (**528**) and 1,3-dithiole-2-thiones (**529**) into 1,3-dithiolylium salts (**530**) ⟨66AHC(7)39⟩. In the pyrazole series (**531**) also loses an *N*-methyl group to yield (**532**).



(**527**) (**528**) (**529**) (**530**)

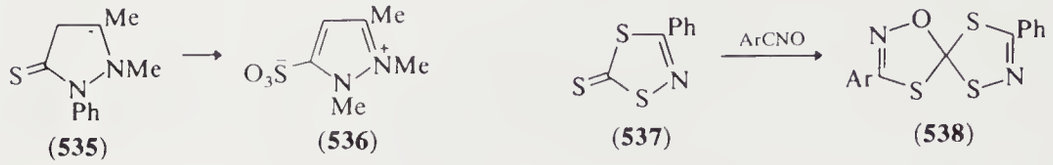
(**531**) (**532**)

(iv) However, aryl-1,2,4-dithiazoline-3-thiones are oxidized to the 3-ones (**533**→**534**).



(**533**) (**534**)

(v) Strong oxidation forms a sulfonic acid or betaine as, for example, in the pyrazole (**535**→**536**), thiazole and tetrazole series.



(**535**) (**536**) (**537**) (**538**)

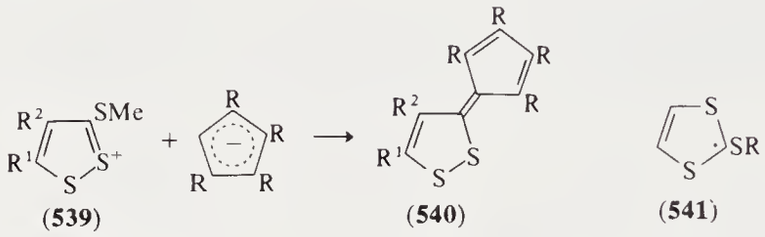
(vi) Cycloaddition across the C=S bond can lead to spiro derivatives, *e.g.* (**537**)→(**538**).

3.4.3.8.3 Alkylthio groups

2-Alkylthiothiazoles rearrange thermally into the 3-alkylthiazoline-2-thiones; in the imidazole series a thermal equilibrium is reached.

Alkylthio groups are oxidized to sulfoxides by H_2O_2 and readily by various oxidizing reagents to sulfones, *e.g.* in the imidazole series. The SR group is replaced by hydrogen with Raney nickel, and dealkylation is possible, *e.g.* of 3-alkylthio-1,2-dithiolyliums to give 1,2-dithiole-3-thiones by various nucleophiles ⟨80AHC(27)151⟩.

Alkylthio groups are replaced in nucleophilic substitutions. Such reactions are easy in cationic derivatives; for example, in the 1,2-dithiolylium series (**539**), substituted cyclopentadienyl ion gives fulvene derivatives (**540**) ⟨66AHC(7)39⟩. 2-Methylthio groups in 1,3-dithiolylium ions are substituted by primary amines or secondary amines ⟨80AHC(27)151⟩, and similar reactions are known for 2-alkylthiothiazoles.



(**539**) (**540**) (**541**)

1,3-Dithiole-2-thiones trap radicals to give neutral stabilized radicals (**541**) ⟨80AHC(27)31⟩.

3.4.3.8.4 Sulfonic acid groups

Azolesulfonic acids frequently exist as zwitterions. The usual derivatives are formed, *e.g.* pyrazole-3-, -4- and -5-sulfonic acids all give sulfonyl chlorides with PCl_5. The sulfonic acid groups can be replaced by nucleophiles under more or less vigorous conditions, *e.g.* by hydroxy in imidazole-4-sulfonic acids at 170 °C, and by hydroxy or amino in thiazole-2-sulfonic acids.

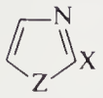
3.4.3.9 Halogen Atoms

3.4.3.9.1 Nucleophilic displacements: neutral azoles

As discussed in Section 3.4.3.1, nucleophilic replacements of halogen atoms are facilitated by mesomeric stabilization in the transition state for some haloazoles, depending on the number and orientation of the ring heteroatoms and halogen. Additional to this, and just as in benzene chemistry, all types of halogen atoms are activated toward necleophilic displacement by the presence of other electron-withdrawing substituents. Halogen atoms in the 4- and 5-positions of imidazoles, thiazoles and oxazoles and those in all positions of pyrazoles and isoxazoles are normally rather unreactive, but are labilized by an α or γ electron-withdrawing substituent. Reactions of *N*-unsubstituted azoles containing a ring NH group are often difficult because of the formation under basic conditions of unreactive anions.

Halogen atoms in the 2-position of imidazoles, thiazoles and oxazoles (**542**) undergo nucleophilic substitution reactions. The conditions required are more vigorous than those used, for example for

α- and γ-halopyridines, but much less severe than those required for chlorobenzene. Thus in compounds of type (**542**; X = Cl, Br) the halogen atom can be replaced by the groups NHR, OR, SH and OH (in the last two instances, the products tautomerize ; see Sections 3.4.3.7 and 3.4.3.8.1).

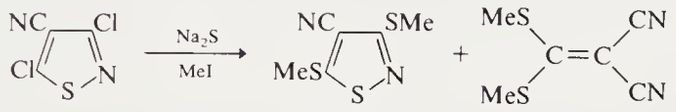


(**542**)

The 4- and 5-haloimidazoles and 4- and 5-halooxazoles are less reactive toward nucleophilic substitution than the 2-halo analogues, but still distinctly more reactive than unactivated phenyl halides. Thus a bromine atom in the 4- and 5-position of 1-methylimidazole requires lithium piperidide to react, whereas the 2-bromo analogue is converted into 2-piperidinoimidazole by piperidine at 200 °C. The chloro group of 5-chloro-4-nitroimidazole can be replaced by an alkylmercapto group ⟨70AHC(12)103⟩. The relative reactivities with respect to nucleophilic displacement increase in the order Cl < Br < I; fluoro compounds have been little studied but 4-fluoroimidazoles are relatively unreactive. 5-Halothiazoles react unexpectedly rapidly with methoxide, the 4-halothiazoles less readily.

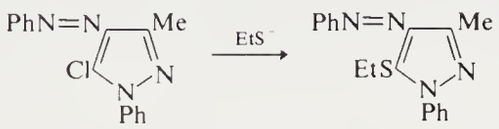
3-Chloro-5-arylisoxazoles undergo nucleophilic displacement with alkoxide ion. Halogen atoms in the 5-position of the isoxazole nucleus are readily displaced if an activating group is present in the 4-position ⟨63AHC(2)365⟩.

Halogens attached to the pyrazole nucleus are normally very inert. If there is an electron-reactivity. 5-Halogens, particularly when activated by an electron-withdrawing group such as nitro in the 4-position, readily undergo nucleophilic displacement to give hydroxy, alkoxy, alkylthio, amino and cyano derivatives. However, a 3-halogen atom, even when activated, is less reactive than a halogen in the 5-position, and replacement is often accompanied by ring cleavage, *e.g.* Scheme 57 ⟨72AHC(14)1⟩. 4-Haloisothiazoles are still less reactive, but can react with copper(I) cyanide to give the corresponding nitrile ⟨65AHC(4)107⟩.



Scheme 57

Halogens attached to the pyrazole nucleus are normally very inert. If there is an electron-withdrawing group in the 4-position, then the halogen atom in the 5-position of a pyrazole ring becomes activated, for example Scheme 58 ⟨66AHC(6)347⟩. However, such an electron-withdrawing group in the 4-position only activates the chlorine atom in the 5-position and not one in the 3-position because of the influence of partial bond fixation ⟨66AHC(6)347⟩ (see discussion in Section 3.4.3.1).

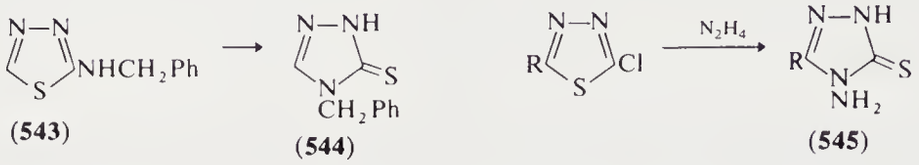


Scheme 58

5-Halo-1-methyl-1,2,3-triazoles undergo substitution reactions with amines, but the 4-halo analogues do not. 5-Chloro-1,4,-diphenyl-1,2,3-triazole with sodium cyanide in DMSO gives the cyano derivative ⟨63JCS2032⟩. 1-Substituted 3-chloro- and 5-chloro-1,2,4-triazoles both react with amines.

5-Chlorine atoms in 1,2,4-oxadiazoles can be replaced by amino, hydroxy or alkoxy groups ⟨76AHC(20)65⟩. 5-Halo-1,2,4-thiadiazoles are also quite reactive: silver fluoride gives the fluorides, in concentrated hydrochloric acid a 5-hydroxy group is introduced, and thiourea reacts, as do various amines. Sodium sulfite gives sulfonic acids, and reactive methylene compounds give the expected substitution products ⟨65AHC(5)119⟩. By contrast, halogens in the 3-position of 1,2,4-thiadiazoles are inert toward most nucleophilic reagents: thus 3-chloro-5-phenyl-1,2,4-thiadiazole resists aminolysis and thiourea; however, a 3-alkoxy group is introduced by sodium alkoxide ⟨65AHC(5)119⟩.

Halogens on the 1,2,5-thiadiazole ring are highly reactive and easily converted into ethers by refluxing with alkoxides ⟨68AHC(9)107⟩. 2-Chloro-1,3,4-thiadiazole and benzylamine give a mixture of (**543**) and (**544**) ⟨68AHC(9)165⟩, the latter resulting from a Dimroth rearrangement (see Section 3.4.3.5.1). With hydrazine, (**545**) is similarly formed ⟨68AHC(9)165⟩.

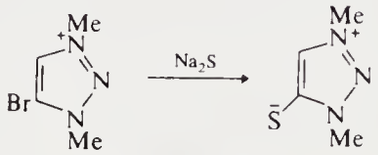


(**543**) (**544**) (**545**)

Halogen atoms at the 5-position of tetrazoles are reactive and easily replaced by nucleophiles. 5-Bromo-1-methyltetrazole is significantly more reactive than the 2-methyl isomer ⟨77AHC(21)323⟩.

3.4.3.9.2 Nucleophilic displacements: haloazoliums

Halogen atoms in cationic olium rings are very reactive. The halogen atom in the quaternary salts of 3- and 5-halo-1-phenylpyrazoles is replaced at 80–100 °C by hydroxy, alkoxy, thiol, amino or cyano groups ⟨66AHC(6)347⟩. 3-Halo-1,2-dithiolyliums are converted into 1,2-dithiol-3-ones by water and react readily with other nucleophiles ⟨80AHC(27)151⟩. Displacement of bromine from triazolium salts takes place easily, *e.g.* as in Scheme 59 ⟨74AHC(16)33⟩.



Scheme 59

3.4.3.9.3 Other reactions

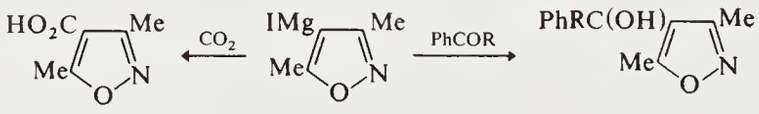
Nuclear halogen atoms also show many of the reactions typical of aryl halogens.

(i) They can be replaced with hydrogen atoms by catalytic (Pd, Ni, *etc.*) or chemical reduction (HI or Zn/H_2SO_4). For example, halopyrazoles with HI and red phosphorus at 150 °C give pyrazoles ⟨66AHC(6)347⟩, and 5-bromo-1,2,4-thiadiazole is reduced by Raney nickel to the parent heterocycle. 2-Bromothiazole can be reduced electrochemically.

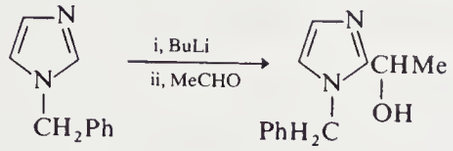
(ii) They give Grignard reagents; however, in the preparation of these it is sometimes necessary to add ethyl bromide to activate the magnesium ('entrainment method'). Pyrazolyl Grignard reagents have been obtained by the entrainment reaction ⟨66AHC(6)347⟩. 4-Iodoisoxazoles give Grignard reagent ⟨63AHC(2)365⟩. The 4- and 5-halooxazoles undergo halogen–metal exchange with *n*-butyllithium to give 4- and 5-lithiooxazoles ⟨74AHC(17)99⟩. Halothiazoles give Grignard reagents and lithio derivatives.

3.4.3.10 Metals and Metalloid-linked Substituents

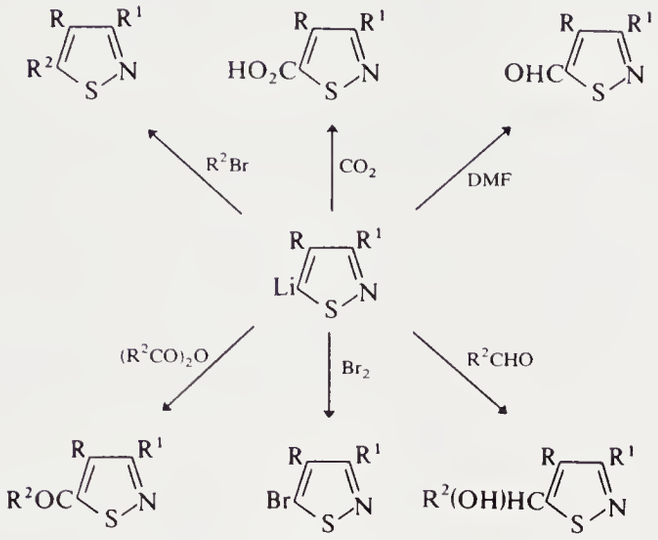
Metallated azoles frequently show expected properties, especially if not too many heteroatoms are present. Thus Grignard reagents prepared from halogen–azoles (see Section 3.4.3.9.3) show normal reactions, as in Scheme 60. 2-Lithioimidazoles react normally, *e.g.* with acetaldehyde (Scheme 61) ⟨70AHC(12)103⟩; 5-lithioisothiazoles (see Scheme 62) ⟨72AHC(14)1⟩ and 2-lithiothiazoles undergo many of the expected reactions.



Scheme 60

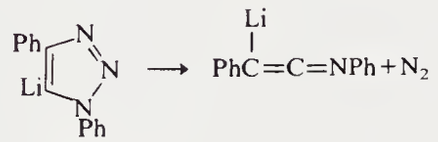


Scheme 61



Scheme 62

However, as the number of heteroatoms increases, the stability decreases: the 5-lithio derivatives of 1,2,3-triazoles (**546**) ring-open spontaneously ⟨74AHC(16)33⟩. 1-Methyltetrazol-5-yllithium decomposes to nitrogen and lithium methylcyanamide above −50 °C, although it gives the expected Grignard-like reactions with bromocyanogen, esters, ketones and sulfur at lower temperatures ⟨77AHC(21)323⟩.

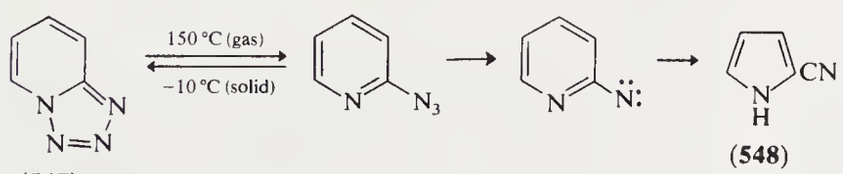


(**546**)

Acetoxymercurioxazoles ⟨74AHC(17)99⟩ and acetoxymercurithiazoles with halogens give the corresponding halooxazoles in good yield. 4-Acetoxymercuripyrazoles show many of the reactions of phenylmercury(II) acetate: removal by HCl, conversion to Br by bromine, and to SCH_2Ph by $(SCN)_2/PhCH_2Cl$.

3.4.3.11 Fused Heterocyclic Rings

A wide variety of such derivatives is known; their properties are usually those of the individual ring systems. However, some unique reactions arise from the special juxtaposition of the two rings, *e.g.* tetrazolopyridines (**547**) on photolysis yield cyanopyrroles (**548**) ⟨81AHC(28)231⟩.



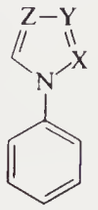
(**547**) (**548**)

3.4.3.12 Substituents Attached to Ring Nitrogen Atoms

3.4.3.12.1 N-*Linked azole as a substituent*

It is instructive to consider *N*-substituted azoles in reverse, *i.e.* the azole ring as the substituent linked to some other group. Hammett and Taft σ-constant values for azoles as substituents are given in Table 11. The values show that all the azoles are rather weak net resonance donors, imidazole being the strongest. They are all rather strong inductive acceptors, with pyrazole considerably weaker in this respect than imidazole or the triazoles.

Table 11 Hammett and Taft σ-Constants for Azoles as Substituents in a Benzene Ring ⟨81JCR(S)364⟩



	Azole				
	X	*Y*	*Z*	σ_I	σ_{R°
3	N	—	—	0.30	−0.06
2	—	N	—	0.51	−0.15
7	N	N	—	0.53	−0.10
5	N	—	N	0.53	−0.12
4	N	N	—	0.66	−0.10

N-Linked azole rings behave as good leaving groups, the more so the more nitrogen atoms contained in the ring (*cf.* Section 3.4.3.12.4).

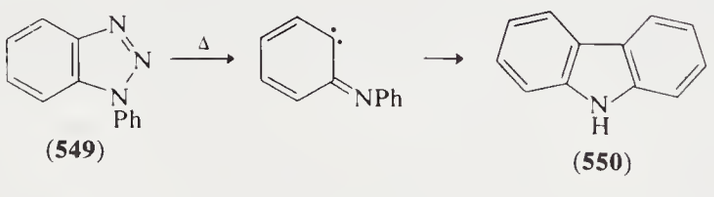
3.4.3.12.2 Aryl groups

Electrophilic substitution occurs readily in *N*-phenyl groups, *e.g.* 1-phenyl-pyrazoles, -imidazoles and -pyrazolinones are all nitrated and halogenated at the *para* position. The aryl group is attacked preferentially when the reactions are carried out in strongly acidic media where the azole ring is protonated.

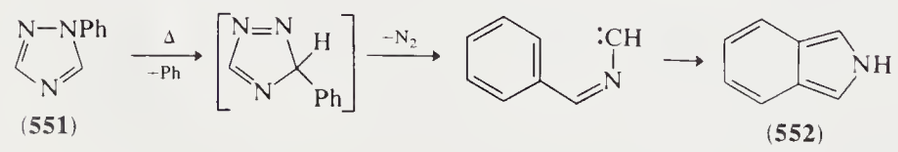
The azole ring can activate metallation at the *ortho* position of an *N*-phenyl group, as in 1-phenylpyrazoles.

If the *N*-aryl group is strongly activated, then it can be removed in nucleophilic substitution reactions in which the azole anion acts as leaving group. Thus 1-(2,4-dinitrophenyl)pyrazole reacts with N_2H_4 or NaOMe.

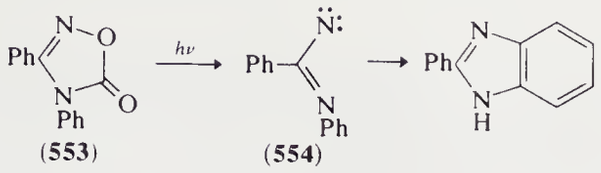
On pyrolysis, 1-arylimidazoles rearrange to 2-arylimidazoles. In other systems pyrolysis causes more deep-seated changes. 1-Arylbenzotriazoles (**549**) on pyrolysis or photolysis give carbazoles (**550**) *via* intermediate nitrenes ⟨81AHC(28)231⟩. 1-Phenyl-1,2,4-triazole (**551**) pyrolyzes to isoindole (**552**) *via* a carbene intermediate ⟨81AHC(28)231⟩ and another example of participation of *N*-phenyl groups is found in the formation of benzimidazoles from tetrazoles (see Section 3.4.1.2.1). In the oxadiazolinone series (**553**), a nitrene intermediate (**554**) is also probably formed, which then ring closes ⟨70AHC(11)1⟩.



(**549**) (**550**)



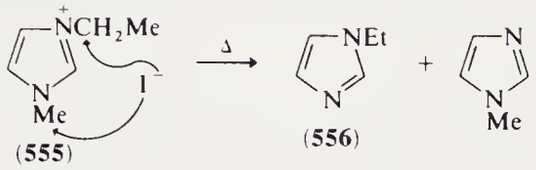
(**551**) (**552**)



(553) (554)

3.4.3.12.3 Alkyl groups

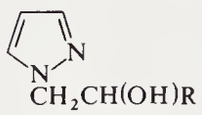
N-Alkyl groups in azolium salts can be removed by nucleophilic S_N2 reactions; soft nucleophiles such as PPh_3 and I^- are effective. Sometimes there is competition; for example, in (**555**) the methyl group is the more readily removed to give mainly *N*-ethylimidazole (**556**) ⟨80AHC(27)241⟩. This reaction has been studied quite extensively in the imidazolium series. The 1,2- and 1,3-dialkyltriazolium salts undergo nucleophilic displacement on heating ⟨74AHC(16)33⟩, and 2-alkylisothiazolium salts are reconverted into isothiazoles on distillation ⟨72AHC(14)1⟩. Pyrazolium salts similarly give pyrazoles. The benzyl group in 1-benzyl-1,2,3-triazoles is removed by reduction with sodium in liquid ammonia or catalytic reduction.



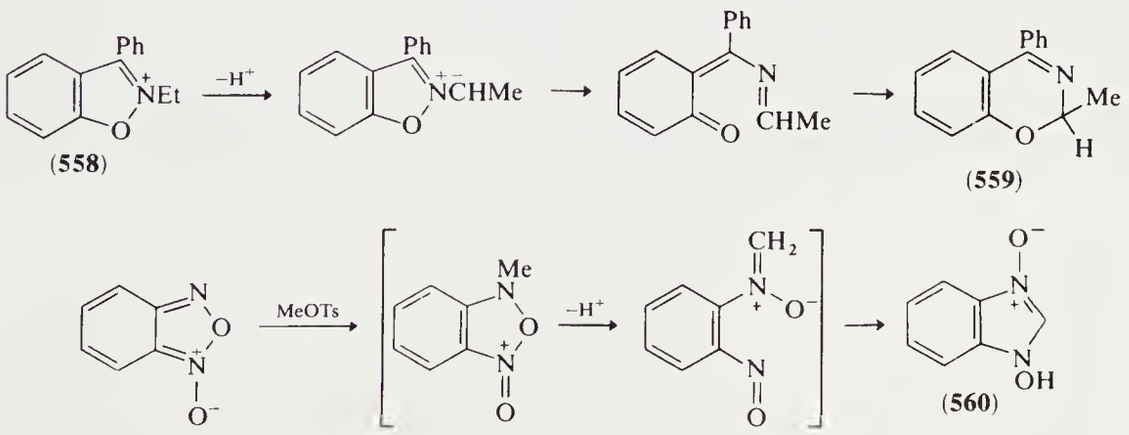
(555) (556)

N-Alkyl groups in neutral azoles can rearrange thermally to carbon. For example, 2-alkylimidazoles can be prepared in this way in a reaction which is irreversible, uncatalyzed, intramolecular and does not involve radicals ⟨80AHC(27)241⟩. *N*-Vinyl and *N*-alkyl groups in imidazoles also rearrange thermally to the 2- and 4-ring positions.

Deprotonation can occur at the α-CH of azole *N*-alkyl groups: treatment of 1-methylpyrazole with *n*-BuLi followed by aldehydes gives products of type (**557**). Such proton loss is facilitated in cationic azido rings, and the ylides so formed sometimes undergo rearrangement. Thus quaternized 1,2-benzisoxazoles (**558**) lose a proton and then rearrange to 1,3-benzoxazines (**559**) ⟨67AHC(8)277⟩. Quaternized derivatives of benzofuroxan formed *in situ* undergo rearrangement to hydroxybenzimidazole *N*-oxides (**560**) ⟨69AHC(10)1⟩. Reactions of this type are also known for *N*-alkylazolinones.



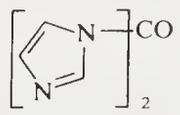
(557)



(558) (559) (560)

3.4.3.12.4 Acyl groups

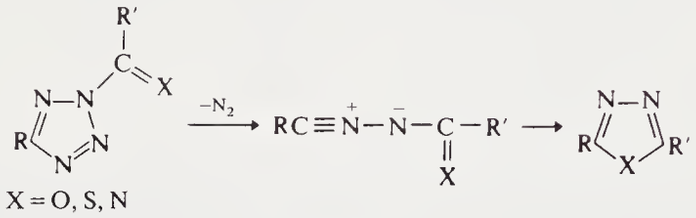
An azole ring is quite a good leaving group, far better than NR_2. Hence *N*-acylazoles are readily hydrolyzed. Their susceptibility to nucleophilic attack gives rise to the synthetic utility of compounds such as carbonyldiimidazole (**561**) which have been used, for example, in peptide syntheses. *N*-Acylazoles offer mild and neutral equivalents of acid chlorides. The leaving group ability of the azole ring increases with the number of nitrogen atoms it contains.



(**561**)

Acyl derivatives of azoles containing two different environments of nitrogen atoms can rearrange. For example, 1-acyl-1,2,3-triazoles are readily isomerized to the 2*H*-isomers in the presence of triethylamine or other bases; the reaction is intermolecular and probably involves nucleophilic attack by N-2 of one triazole on the carbonyl group attached to another ⟨74AHC(16)33⟩.

2-Acyltetrazoles may lose nitrogen spontaneously to give oxadiazoles, and thiadiazoles can be prepared similarly from 2-thioacyltetrazoles (Scheme 63) ⟨77AHC(21)323⟩.



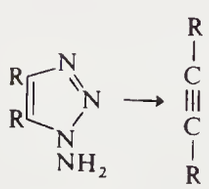
Scheme 63

3.4.3.12.5 N-Amino and N-nitro groups

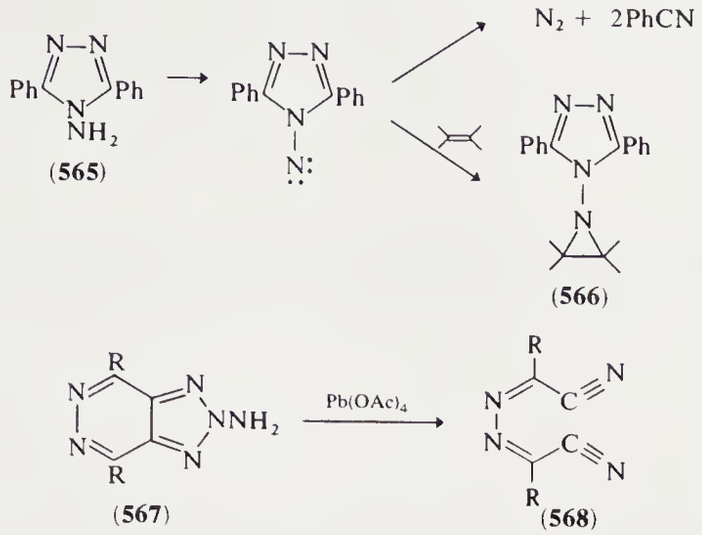
N-Amino groups are replaced by hydrogen on treatment with nitrous acid (*e.g.* **562**→**563**) ⟨80AHC(27)241⟩ or phosphorus trichloride (1,2,4-triazole-4-acylimines are converted into triazoles ⟨74AHC(17)213⟩).

(**562**) (**563**)

N-Aminoazoles can be oxidized to nitrenes which then fragment or ring expand in various ways. 1-Amino-1,2,3-triazoles (**564**) lose two moles of nitrogen to give alkynes ⟨74AHC(16)33⟩. *N*-Aminotriazoles (**565**) and -tetrazoles on oxidation with lead tetraacetate fragment to benzonitrile or benzyne ⟨81AHC(28)231⟩; however, the intermediate nitrene can be trapped as an aziridine (**566**). Similarly, the *N*-aminopyridazinotriazoles (**567**) undergo oxidative fragmentation to give open-chain compounds (**568**) ⟨81AHC(28)231⟩. *N*-Aminopyrazoles can ring expand to 1,2,3-triazines.



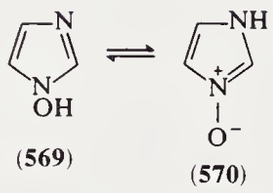
(**564**)



1-Nitropyrazoles rearrange to 4-nitropyrazoles in H_2SO_4 and to 3-nitropyrazoles thermally. Similar rearrangements are known for *N*-nitro-1,2,4-triazoles.

3.4.3.12.6 N-*Hydroxy groups and* N-*oxides*

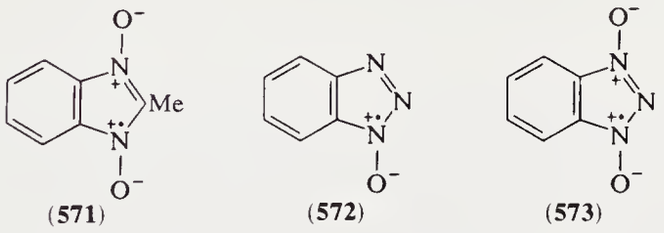
Compounds of this type are tautomeric: in general, the *N*-oxide form (*e.g.* **570**) is favored by polar media, the *N*-hydroxy form (*e.g.* **569**) by non-polar media.



N-Hydroxy groups can be acetylated (Ac_2O) and *O*-alkylated in basic media by methyl iodide. 1-Hydroxypyrazole 2-oxides are quite strong acids.

Azole *N*-oxide groups are readily removed by reduction with Zn/HOAc, HI or PCl_3, *e.g.* in the pyrazole series. 1,2,3-Thiadiazole 3-oxides isomerize on irradiation to the corresponding 2-oxides.

Oxidation of *N*-hydroxyazoles can give cyclic nitroxyls (*e.g.* **571–573**) ⟨79AHC(25)205⟩.



3.4.3.12.7 N-*Halo groups*

Generally these derivatives are rather unstable and behave as oxidizing and halogenating agents. 1-Iodoimidazoles are more stable than other analogues.

3.5
Reactivity of Small and Large Rings*

3.5.1 GENERAL SURVEY

Chapter 3.5 attempts to give an overview of the reactivity of 'small or large' ring systems treated individually in the monograph chapters of Part 5 of CHEC. The great diversity of these systems presents a serious problem of organization. In structuring the chapter, the nature of the reaction and the distance of the site of attack from the heteroatoms were used.

3.5.1.1 Neutral Molecules

The reactivity of small (three- and four-membered) heterocyclic rings is dominated by the effects of ring strain, which facilitates all modes of ring opening. Aromaticity is not observed, antiaromaticity is present in only a few isolated examples, and thus does not play a general role. Many reactions are initiated by unimolecular ring opening, to give diradicals or ylides, whose reaction products are then observed. Extrusion of stable as well as unstable moieties occurs, assisted by the ring strain. Four-membered systems tend to cleave into two two-member fragments (consisting of two former ring atoms and their ligands). Attack on ring carbons concomitant with ring opening is very common, and is usually subject to electrophilic catalysis.

Large heterocyclics, *i.e.* those with more than six ring members, often show little effect of ring strain on the reactivities of the neutral molecules. Factors very important for large ring reactivity are unsaturation, especially polyenic and aromatic characteristics, and the steric accessibility of heteroatoms and functional groups, as well as the possibility of transannular reactions. The majority of unsaturated large rings are not aromatic, even where the Hückel rule seems to be formally obeyed.

3.5.1.2 Cations

Onium ions of small and large heterocyclics are usually produced by electrophilic attack on a heteroatom. In most three- and four-membered rings nucleophilic attack on an adjacent carbon and ring opening follow immediately, stabilizing the molecule. In large rings the onium ion behaves as would its acyclic analogue, except where aromaticity or transannular reactions come into play (each with its electronic and steric pre-conditions). A wide diversity of reactions is observed.

Cations of a different kind may be derived from heterocyclics by removing a leaving group with its bonding electrons, *e.g.* a halide ion from an *N*-halo moiety. Such cations, 'nitrenium ions', were also assumed to be reactive intermediates in reactions of other *N*-halo heterocycles.

3.5.1.3 Anions

Anions of small heterocyclics are little known. They seem to be involved in some elimination reactions of oxetan-2-ones ⟨80JA3620⟩. Anions of large heterocycles often resemble their acyclic

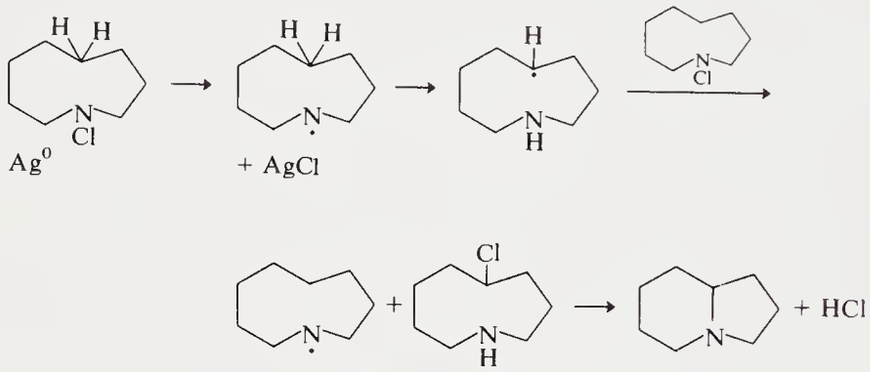
*Based on Chapter 5.02 of 'Comprehensive Heterocyclic Chemistry', by W. Lwowski, New Mexico State University.

counterparts. However, anion formation can adjust the number of electrons in suitable systems so as to make a system conform to the Hückel rule, and render it aromatic if flat geometry can be attained. Examples are found in CHEC 5.20. Anion formation in selected large heterocycles can also initiate transannular reactions (see also Section 3.5.6 below).

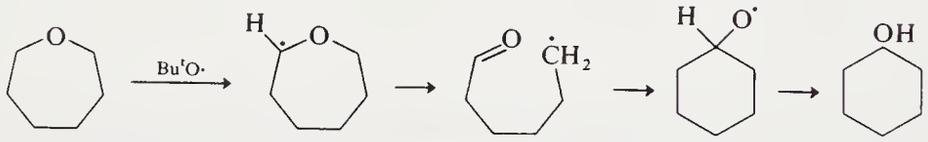
3.5.1.4 Radicals

Small-ring radicals with the unpaired electron at the heteroatom or at a carbon adjacent to a heteroatom undergo ring cleavage as the predominant mode of stabilization, as known for oxaziranes ⟨78CJC2985, 77TL4289, 76HCA880, 76JCS(P2)1044⟩, aziridines (CHEC 5.04.3.9), diaziridines (CHEC 5.08.3.2.3), diazirines ⟨79JA837⟩, oxaziridines (CHEC 5.08.3.1.5) and thietanes (CHEC 5.14.3.10.1). The heteroatom is usually retained in the product, except in thiirane cleavages (CHEC 5.06.3.7), where desulfurization occurs. Thietanes, in contrast, are less readily desulfurized (CHEC 5.14.3.10.1). Oxaziridinyls display a variety of reactions, including N—O and N—C cleavage (CHEC 5.08.3.1.5); diaziridinyls behave analogously, with C—N and N—N cleavage (CHEC 5.08.3.2.3).

Large-ring heterocyclic radicals are not particularly well known as a class. Their behavior often resembles that of their alicyclic counterparts, except for transannular reactions, such as the intramolecular cyclization of 1-azacyclononan-1-yl (Scheme 1) ⟨72CJC1167⟩. As is the case with alicyclic ethers, oxepane in the reaction with *t*-butoxy radical suffers abstraction of a hydrogen atom from the 2-position in the first reaction step (Scheme 2) ⟨76TL439⟩.



Scheme 1

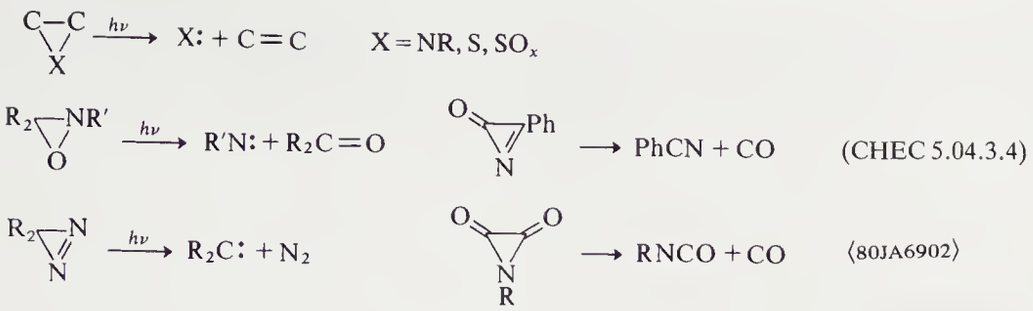


Scheme 2

3.5.2 THERMAL AND PHOTOCHEMICAL REACTIONS, NOT FORMALLY INVOLVING OTHER SPECIES

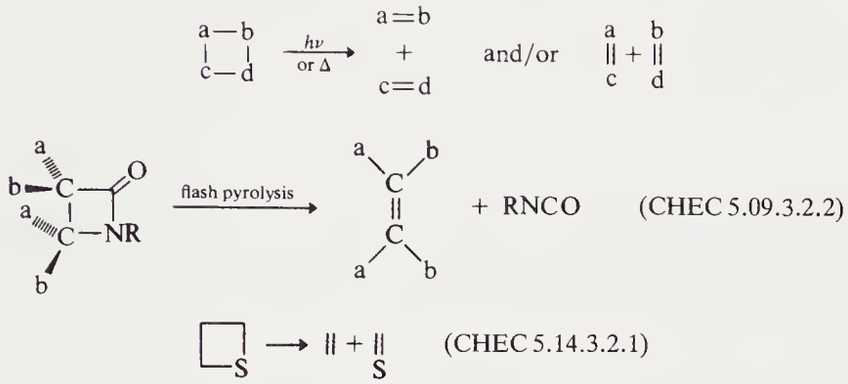
3.5.2.1 Fragmentation Reactions

Fragmentation reactions are particularly common in small rings. Relief of strain and the gain in stability in forming certain common fragments (such as N_2, CO_2), as felt in the transition state of the rate determining step, are important driving forces. Three-membered rings fragment to give moieties a—b (usually unsaturated) and c. The latter might be a stable molecule, such as CO, but also a carbene or nitrene, atomic sulfur or singlet SO, to name the most common ones. Scheme 3 gives examples.

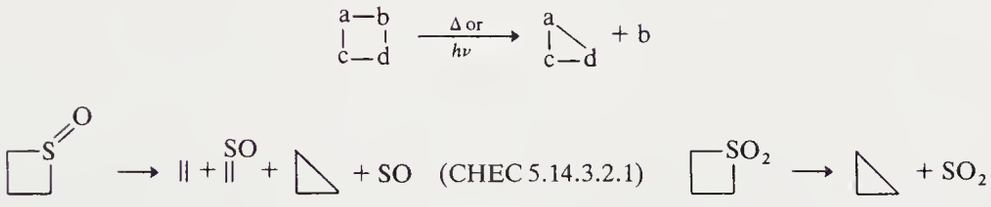


Scheme 3

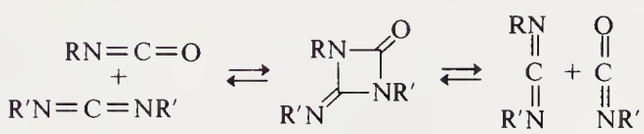
Four-membered heterocycles most often give fragments containing two ring atoms with their respective ligands. However, [3 + 1] fragmentation is well known, giving an atom (such as S) or stable species (such as SO_2) and often a three-membered ring. Examples are found in Schemes 4 and 5. The [2+2] fragmentations are often stereospecific and the fragmentation can be reversible. The reversibility can lead to interconversions as seen in Scheme 6; the RN: moieties of an isocyanate and a carbodiimide are exchanged *via* a 3-imino-1,3-diazetidin-2-one ⟨69ACR186⟩.



Scheme 4



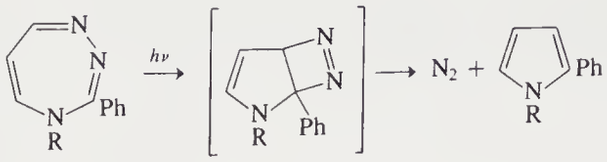
Scheme 5



Scheme 6

Nitrogen, CO_2, SO_2, RCN, RNCO and RNCS are particularly common fragments containing two of an original four ring atoms.

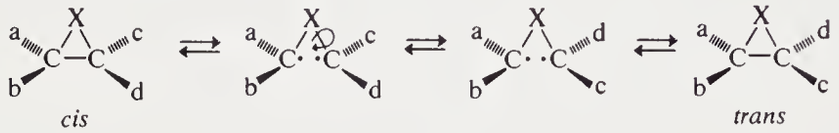
The fragmentation of large heterocyclics occurs less readily, since the ring strain is usually less. The most favorable leaving moieties, such as N_2, can of course be extruded easily (often giving 1,*n* diradical species). Thus, 1,2,4-triazepines can lose nitrogen to give pyrroles (Scheme 7; CHEC 5.18.7.2). Most often, fragmentations of large heterocyclics can be classified either as retrocycloadditions, or they are analogous to what would be expected from acyclic counterparts of the large rings. The fragmentations may be orbital symmetry controlled. For example, 2,7-dihydrothiepin 1,1-dioxide loses SO_2 to give *cis*-hexatriene (CHEC 5.17.2.3.2). The orbital control of thermal extrusions from thiepins has been studied in some detail (CHEC 5.17.2.4.1).



Scheme 7

3.5.2.2 Rearrangements

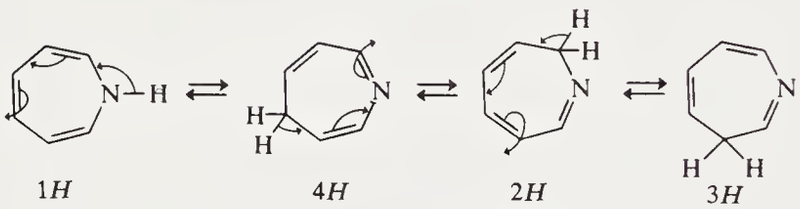
(a) *Cis–trans* isomerizations are commonly observed upon heating or irradiating three-membered heterocyclics. The formation of 1,3-diradicals leads to rotation about the single bonds, and the isomerization has been used to probe the bond strengths of the 2,3-bond of such heterocyclics (Scheme 8). *Cis–trans* isomerizations in large rings can be due to retrocycloadditions or the temporary conversion of parts of the heterocycle, such as dehydrogenation–hydrogenation reactions. Diradical formation to give long chain 1,ω-diradicals does not usually lead to recyclization, due to unfavorable entropy factors.



cis *trans*

Scheme 8

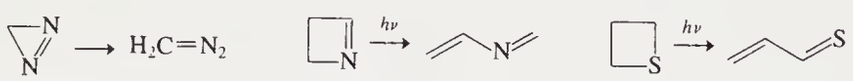
(b) Hydrogen shifts are common in large, unsaturated rings, such as azepines. Series of 1,5-hydrogen shifts, thermally allowed, connect the 1*H*, 2*H*, 3*H* and 4*H* isomers of unsubstituted azepines, oxepins and thiepins. While the sigmatropic mechanism does allow the interconversion of the isomers, base catalysis has been observed in some cases. Ionic mechanism(s) must therefore be considered (Scheme 9).



1*H* 4*H* 2*H* 3*H*

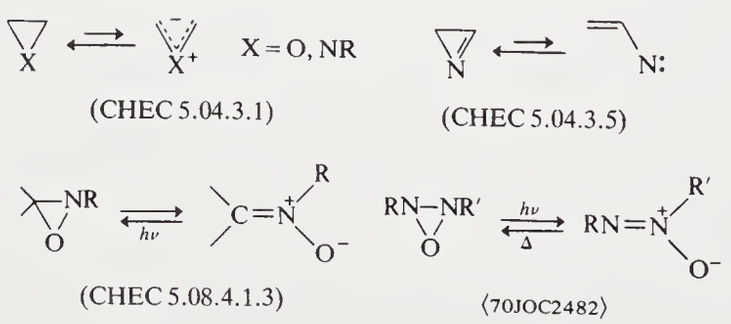
Scheme 9

(c) Ring–chain isomerizations are common with small heterocycles, with the ring strain assisting the opening. The reverse reaction is often found where reactive opening products are obtained (see isomerizations). Scheme 10 gives a few examples of irreversible ring openings, and Scheme 11 shows some which are readily or spontaneously reversed.



(CHEC 5.08.3.3.2) (CHEC 5.09.4.2.2) (CHEC 5.14.3.2.2)

Scheme 10

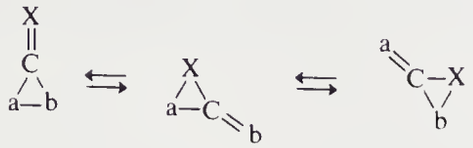


(CHEC 5.04.3.1) (CHEC 5.04.3.5)

(CHEC 5.08.4.1.3) ⟨70JOC2482⟩

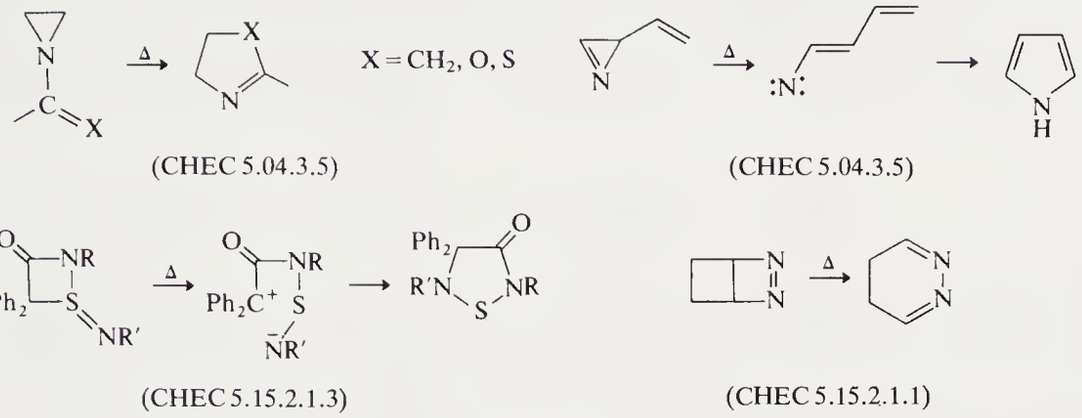
Scheme 11

(d) Ring–ring valence isomerizations occur in small and large rings, with or without changes of ring size. An example of the latter course is the intriguing interconversion of three-membered rings with exocyclic double bonds (Scheme 12) observed with methylene-aziridines ⟨73AG(E)414, 78AG(E)213⟩, -aziridinimines ⟨70AG(E)381⟩ and -diaziridinimines ⟨69AG(E)449⟩.



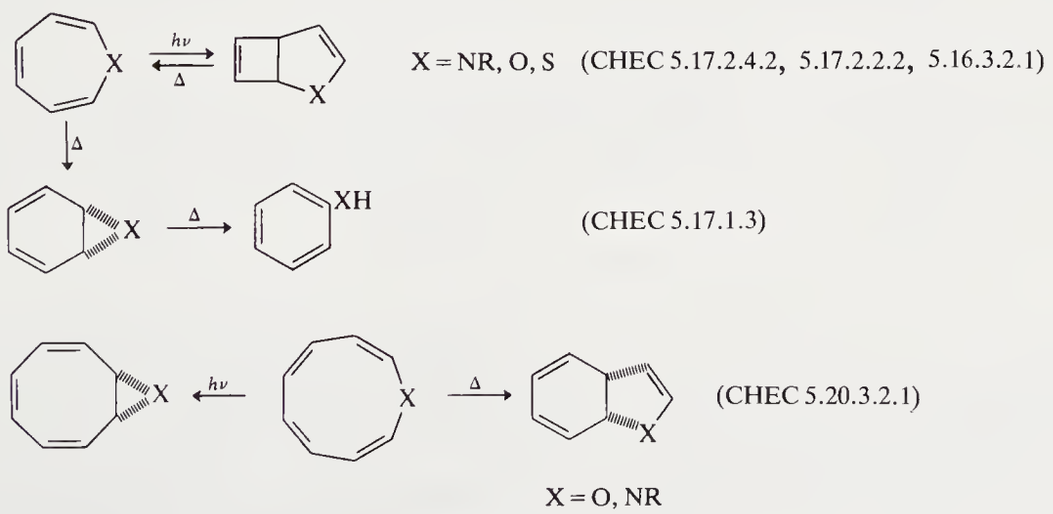
Scheme 12

Ring expansion of small rings is once again favored by ring strain, and many 3→5 conversions are known. Four-membered rings can expand to five- or six-membered ones. Examples are given in Scheme 13.



Scheme 13

Large rings isomerize to two condensed smaller ones, by transannular reactions of many bond-making mechanisms, and by electrocyclic reactions. Seven-membered, fully unsaturated systems can convert to [3.2.0] and to [4.1.0] isomers. The former conversion is allowed photochemically, the latter thermally. Consequently, the chemistry of azepines, oxepins and thiepins is often governed by the rate and activation barrier (or the photochemical conditions and parameters) prevailing. Thiepins, for example, extrude sulfur *via* the thianorcaradiene isomer, and sulfur loss is likely to occur when a given system isomerizes to the [4.1.0] isomer more rapidly than competing reactions occur through the monocyclic isomer. Depending on the nature of the heteroatom (and the presence of other heteroatoms in the ring) and the substituents, the heterepine–heteranorcaradiene rearrangement can be fast or slow, and one or the other component can be dominant in the equilibrium. Photoinduced rearrangement leads to [3.2.0] systems, which may revert to the seven-membered monocycle thermally—perhaps by homolytic cleavage of the common bond. Both types of bicyclization are observed in systems containing N, O or S (including SO and SO_2) as heteroatoms. Scheme 14 gives examples.



Scheme 14

2*H*-Azocinones are in thermal equilibrium with 8-azabicyclo[4.2.0]octa-3,5-dienones, as measured by NMR (CHEC 5.19.2.3).

3.5.3 ELECTROPHILIC ATTACK ON RING HETEROATOMS

The basicities of saturated heterocycles are similar to those of analogous open chain systems, with the exception of three-membered heterocycles, in which the basicity is markedly reduced. Table 1 gives pK_a values for the equilibria between free and monoprotonated heterocycles. As the ring size increases, the protonated species become more stable and the pK_a values approach those of the open chain analogues. Increasing basicity (thiirane < oxirane < aziridine) prevails in gas phase proton affinities (Table 2) ⟨80JA5151⟩.

Table 1 Basicities for some Heterocycles: pK_a Values for the Equilibria Between Parent and Monoprotonated Species in Water

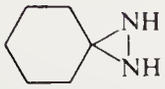
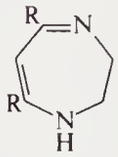
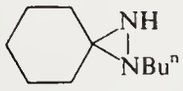
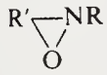
Parent species	pK_a	*CHEC number/ref.*	*Parent species*	pK_a	*CHEC number/ref.*
	8.04	63PMH(1)1		11.27	63PMH(1)1
	4.6	5.08.2.3.1		13–14	5.18.2.3
	6.4	5.08.2.3.1		−2.02	5.17.2.1.3
	0.13 to −1.81	5.08.3.1.3		−2.08	5.17.2.1.3
	11.29	63PMH(1)1			

Table 2 Gas Phase Proton Affinities of Small Heterocycles ⟨80JA5151⟩

Heterocycle	*Proton affinity* (kJ mol^{-1})	*Open chain analogue*	*Proton affinity* (kJ mol^{-1})
	902.5	Me—NH—Me	922.6
	793.3	Me—O—Me	807.9
	812.9	Me—S—Me	839.7

Protonation or Lewis acid complexation of a heteroatom invites nucleophilic attack, including nucleophilic attack by a parent molecule. Oligomerization and polymerization are thus often the results of bringing heterocycles into an acid environment without making sure that all of the potentially nucleophilic sites are protonated.

Alkylation, acylation, *etc.* at the heteroatom lead to onium salts. In three-membered rings these are difficult to isolate, and very weakly nucleophilic counterions must be used, such as BF_4^-.

However, with care, aziridines can be acylated and nitrosated on the nitrogen atom. They form salts with acids but are less basic (pK_a *ca.* 8) than normal secondary amines (pK_a *ca.* 11).

Thietane can be oxidized to a sulfone. Azetidine forms salts and can be acylated (with RCOCl) or nitrosated (with HNO_2).

In large rings the fate of the onium ions depends mostly on the structure and degree of unsaturation of the particular compound, and the onium salts range from completely stable to highly unstable.

3.5.4 NUCLEOPHILIC ATTACK ON RING HETEROATOMS

Nucleophilic attack on ring heteroatoms is found most often in two situations: (1) where the heteroatom in question is sulfur, and (2) in small rings with two heteroatoms. For examples of the former, see CHEC 5.14.3.5.2 and CHEC 5.06.3.4. Oxaziridines are attacked on oxygen when bulky ring substituents are present, otherwise the nitrogen is attacked, resulting in nitrogen transfer and the formation of a carbonyl compound (CHEC 5.08.3.1.4), while the ring carbon is altogether inert toward nucleophilic attack.

3.5.5 NUCLEOPHILIC ATTACK ON RING CARBON ATOMS

The ring opening of small heterocycles by nucleophilic attack on a carbon adjacent to a heteroatom is exceedingly common. Only in oxaziridines is the ring carbon inert relative to the two ring heteroatoms (CHEC 5.08.3.1.4). In the other three-membered rings, nucleophilic ring opening leads to the corresponding heteroanion or to the XH compound, according as to whether the heteroatom is being protonated before or concurrently with the ring opening respectively. The reaction can be stereospecific in any of these cases. Alternatively, ring opening can occur before the nucleophilic attack, either after protonation of the heteroatom (to give a carbocation), or due to ylide formation. In the latter cases the reactions become non-stereospecific or partially stereospecific, depending on the timing of the processes involved.

3.5.5.1 Reactions of Three-membered Rings

The three-membered rings containing one heteroatom, because of ring strain, are much more reactive than normal ethers, sulfides and amines. Under basic or neutral conditions ring fission takes place preferentially at the least substituted carbon and is accompanied by inversion, *i.e.* S_N2 type); under acid conditions these rules do not always apply because of increasing S_N1 character.

The reactions of these heterocyclic systems include those initiated by the following reagents:

(i) Hydroxide ions: oxiranes→glycols, aziridines→amino alcohols.

(ii) Amines: oxiranes→amino alcohols, aziridines→diamines.

(iii) Hydrogen halides: oxiranes→halohydrins, thiiranes→mercaptohalides, aziridines→halo amines.

(iv) Grignard reagents: oxiranes→alcohols, *e.g.* $C_2H_4O + RMgBr \rightarrow RCH_2CH_2OH$.

(v) Catalytic amounts of either a nucleophilic or an electrophilic reagent can induce polymerization; ring fission occurs first, and the ring fission product reacts with additional molecules of the cyclic starting material giving dimers or high polymers, *e.g.* $\cdots CH_2CH_2—Z—CH_2CH_2—Z—CH_2CH_2\cdots$).

3.5.5.2 Reactions of Four-membered Rings

The properties of azetidine, oxetane and thietane are intermediate between those of aliphatic amines, ethers and sulfides on the one hand and those of the corresponding three-membered ring systems on the other. Ring fission occurs quite readily. Oxetane reacts with Grignard reagents to give alcohols of type $R(CH_2)_3OH$ and with hydrogen bromide to give 1,3-dibromopropane. Hydrogen halides convert azetidine into γ-halo amines.

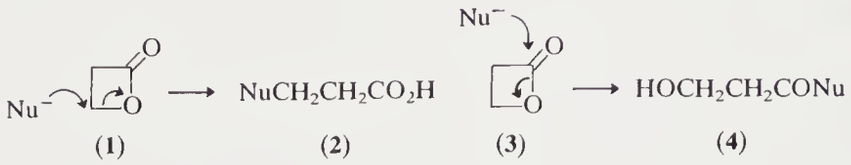
3.5.5.3 Reactions of Carbonyl Derivatives of Four-membered Rings

2-Oxetanones (β-lactones) are readily attacked by nucleophilic reagents. Reaction can occur by:

(i) Alkyl–oxy fission (**1**→**2**), *e.g.* propiolactone with $NaOAc–H_2O$ yields (**2**; Nu = OAc), with MeOH–NaOMe it forms (**2**; Nu = OMe).

(ii) Acyl–oxy fission (**3**→**4**), *e.g.* propiolactone reacts with $MeOH–H^+$ to give (**4**; Nu = OMe).

The reaction of 2-azetidinones (β-lactams) with nucleophilic reagents is accompanied by acyl–nitrogen fission, as is normal for amides (*cf.* **3**→**4**), *e.g.* propiolactam yields β-alanine ($NH_2CH_2CH_2CO_2H$) on hydrolysis.



(1) (2) (3) (4)

3.5.5.4 Large Rings

Nucleophilic attack on ring atoms of large heterocycles is largely confined to saturated systems, saturated parts of partially unsaturated systems, and to carbonyl functions and the like. These reactions are not fundamentally different from those of corresponding acyclic systems, except for transannular reactions.

Transannular nucleophilic attack on ring atoms is best known in systems with seven or more ring members. For example, nucleophilic attack by the ring nitrogen on suitably substituted ring carbons in the 3- or 4-position in azepine derivatives has been studied (CHEC 5.16.3.5.2). However, transannular nucleophilic attack can be found already in four-membered heterocycles. The nitrogen of *N*-*t*-butyl-3-chloroazetidine is, because of the puckered conformation, close enough to the 3-carbon to displace chloride. This, in turn, opens the azabicyclobutanonium ion to give *N*-*t*-butyl-2-chloromethylaziridine ⟨B-77SH(1)38⟩.

In systems of proper geometry, nucleophiles within a side chain may be well connected for attack on ring atoms. For example, an aminomethyl group at the 5-position of a dibenzazepin-2-one was found to attack the carbonyl group (CHEC 5.16.3.5.2). Such reactions should be possible in rings of any size.

Apparent nucleophilic attack on large, fully unsaturated rings may occur by way of attack on a valence tautomer, such as the reaction of oxepin with azide ion. Attack on the oxanorcaradiene valence tautomer leads to ring opening of the three-membered ring, and formation of 5-azido-6-hydroxy-1,3-cyclohexadiene (CHEC 5.17.2.2.4).

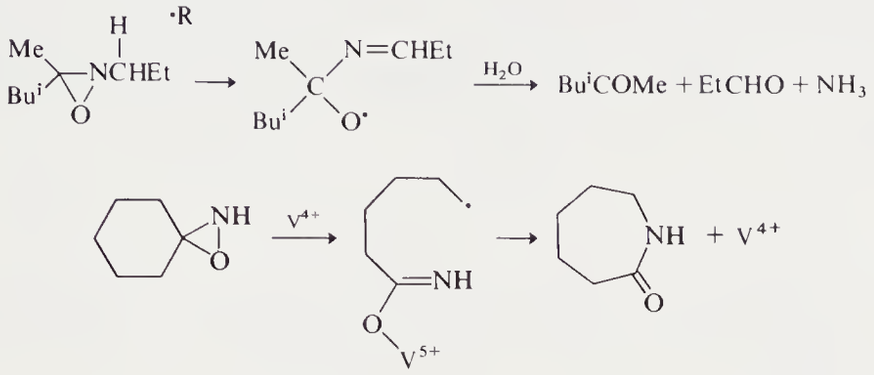
3.5.6 NUCLEOPHILIC ATTACK ON PROTONS ATTACHED TO RING ATOMS

The formation of anions by proton abstraction leads to a very diversified sort of reactions in small and large heterocycles. However, a few rules do generally apply. In the absence of complicating substituents, nitrogen anions can often be formed from small and large heterocycles, and subsequent alkylation, acylation, *etc.* can be achieved ⟨B-76MI50200, 64HC(19-2)886⟩ (CHEC 5.15.2.3). The N-anions of large rings are usually unexceptional (barring transannular reaction). N-Anions of unsaturated large heterocycles are obtained with difficulty, but they are synthetically useful in the azepine field (CHEC 5.16.3.6).

Proton abstraction from ring carbons of small and large heterocycles often leads to ring opening. Oxiranes, for example, are usually converted to carbenes under conditions under which a carbanion is formed, with a few exceptions such as the synthetically useful 2-triphenylsilyl-2-lithiooxirane (CHEC 5.05.3.5). Likewise, oxaziridines can be opened by nucleophilic attack on a hydrogen at carbon-3 ⟨82JOC419⟩ (CHEC 5.08.3.1.4). Thiirane and thiirene 1,1-dioxides give cyclic carbanions, which are easily ring opened (CHEC 5.06.3.6). Large heterocyclics offer a greater variety for ring opening, such as the abstraction of protons from not only the 2- but also the 3-position, leading to ring opening by β-elimination and the formation of ω-unsaturated compounds, such as 6-hydroxy-1-hexene from oxepane (CHEC 5.17.2.1.4).

3.5.7 ATTACK BY RADICALS OR ELECTRON-DEFICIENT SPECIES

Surprisingly little is known about the attack of radicals on small and large heterocycles. Hydrogen abstraction from the heteroatom of small rings leads to ring opening, and in the case of thiiranes to removal of the sulfur (*cf.* Section 3.5.1.4 above). Abstraction of H· exocyclic and α to nitrogen in oxiranes leads to N—O cleavage, and the reaction of vanadium(IV) with the oxygen of 1-oxa-2-azaspiro[2.5]octane gives N—O cleavage and ring expansion to caprolactam (Scheme 15; CHEC 5.08.3.1.5).



Scheme 15

Oxiranes and aziridines are reduced to alcohols and amines, respectively, for example by Ni/H_2, $Zn-NH_4Cl$, P–I, Al–Hg. Thiiranes are desulfurized by radicals (H·, S·), by singlet carbenes and by electrolysis (CHEC 5.06.3.7.1).

Azetidine derivatives, which are less strained, are less sensitive and removal of a hydrogen in the α-position of a substituent on nitrogen does not necessarily lead to ring opening (CHEC 5.09.3.2.5). Thietane rings are opened by radicals attacking on S, while the less strained thiolanes are attacked by hydrogen abstraction at a 2-carbon (CHEC 5.14.3.10.1). In thietane 1,1-dioxides, radicals abstract a hydrogen from the 3-position to give a cyclic radical (CHEC 5.14.3.10.1). Producing radicals exocyclic in the α-position of *N*-substituents of azetidin-2-ones did not result in ring opening (CHEC 5.09.3.2.5).

Saturated large rings may form nitrogen radicals by H abstraction from N, or abstraction may occur in the α- or β-positions in non-nitrogen systems. Oxepane gives the radical in the 2-position, with subsequent cleavage and reclosure of the intermediate carbenoid to cyclohexanol (CHEC 5.17.2.1.5). In unsaturated large systems a variety of reactions, unexceptional in their nature, are found. Some azepines can be brominated by *N*-bromosuccinimide; others decompose under similar conditions (CHEC 5.16.3.7).

Electron-deficient species can attack the unshared electron pairs of heteroatoms, to form ylides, such as in the reaction of thietane with bis(methoxycarbonyl)carbene. The $S^+—C^-$ ylide rearranges to 2,2-bis(methoxycarbonyl)thiolane (CHEC 5.14.3.10.1). *N*-Ethoxycarbonylazepine, however, is attacked by dichlorocarbene at the C=C double bonds, with formation of the *trans* tris-homo compound (CHEC 5.16.3.7).

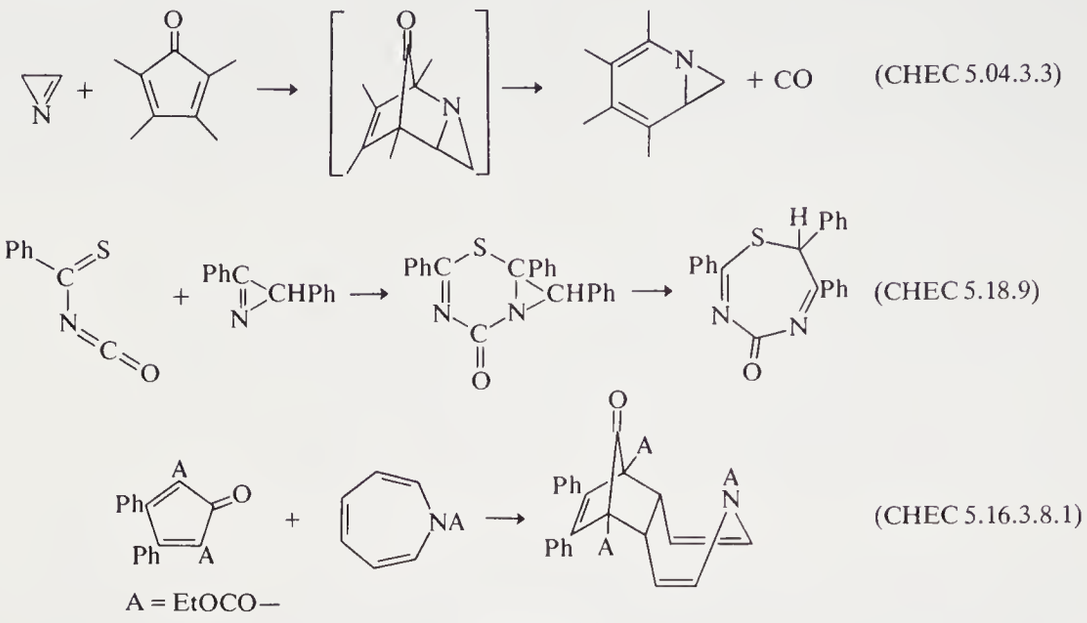
3.5.8 REACTIONS WITH CYCLIC TRANSITION STATES

Concerted cycloadditions are observed with heterocycles of all ring sizes. The heterocycles can react directly, or *via* a valence tautomer, and they can utilize all or just a part of unsaturated moieties in their rings. With three-membered rings, ylides are common reactive valence tautomers. Open chain 4π-systems are observed as intermediates with four-membered rings, and bicyclic valence tautomers are commonly reactive species in additions by large rings. Very often these reactive valence tautomers are formed under orbital symmetry control, by both thermal and photochemical routes.

3.5.8.1 [2 + 4] Cycloadditions

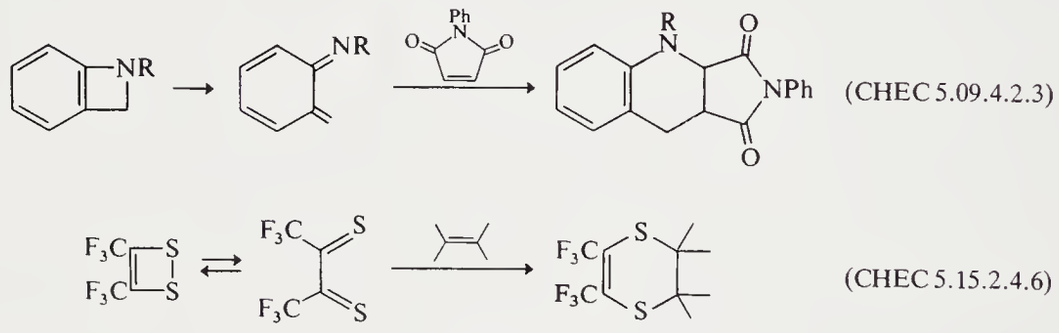
The participation of a single double bond of a heterocycle is found in additions of small and large rings; azirines (CHEC 5.04.3.3) and thietes (CHEC 5.14.3.11) furnish examples. Azepines and

non-aromatic heteronins react in this mode, especially with electron-deficient dienes (Scheme 16; CHEC 5.16.3.8.1).

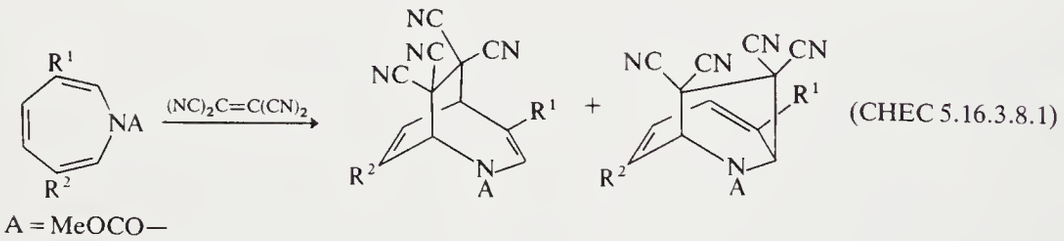


Scheme 16

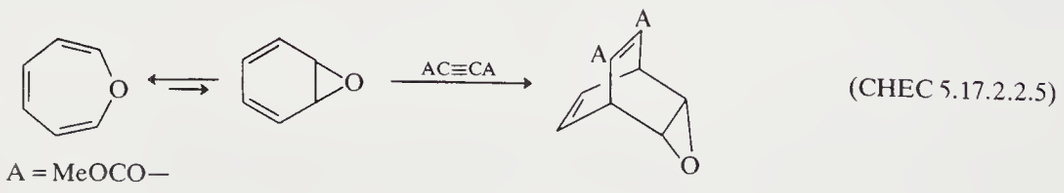
Diene moieties, reactive in [2 + 4] additions, can be formed from benzazetines by ring opening to azaxylylenes (CHEC 5.09.4.2.3). 3,4-Bis(trifluoromethyl)-1,2-dithietene is in equilibrium with hexafluorobutane-2,3-dithione, which adds alkenes to form 2,3-bis(trifluoromethyl)-1,4-dithiins (Scheme 17; CHEC 5.15.2.4.6). Systems with more than two conjugated double bonds can react by [6π + 2π] processes, which in azepines can compete with the [4π + 2π] reaction (Scheme 18; CHEC 5.16.3.8.1). Oxepins prefer to react as 4π components, through their oxanorcaradiene isomer, in which the 4π-system is nearly planar (CHEC 5.17.2.2.5). Thiepins behave similarly (CHEC 5.17.2.4.4). Non-aromatic heteronins also react in orbital symmetry-controlled [4 + 2] and [8 + 2] cycloadditions (Scheme 19; CHEC 5.20.3.2.2).



Scheme 17



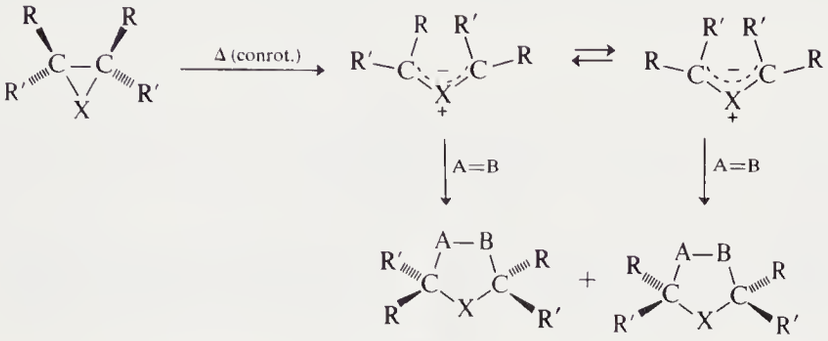
Scheme 18



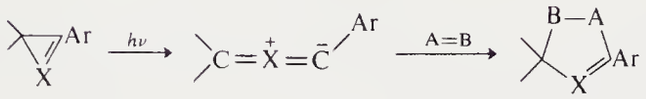
Scheme 19

3.5.8.2 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloadditions in which the heterocycle provides the 1,3-dipole are common with three-membered rings, which can provide ylide intermediates, as has been mentioned above. Ylide formation is usually orbital symmetry-controlled, and may be achieved by thermolysis or photolysis, with the expected stereochemical consequences. Rotation about one of the ylide C—X bonds results in loss of the original stereochemistry. These interconversions often are slow compared to the cycloaddition reactions of the ylides, so that partial stereospecificity is observed. Scheme 20 gives a generalized reaction. Extensive work has been done with aziridines (CHEC 5.04.3.1). Diaziridines behave similarly (CHEC 5.08.3.2.2) ⟨79AHC(24)63⟩. Azirines produce nitrile ylides upon photolysis (Scheme 21; CHEC 5.04.3.2). Examples for oxiranes and thiiranes are found in the corresponding monograph chapters (CHEC 5.05.3.2.1 and 5.06.3.8).



Scheme 20



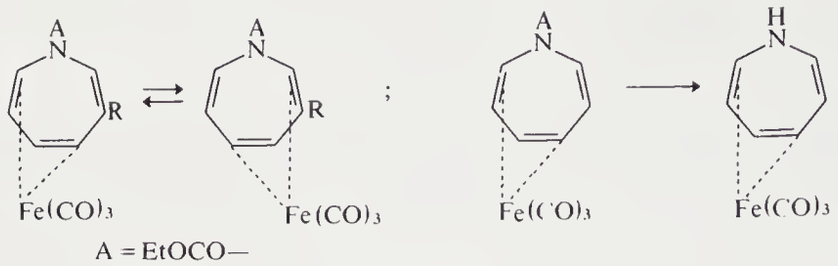
Scheme 21

Heterocyclics of all sizes, as long as they are unsaturated, can serve as dipolarophiles and add to external 1,3-dipoles. Examples involving small rings are not numerous. Thiirene oxides add 1,3-dipoles, such as diazomethane, with subsequent loss of the sulfur moiety (CHEC 5.06.3.8). As one would expect, unsaturated large heterocyclics readily provide the two-atom component for 1,3-dipolar cycloadditions, *e.g.* azepines and thiepins.

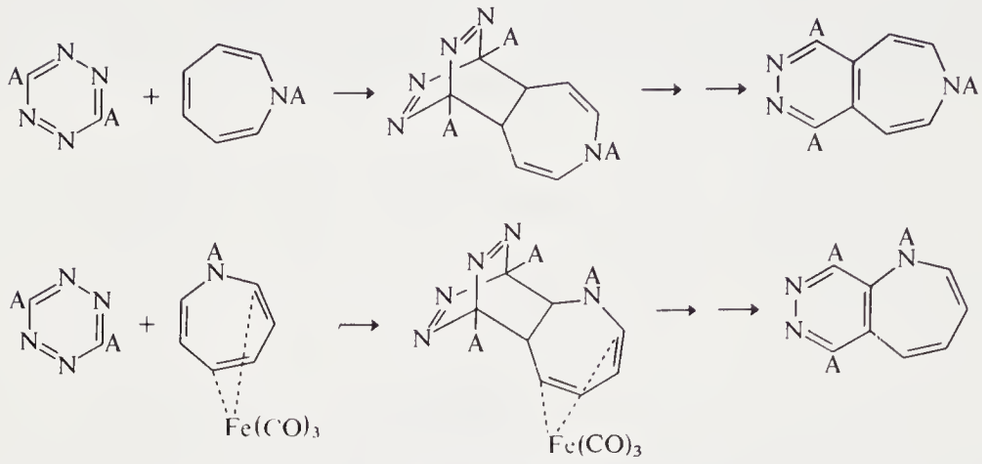
3.5.9 REACTIVITY OF TRANSITION METAL COMPLEXES

Metal complexes of heterocyclics display reactivities changed greatly from those of the uncomplexed parent systems. All of the π-electron system(s) of the parent heterocycle can be tied up in the complex formation, or part can be left to do 'alkenic' reactions. The system may be greatly stabilized in the complex so that reactions, on a heteroatom for example, can be performed which the parent itself would not survive. Orbital energy levels may be split and symmetries changed, allowing hitherto forbidden reactions to occur. In short, a multitude of new reaction modes may be made possible by using complexes. Since decomplexing is usually practically possible, a great many applications seem to await realization. So far the number of examples is limited and is dispersed in the literature, but some background is available ⟨78JHC1057, 81ACR348, 71JA1123⟩. The chemistry of azepines (CHEC 5.16.3.8.1 and 5.16.3.8.2) and diazepines (CHEC 5.18.2) ⟨78JHC1057, 81ACR348⟩ provides examples.

1*H*-Azepine derivatives form a diene complex with tricarbonyliron, leaving uncomplexed the third of the double bonds. If the 3-position is substituted, two different such complexes are possible, and are in equilibrium, as seen in the ^{1}H NMR spectrum. An ester group in the 1-position of the complex can be removed by hydrolysis, to give an NH compound which, in contrast to the free 1*H*-azepine, is stable. The 1-position can then be derivatized in the manner usual for amines (Scheme 22). The same tricarbonyliron complex can, by virtue of the uncomplexed 2,3-double bond, serve as the dienophile with 1,2,4,5-tetrazines. The uncomplexed *N*-ethoxycarbonylazepine also adds the tetrazine, but to the 5,6-double bond. Thus, two isomeric adducts can be synthesized by using or not using the complex (Scheme 23; CHEC 5.16.3.8.1).



Scheme 22



Scheme 23

Tricarbonyliron complexes of 1,2-diazepines do not show the rapid isomerization found in their azepine counterparts (Scheme 22); the iron forms a diene complex with the C=C double bonds in the 4- and 6-positions. The chemistry of the 1,2-diazepine complexes is similar to that of the azepine complexes (CHEC 5.18.2.1) ⟨81ACR348⟩.

Oxepin also forms a diene complex with tricarbonyliron ⟨78JHC1057⟩.

Part 4
Synthesis of Heterocycles

4.1
Overview

4.1.1 AIMS AND ORGANIZATION

The main aim of this part of the book is to provide an introduction to the most efficient ways of making a heterocyclic compound, either by using a known method, or by analogy with existing methods for related compounds. The organization is in accordance with this aim.

The synthesis of a heterocyclic compound can be divided into two parts: ring synthesis, and substituent introduction and modification. The relative importance of the two parts can vary in all proportions, and does vary in a non-random manner for different classes of heterocycles.

The following features generally render the ring synthesis steps of increasing importance relative to substituent modification:

(i) increasing number of heteroatoms;
(ii) increasing number of fused rings;
(iii) decreasing number of endocyclic double bonds.

Substituent modification is based on substituent reactivity as outlined in the reactivity chapters; brief summaries of the scope and limitations of substituent introduction and modification are given for the following important ring systems as they are dealt with:

(i) pyrroles, furans and thiophenes (Section 4.2.3.2);
(ii) pyridines (Section 4.2.4.1);
(iii) azoles (Section 4.3.1.2);
(iv) azines (Section 4.3.1.3);
(v) benzo-fused heterocycles (Section 4.4.1).

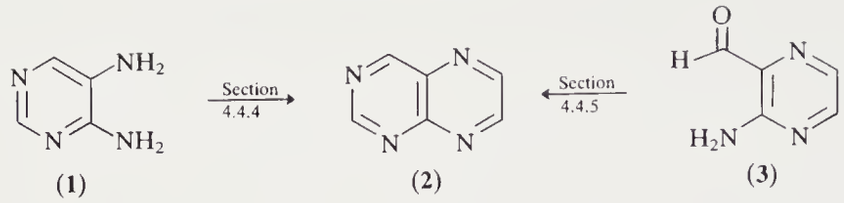
In classifying ring syntheses we believe that it is important to group syntheses as follows: (i) those of related classes of compounds, (ii) those from similar precursors and (iii) methods related mechanistically. The system adopted herein attempts to achieve these (not always completely compatible) aims as far as possible.

The synthesis of ring-fused systems is almost always effected sequentially, *i.e.* a bicyclic ring system is formed by the annelation of a second ring on a monocyclic compound (typified by a substituted benzene). (Intramolecular cycloadditions form an important exception to this generalization.) Thus we subdivide ring syntheses first into those leading to monocyclic and those forming polycyclic compounds. This division is not a rigid one. It applies principally to cases where the preformed ring of a bicyclic system is *aromatic*: thus syntheses of benzimidazoles, for example, are treated separately from those of imidazoles. However, the methods of synthesis of 4,5,6,7-tetrahydrobenzimidazole would show closer analogies to those of 4,5-dimethylimidazole than to those of benzimidazole. Similarly, spiro ring systems are considered with their monocyclic analogues.

Ring-fused systems with ring junction N- or S-atoms are considered separately from their more numerous analogues with only C-atoms at the ring junctions because of considerable differences in the synthetic methods employed.

Mono-, bi- and tri-cyclic systems are further classified firstly according to the number and orientation of their heteroatoms and secondly by the degree of unsaturation in the system. Hence the classification is *not* primarily by ring size, and this enables many related synthetic methods to be discussed together.

In the case of ring-fused systems containing two or more heterocyclic rings, synthetic methods are classified according to the ring being formed. This means that pteridine syntheses are placed in different sections according to routes (**1**)→(**2**) or (**3**)→(**2**).



(1) (2) (3)

The system just outlined is that adopted in Chapters 4.2–4.5. The remainder of the present chapter, Sections 4.1.2–4.1.4, now reviews the main types of mechanistic classes of reaction used in the preparation of heterocyclic rings.

4.1.2 RING FORMATION FROM TWO COMPONENTS

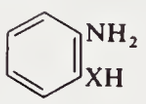
4.1.2.1 By Reaction Between Electrophilic and Nucleophilic Carbons

Reactions of this type can occur either between a binucleophile and a bielectrophile, or between two molecules each containing both a nucleophilic and an electrophilic center, *e.g.* $HSCH_2CO_2H$.

Rings of many sizes can be made by this approach. Thus, reaction of a 1,2-binucleophile with a 1,3-bielectrophile leads to a five-membered heterocycle, as would the reaction of a 1,4-binucleophile with a 1,1-bielectrophile.

Table 1 lists some of the common binucleophiles utilized in heterocyclic synthesis, the numerical prefixes referring to the positions of the nucleophilic centers relative to each other. Higher order binucleophiles, *e.g.* 1,5-systems, are analogous.

Table 1 Some Examples of Commonly Encountered Binucleophiles

1,2-Systems	*1,2-Systems*	*1,3-Systems*	*1,3-Systems*	*1,4-Systems*	*1,4-Systems*
H_2NNH_2	H_2NOH	$RC(=S)NH_2$	$RC(=NH)NH_2$	$H_2N(CH_2)_2NH_2$	$RC(=S)NHNH_2$
RNHNHR	RNHOH	$RC(=S)NHR$	$RC(=NH)NHR$	$H_2N(CH_2)_2OH$	$RC(=Se)NHNH_2$
H_2NNR_2	R_2NOH	$RC(=Se)NH_2$	$H_2NC(=NH)NH_2$	$H_2N(CH_2)_2SH$	$RC(=NH)NHNH_2$
$RNHNR_2$	$RCH{=}NNH_2$	$RC(=Se)NHR$	$H_2NC(=S)NH_2$		$RC(=NH)NHOH$
	$RCH{=}NOH$		$H_2NC(=Se)NH_2$		$H_2NC(=S)NHNH_2$

4.1.2.2 Ring Formation *via* Cycloaddition

Three reactions are of great importance: [2 + 2] cycloaddition, 1,3-dipolar cycloaddition and Diels–Alder reactions ([4 + 2] cycloadditions), which lead to four-, five- and six-membered rings, respectively. [3 + 3] Cycloadditions are known (see Section 4.3.8.2) but are of less importance.

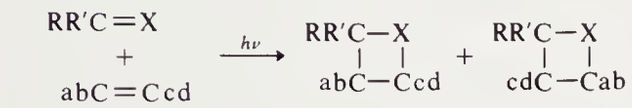
4.1.2.2.1 [2 + 2] Cycloadditions

Concerted thermal [2 + 2] cycloadditions forming heterocycles have been reviewed ⟨77AHC(21)245⟩ and cross references to some examples discussed in the present book are given in Table 2.

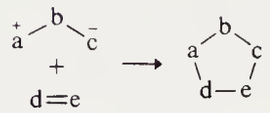
Table 2 Four-membered Heterocyclic Rings from [2 + 2] Cycloaddition Reactions

Heteroatom position(s)	*Section*	*Precursors with heteroatom(s)*
1	4.2.1.1.2	C=O, C=S
1,2	4.3.2.2.1	N=N
1,2	4.3.2.2.2	N=O
1,2	4.3.2.2.4	O=O
1,2	4.3.2.2.5	S=O
1,3	4.3.3.1.3	C=S, C=N

The Woodward–Hoffmann rules predict high activation energies for the suprafacial–suprafacial addition of two carbon–carbon double bonds. However, polar effects may lower these ⟨74AF(3)751⟩. [2 + 2] Photocycloadditions are common and usually involve diradical intermediates: photo-excited ketones react with a variety of unsaturated systems (Scheme 1). Both the singlet and the triplet (n, π^*) excited states of the ketones will form oxetanes with electron-rich alkenes. With electron-deficient alkenes only the singlet states give oxetanes. Diradicals are the immediate precursors to the oxetanes in all cases, but the diradicals are formed by different mechanisms, depending on the availability of electrons in the two components.



Scheme 1



Scheme 2 A 1,3-dipolar cycloaddition reaction

4.1.2.2.2 1,3-Dipolar cycloadditions

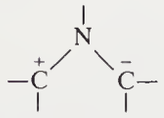
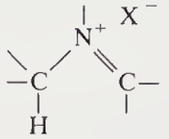
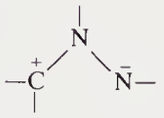
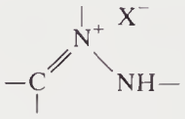
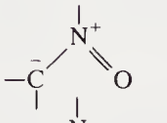
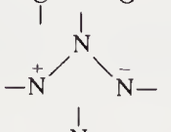
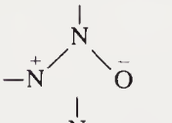
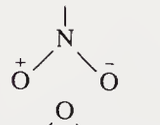
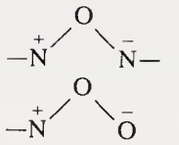
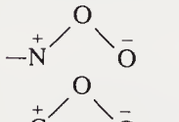
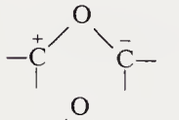
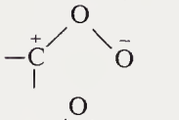
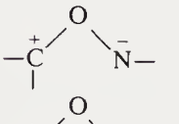
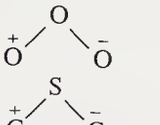
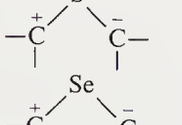
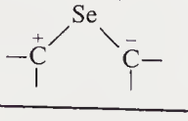
This synthesis of a variety of five-membered heterocycles involves the reaction of a neutral four-π-electron–three-atom system, the dipole, with a two-π-electron system, the dipolarophile (Scheme 2). Table 3 illustrates 1,3-dipoles with a double bond and with internal octet stabilization, the propargyl–allenyl anion type.

Table 3 1,3-Dipoles with a Double Bond and Internal Octet Stabilization; Propargyl-allenyl Anion type

Nitrile ylide	$-\overset{+}{C}=N-\overset{-}{C}\diagup\diagdown \leftrightarrow -C\equiv\overset{+}{N}-\overset{-}{C}\diagup\diagdown$	*in situ* from $-\underset{Cl}{C}=N-CH\diagup\diagdown$
Nitrile imine	$-\overset{+}{C}=N-\overset{-}{N}- \leftrightarrow -C\equiv\overset{+}{N}-\overset{-}{N}-$	*in situ* from $-\underset{Cl}{C}=N-NH-$
Nitrile oxide	$-\overset{+}{C}=N-\overset{-}{O} \leftrightarrow -C\equiv\overset{+}{N}-\overset{-}{O}$	*in situ* from $-\underset{Cl}{C}=NOH$
Nitrile sulfide	$-\overset{+}{C}=N-\overset{-}{S} \leftrightarrow -C\equiv\overset{+}{N}-\overset{-}{S}$	Thermal fragmentation of an oxathiazolone
Diazoalkane	$\diagdown\overset{+}{C}-N=\overset{-}{N} \leftrightarrow \diagdown C=\overset{+}{N}=\overset{-}{N}$	Usually stable
Azide	$-\overset{+}{N}-N=\overset{-}{N} \leftrightarrow -N=\overset{+}{N}=\overset{-}{N}$	Usually stable
Nitrous oxide	$\overset{+}{N}=N-\overset{-}{O} \leftrightarrow N\equiv\overset{+}{N}-\overset{-}{O}$	Stable

1,3-Dipoles without a double bond but with internal octet stabilization, the allyl anion type, are shown in Table 4. 1,3-Dipoles without octet stabilization, such as vinylcarbenes and iminonitrenes, are all highly reactive intermediates with only transient existence.

Table 4 1,3-Dipoles Without a Double Bond but With Internal Octet Stabilization; Allyl Anion Type

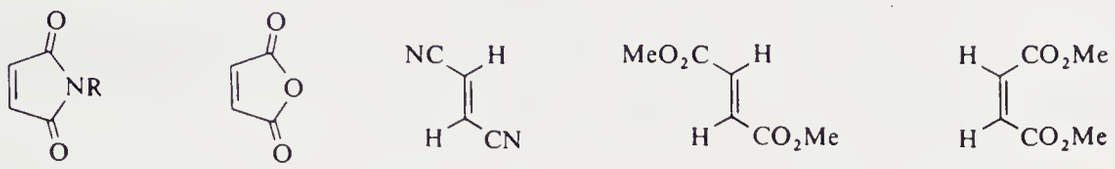
Azomethine ylide		*in situ* from  or aziridines
Azomethine imine		*in situ* from 
Nitrone		Stable
Azimine		From heterocycles
Azoxy compound		Stable
Nitro compound		Stable
Nitroso imine		
Nitroso oxide		
Carbonyl ylide		From oxiranes or heterocycles
Carbonyl oxide		From carbene + O_2
Carbonyl imine		
Ozone		Stable
Thiocarbonyl ylide		From heterocycles
Selenocarbonyl ylide		From heterocycles

Dipolarophiles utilized in these cycloadditons leading to five-membered heterocycles contain either double or triple bonds between two carbon atoms, a carbon atom and a heteroatom, or two heteroatoms. These are shown in Scheme 3 listed in approximate order of decreasing activity from left to right.

Alkynic dipolarophiles

$NCC{\equiv}CCN$, $CF_3C{\equiv}CCF_3$, $RO_2CC{\equiv}CCO_2R$, benzyne, $R^1COC{\equiv}CCOR$, $HC{\equiv}CCO_2R$, $R^2C{\equiv}CCO_2R$, $R^2C{\equiv}CR^2$, $R^2C{\equiv}CH$ (R = Me, Et; R^1 = alkyl, aryl; R^2 = aryl, heteroaryl)

Alkenic dipolarophiles



R = Me, Et, Ph

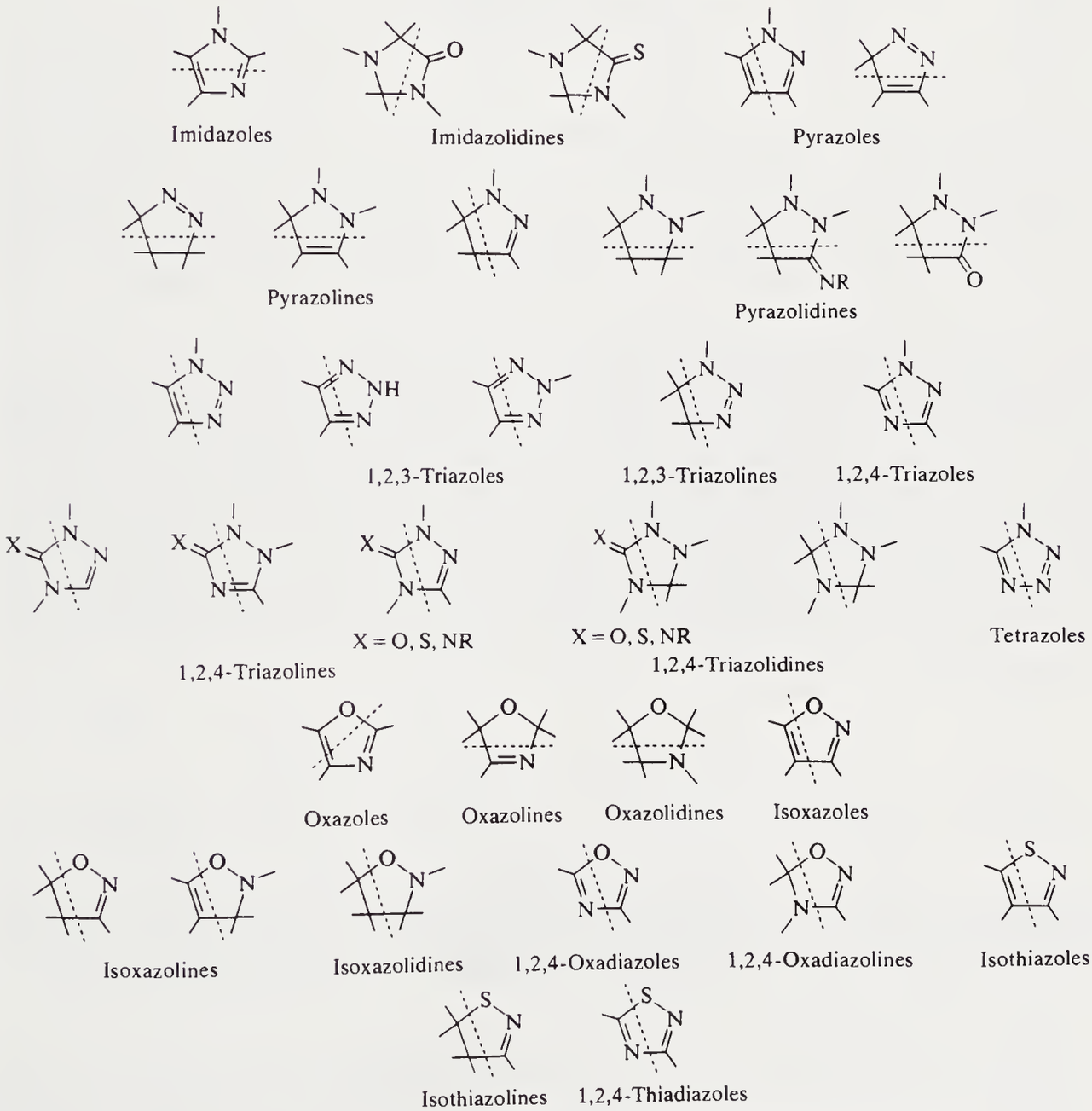
$CH_2{=}CHCN$, $CH_2{=}CHCOMe$, $CH_2{=}CHCO_2Et$, $CH_2{=}CMeCO_2Me$, $EtO_2CN{=}NCO_2Et$, $PhCH{=}CHNO_2$, $PhCCl{=}CHNO_2$, $PhCH{=}CH_2$, $PhCH{=}CHPh$

Heterocumulenes

R^1CONCO, R^1CONCS, RNCO, RNCS

R^1 = aryl, CCl_3; R = alkyl, aryl

Scheme 3 Frequently used dipolarophiles



Scheme 4 Some five-membered ring systems available by 1,3-dipolar cycloadditions

Several five-membered ring systems readily available by 1,3-dipolar cycloadditions are shown in Scheme 4. The dotted line indicates how the system was constructed, the line bisecting the two new bonds being formed in the cycloaddition.

4.1.2.2.3 Diels–Alder reactions

One or several heteroatoms can be introduced into a six-membered ring from either the diene or the dienophile component of a Diels–Alder reaction. Table 5 gives examples of both these possibilities together with the section where the reaction is covered.

Table 5 Six-membered Heterocyclic Rings Prepared by Diels–Alder Reactions

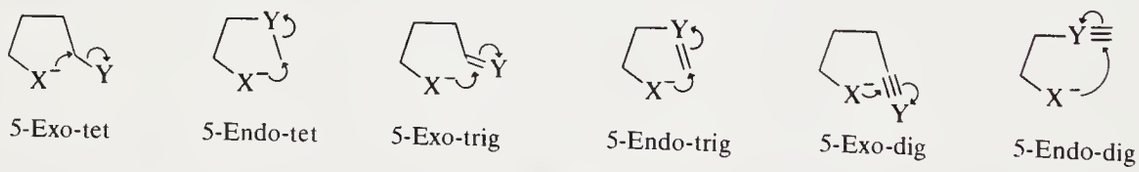
Type	*Heteroatom position(s)*	*Section*	*Heterodienes*	*Heterodienophiles*
Monocyclic	1	4.2.2.1	C=C—C=O, C=C—C=N	C=N, C=O, C=S
Monocyclic	1	4.2.4.3.1	1,2,4-Triazines	—
Monocyclic	1,2	4.3.2.3.2	—	N=N, N=O, O=O, N=S
Bicyclic	1	4.4.2.3.4	Ph—N=C	—
Bicyclic	1	4.4.2.3.5	Anthranils	—
Bicyclic	1	4.4.2.4	Benzazetes	—
Bicyclic	1,4	4.4.6.1	*o*-Benzoquinone diimine	—
Bicyclic	1,4	4.4.6.2	*o*-Nitrosophenol	—
Bicyclic	1,3,5	4.6.1	C=N—C=S	Azirine

4.1.3 RING CLOSURE OF A SINGLE COMPONENT

In general, syntheses in which a C—Z bond is formed in the last stages are more important for the preparation of monocyclic compounds, whereas those syntheses in which a C—C bond is formed in the last stage are important for the benzo derivatives. The ring closure may be of a chain containing a nucleophile and an electrophile at the ends, or homolytic, or electrocyclic.

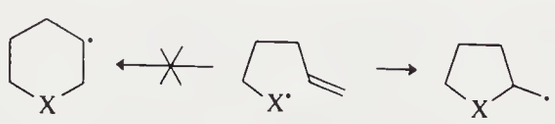
4.1.3.1 By Reaction between Electrophilic and Nucleophilic Centers

A set of guidelines predicts the facility of different ring closures ⟨76CC734⟩. For a process involving formation of a five-membered ring by nucleophilic attack of one terminal atom upon the other, the possibilities are shown in Scheme 5. The prefixes *exo* and *endo* indicate whether the breaking bond is exocyclic or endocyclic to the ring being formed. The suffixes refer to tetrahedral, trigonal and digonal carbon atoms, respectively. Of the cases indicated, those termed 5-endo-tet and 5-endo-trig are disfavored when X is a first-row element, in this case nitrogen or oxygen. These restrictions arise from the stereochemical requirements of the respective transition states, but these may not apply when atoms such as sulfur, selenium and tellurium are involved because of the larger atomic radii and bond distances. Thus, a 5-exo-trig ring closure involving sulfur has been observed ⟨76CC736⟩.

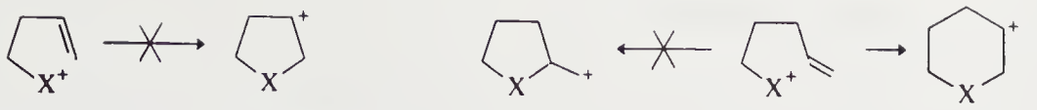


Scheme 5

Application of similar considerations to homolytic ring closures indicates that a 5-exo-trig closure will be preferred to a 6-endo-trig mode (Scheme 6) ⟨80CC482⟩. For cationic closures the 5-endo-trig mode is unknown in contrast to the well-established 6-endo-trig closure (Scheme 7).



Scheme 6



Scheme 7

The rules have been extended to rings of other sizes.

4.1.3.2 Electrocyclic Reactions

Electrocyclic ring closures are particularly important in the formation of six-membered rings: many are hetero analogues of the hexatriene–cyclohexadiene transformation (**4**→**5**) and can be considered as Cope rearrangements. As discussed in Section 3.2.1.6.1, they are frequently involved in ring interconversions initiated by nucleophilic attack on a six-membered ring. Further examples are discussed in Sections 4.2.3.5 (preparation of seven-membered rings) and 4.4.8.2.2.ii (formation of bicyclic 6,6 ring systems).

Photochemically initiated electrocyclizations can be used to form five-membered rings (*e.g.* Section 4.5.1.1.2.i).

The formation or rupture of ring bridges often involves electrocyclic reactions (*e.g.* Sections 4.4.4.1, 4.4.8.3.4 and 4.6.1).

4.1.3.3 By Radical, Carbene or Nitrene Intermediates

Representative examples of ring syntheses involving carbenoid (Table 6) or nitrenoid intermediates (Table 7) are given. In many cases, the free carbene or nitrene is probably not involved, and the distinction between insertion and addition reactions given in the table is not always clear cut. Such reactions are particularly useful for the preparation of tricyclic compounds.

Table 6 Heterocyclic Rings Prepared from Carbenoid Intermediates

Ring size	*Heteroatom position(s)*	*No. of rings*	*Section*	*Carbene precursor*	*Other reaction site*	*Reaction type*
3	1	1	4.2.1.1.1.iii	CH_2N_2	C=O, C=S, $C=N^+$	Addition
6	1,2	3	4.4.4.4	$RC\equiv\overset{+}{N}-\bar{N}R'$	C=C	Addition
5	1	3	4.5.1.1.4	RNC	Benzene ring	Insertion

Table 7 Heterocyclic Rings Prepared from Nitrenoid Intermediates

Ring size	*Heteroatom position(s)*	*No. of rings*	*Section*	*Nitrenoid precursor(s)*	*Other reaction site*	*Reaction type*
3	1	1	4.2.1.1.1.ii	RN_3, $R_2S^+NH^-$	C=C	Addition
3	1,2	1	4.3.2.1	NH_2OSO_3H	C=N	Addition
5	1,3	2	4.4.5.1.2	Tetrazole, oxadiazole	Benzene ring	Insertion
5	1	3	4.5.1.1.2.iii	Benzotriazole, pyridotriazole	Benzene ring	Insertion
5	1	3	4.5.1.1.3	RNO_2, RN_3	Benzene ring	Insertion
6	1	3	4.5.1.2	RN_3	CH_3	Insertion
6	1,2	3	4.5.2	RN_3	N=O	Addition
6	1,4	3	4.5.4.2	RNO_2	Benzene ring	Insertion
5	1,2,3	4	4.6.4.1	RN_3	N	Addition

4.1.3.4 By Intramolecular Cycloadditions

An intramolecular cycloaddition reaction results in the simultaneous formation of two new rings. Examples include the formation of an octahydroquinoline (Section 4.4.2.3.4) and a tetrahydrobenzo[*c*]pyrrole (Section 4.4.3.1) by intramolecular Diels–Alder reactions, and of a chromenopyrrole derivative by an intramolecular 1,3-dipolar cycloaddition (Section 4.5.1.2).

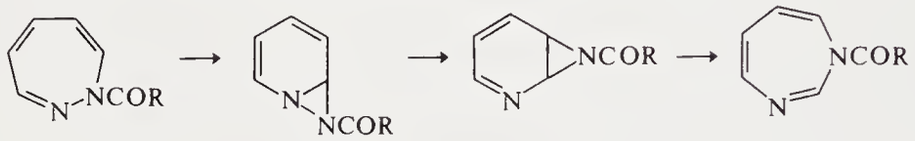
4.1.4 MODIFICATION OF AN EXISTING RING

The conversion of one heterocyclic ring into another is treated as a reaction of the initial compound in the appropriate reactivity section in Chapters 3.2–3.5 (for a review see ⟨B-73MI50300⟩). Here we present a brief overview.

4.1.4.1 Ring Atom Interchange

Such reactions are particularly important in the photochemical isomerization of five- (Sections 3.3.1.2 and 3.4.1.2) and six-membered rings (Section 3.2.1.2); however, they possess relatively little synthetic importance.

Reactions of this type are also implicated in the isomerization of large ring systems through bicyclic ones, *e.g.* the 1,2- to 1,3-diazepine conversion (Scheme 8) (CHEC 5.18.2.2).



Scheme 8

4.1.4.2 Incorporation of New Ring Atoms: No Change in Ring Size

Important reactions of this type include the replacement of a ring oxygen by a ring sulfur or nitrogen. Table 8 gives some examples and references to the section where they are discussed.

Table 8 Heterocyclic Ring Interconversions: No Change in Ring Size

Product ring size	*Product heteroatom position(s)*	*No. of rings*	*Section*	*Interconversion(s)*
3	1	1	4.2.1.5.2	Oxirane→thiirane; oxirane→aziridine
5	1	1	4.2.3.5.2	Furan→thiophene or pyrrole; oxazole or various mesoionics→furan, thiophene or pyrrole
6	1	1	4.2.3.5.2	α- or γ-Pyrone→α- or γ-pyridone
6	1	1	4.2.4.3.2	Pyrylium→pyridine, pyridinium, thiinium
5	1,2	1	4.3.2.2.4	1,2-Dithiolylium→pyrazole, isothiazole; isoxazole→pyrazole
6	1,3	1	4.3.3.3.3	1,3-Oxazine, 1,3-thiazine→pyrimidine; *s*-triazine→pyrimidines
5	1,2,4	1	4.3.6.1.3	Tetrazole→oxadiazole, thiadiazole, triazole
6	1,3,5	1	4.3.7.3	Pyrimidine, 1,3,5-oxadiazine→*s*-triazine
6	1,3	2	4.4.5.2.3	3,1-Benzoxazine and -benzothiazine→quinazolone

4.1.4.3 Ring Expansions

Examples treated in this book are summarized in Table 9. One frequently found type consists of ring expansions of cyclic conjugated systems with an exocyclic ylide function, such as pyridine *N*-oxides or *N*-imides; incorporation of the exocyclic half of the ylide function expands the ring by one member.

Table 9 Formation of New Heterocycle by Ring Expansion of Existing Heterocycle

Product ring size	*Product heteroatom position(s)*	*No. of rings*	*Section*	*Interconversion(s)*
4, 5, 6	1	1	4.2.1.5.1	Oxiranes→oxetanes, tetrahydrofurans; azirines→pyrrolidines; tetrahydrofurans→pyrans
5, 6	1	1	4.2.3.5.1	Oxiranes→dihydrofurans; azirine→pyrrole; diketene→pyrones; isoxazoles→pyridones
6	1	1	4.2.4.3.1	Furans→pyridines, pyrones
7	1	1	4.2.4.4	Bicyclic azirines and oxiranes→azepines, oxepins
6	1,2	1	4.3.2.3.3	Pyrrolidines→1,3-oxazines
7	1,3	1	4.3.3.4.2	Pyridine oxides, 1,3-oxaziniums, pyryliums→1,3-oxazepines
6	1,4	1	4.3.4.1.3	Aziridine→piperazine, pyrazines; oxiranes→1,4-dioxanes, 1,4-oxazines; thiiranes→1,4-dithianes
6	1,2,3	1	4.3.5.3	1,2-Dithioles→1,3,2-dithiazine
6	1	2	4.4.2.3.5	Indoles, isatins, anthranils→quinolines
7	1	2	4.4.4.4	Quinolines→benzodiazepine
6	1,3	2	4.4.5.2.3	Benzisoxazoles→1,3-benzoxazines
6	1,4	2	4.4.6.4	Benzofuroxans→quinoxalines
7	1,3,5	2	4.4.8.3.4	Quinoxalines→3,1,5-benzoxadiazepines
6	1,4	3	4.5.4.1	Benzofuroxans→phenazines
7	1,2	3	4.5.4.4	Acridines→dibenz[*c,f*][1,2]oxazepines

4.1.4.4 Ring Contractions

The isomerization of large rings into bicyclic systems by electrocyclic reaction has been mentioned (Section 4.1.3.2).

Other examples of ring contractions are given in Table 10. They fall into three main classes. The total loss of one or two (or sometimes more) ring members from the heterocycle, concerted with or followed by formation of a new ring, is a versatile synthetic method. Loss of N_2, CO, CO_2, S, SO, SO_2, $H_2C{=}CH_2$, *etc.* is common.

Table 10 Formation of New Heterocycle by Ring Contraction of Existing Heterocycle

Product ring size	*Product heteroatom position(s)*	*No. of rings in product*	*Section*	*Reaction types*
3–6	1	1	4.2.1.5.3	Loss of SO_2, C_2H_4; extrusion of C
5, 6	1	1	4.2.3.5.3	Extrusion of C
4	1,2	1	4.3.2.2.6	Loss of CO
5	1,2	1	4.3.2.3.4	Extrusion of C_2
5	1,2	1	4.3.6.1.3	Replacement of CO
4	1	2	4.4.2.1.2.ii	Loss of N_2
5	1	2	4.4.2.2.6	Extrusion of C (Wolff, Meerwein, *N*-oxide rearrangements)

The second major reaction type is the extrusion of one or more atoms from the ring to form a new substituent or side chain.

Finally the ring can react with another reagent to exchange two or three ring atoms for one or two provided by the reagent.

4.1.4.5 Ring Closure with Simultaneous Ring Opening

The generalized monocyclic rearrangement has been discussed in Section 3.4.3.1.9; it results in the conversion of one five-membered ring into another.

4.2

Synthesis of Monocyclic Rings with One Heteroatom

4.2.1 RINGS CONTAINING NO ENDOCYCLIC DOUBLE BONDS

For all the saturated monocycles with one heteroatom intramolecular nucleophilic displacement with the formation of C—Z bond(s) is an important preparative method (Sections 4.2.1.2.1–5).

Further significant synthetic routes for the various ring sizes are:

(i) for three-membered rings, electrocyclic addition to double bonds (Section 4.2.1.4);
(ii) for four-membered rings, [2 + 2] photocyclizations;
(iii) for five- and six-membered rings, formation of one C—C bond;
(iv) for six-membered and larger rings, ring expansion of carbocycles (Section 4.2.1.4).

4.2.1.1 From Acyclic Compounds by Concerted Formation of Two Bonds

4.2.1.1.1 Three-membered rings

(i) Oxiranes are formed by direct oxidation of alkenes with oxygen (catalytic) or peracids (*e.g.* $PhCO_3H-CHCl_3$ at 20 °C). This reaction is facilitated by alkylation of the C=C bond of the alkene and hindered by the presence of electron-withdrawing groups. Peracids commonly react stereospecifically — the formation of both bonds overlaps in time, and is followed by loss of carboxylate ion or carboxylic acid. Hydrogen bonding by groups attached to the alkene component steers the peracid to one or the other face of the alkenic double bond, in competition with solvent hydrogen bonding and non-bonding interactions in the activated complex.

Electron-deficient C=C double bonds are resistant to electrophilic attack, but are converted into oxiranes by nucleophilic oxidants such as HO_2^-.

Transition metal-catalyzed epoxidations, by peracids or peroxides, are complex and diverse in their reaction mechanisms (CHEC 5.05.4.2.2). The use of *t*-butyl hydroperoxide with titanium tetraisopropoxide in the presence of tartrates gave asymmetric epoxides of 90–95% optical purity ⟨80JA5974⟩.

(ii) Electrophilic nitrogen reagents attack alkenes. Nitrenes, R—N, add to alkenes stereospecifically if the nitrenes are in the singlet state and non-stereospecifically when they are in the triplet state to give aziridines.

Electrophilic nitrogen compounds, such as arenesulfonyloxyamines, can convert alkenes to aziridines without the intervention of free nitrenes ⟨80CC560⟩. The ylide $Ph_2S^+—\bar{N}H$ adds stereospecifically to *E* and *Z* conjugated alkenes, and chiral sulfimides can transfer chirality to the aziridines formed ⟨80T73⟩.

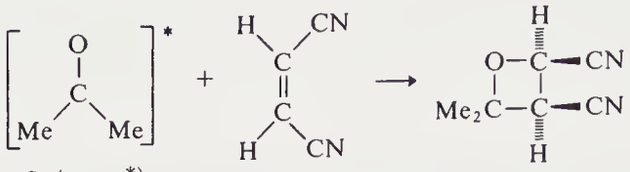
(iii) Thiiranes can be made from 'nascent sulfur', such as is obtained by the thermolysis of diethyl tetrasulfide ⟨64HC(19-1)591⟩.

(iv) The attack by the carbon of diazomethane on sp^2 carbons of carbonyl and thiocarbonyl groups and iminium ions, followed by loss of nitrogen, leads to the corresponding oxiranes, thiiranes and aziridines, respectively.

4.2.1.1.2 Four-membered rings

(i) Electron-deficient alkenes react with singlet $n\rightarrow\pi^*$ excited carbonyl compounds to give oxetanes (*e.g.* **1**), often with high stereospecificity. Isomerization of the alkene in the triplet

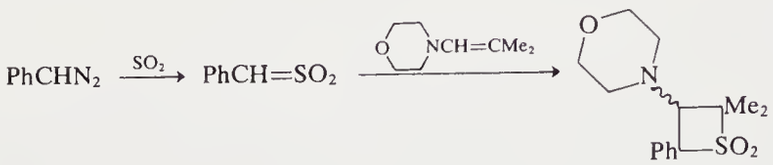
quenching process can destroy the stereochemical integrity.



$S_1 (n \rightarrow \pi^*)$

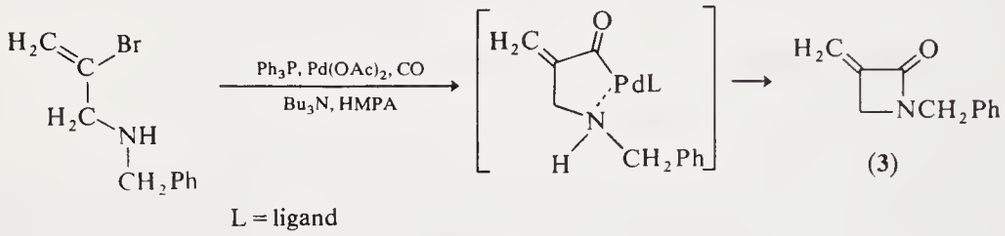
(1)

(ii) Thietanes are produced efficiently from [2 + 2] photocyclization of thiones to vinyl ethers and other alkenes (see CHEC 5.14.4.1.2). Sulfenes add to electron-rich alkenes to give thietane 1,1-dioxides, *e.g.* (**2**) ⟨77BCJ1179⟩.



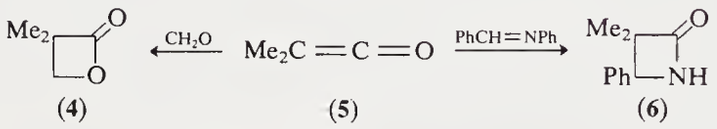
(**2**) 62%

(iii) 2-Azetidinones (**3**) are obtained from β-haloamines and CO with Pd catalysis (Scheme 1). They also result from the cycloaddition of imines to ketenes, *e.g.* (**5**)→(**6**).



L = ligand

Scheme 1

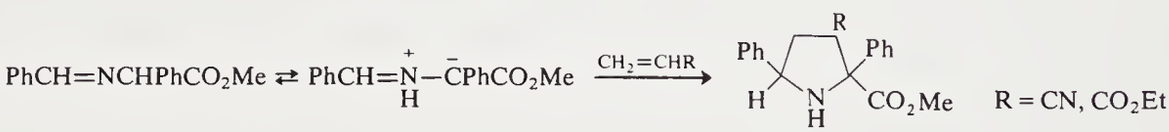


(**4**) (**5**) (**6**)

(iv) 2-Oxetanones (β-lactones) are also conveniently prepared from ketenes (**5**→**4**).

4.2.1.1.3 Five-membered rings

Appropriate *N*-alkylimines undergo cycloadditions through their azomethine ylide tautomers (Scheme 2) ⟨78CC109, 78TL2885, 84JCS(P1)41⟩.



Scheme 2

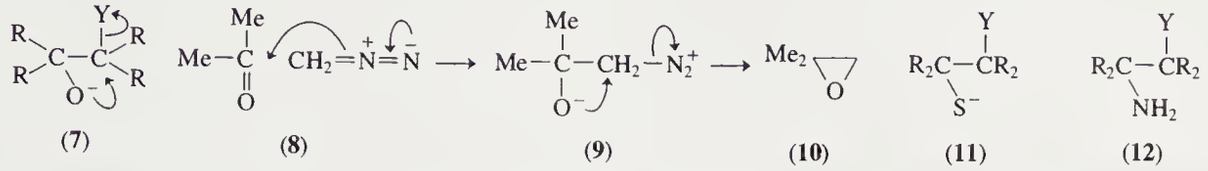
4.2.1.2 From Acyclic Compounds by Formation of One or Two C—Z Bonds

4.2.1.2.1 Three-membered rings

(i) Oxiranes are formed by the action of alkali on β-hydroxy-halides (**7**; Y = Br, Cl), -tosylates (**7**; Y = TsO) and -quaternary ammonium ions (**7**; Y = NMe_3^+). They also result as by-products in

the reaction of diazoalkanes with ketones (*e.g.* **8**→**10**), and by the Darzens addition of $R\bar{C}ClCO_2Et$ ions to ketones.

(ii) Thiiranes are prepared by similar methods, alkali treatment of β-mercaptohalides (**11**), and in the reaction of diazomethane with thioketones (*cf.* **8**).



(7) (8) (9) (10) (11) (12)

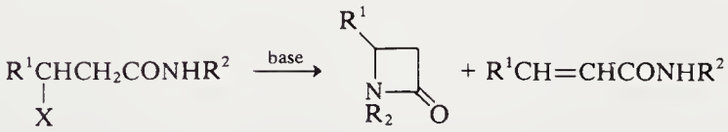
(iii) β-Amino-halides and -sulfates (**12**; Y = Br, Cl, SO_4^-) give aziridines on heating or on treatment with alkali. Aziridinones with bulky *N*-substituents are synthesized by base-catalyzed cyclization of α-haloamides.

4.2.1.2.2 Four-membered rings

Bond formation α to the heteroatom is a common path to azetidines, oxetanes, thietanes and many oxo derivatives. Attack by the heteroatom on the γ-position is disfavored by the entropy factor; the reaction rates for cyclization are about 100 times less than for attack on β-positions. However, *exo*-unsaturation can change this relation drastically: in dimethyl sulfoxide at 50 °C, β-bromopropionate ion cyclizes about 250 times more rapidly than bromoacetate.

Cyclization of 3-bromo- or 3-chloro-amines gives azetidines and azetidinium salts. γ-Displacement is also used to make azetidin-2-ones (β-lactams) from β-amino acid derivatives, such as mixed anhydrides, acid halides, *etc.* Treating free β-amino esters with two equivalents of Grignard reagent leads to an azetidin-2-one *via* the N-anion. Good yields were obtained by using phase transfer catalysis in the reaction of *N*-alkyl-3-bromopropionamides and potassium hydroxide ⟨80H(14)467⟩.

N-Substituted 3-halopropanamides (**13**) are cyclized by $NaNH_2$ to β-lactams; elimination to α,β unsaturated amides can be minimized ⟨79TL549⟩.

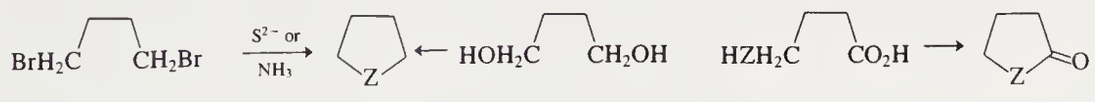


(13)

The salts of β-halo acids cyclize in ionizing media to oxetan-2-ones, as do β-diazonium carboxylates ⟨64HC(19-2)787⟩. Thietanes are obtained analogously.

4.2.1.2.3 Five-membered rings

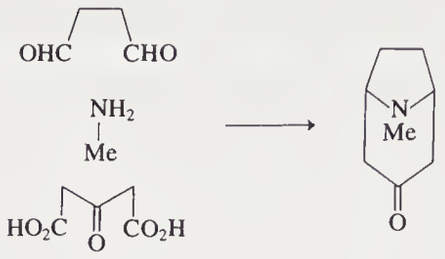
Pyrrolidine (**15**; Z = NH) and thiolane (**15**; Z = S) can be prepared from tetramethylene dibromide (**14**), and tetrahydrofuran (**15**; Z = O) is obtained from the diol (**16**).



(14) (15) (16) (17) (18)

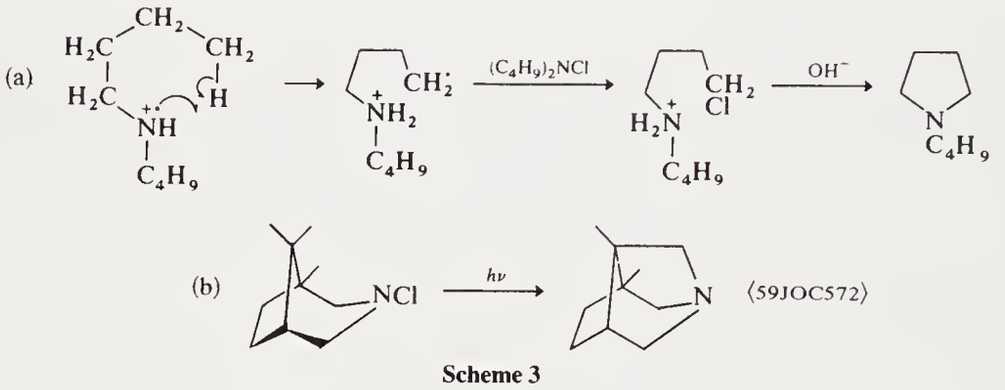
γ-Hydroxy and γ-thiol acids (**17**; Z = O, S) usually cyclize spontaneously to give lactones and thiolactones (**18**). γ-Amino acids (**17**; Z = NH) require heating to effect lactam formation (**18**; Z = NH).

Pyrrolidines may also be prepared by Mannich reactions, *e.g.* the formation of tropinone by reaction (**19**)→(**20**); reactions of this type are involved in alkaloid biogenesis.



(19) (20)

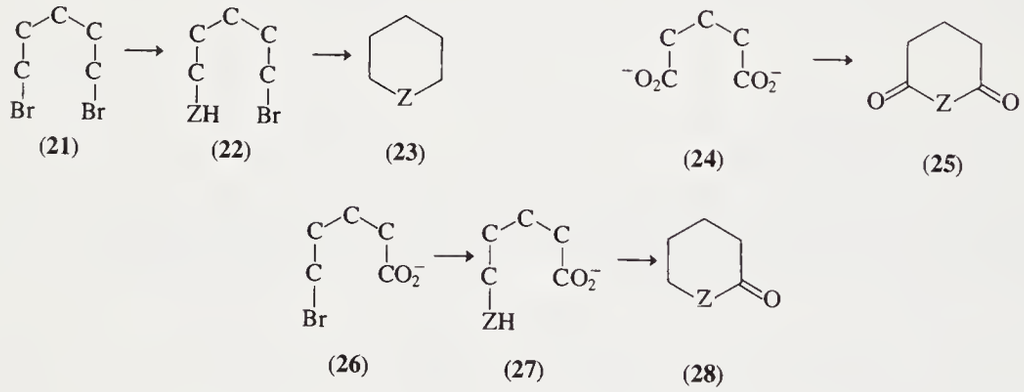
The synthesis of pyrrolidines by the free radical transformation of *N*-chloroamines, the Hofmann–Loeffler–Freytag reaction, is of preparative significance. The key step is the formation of a radical cation which abstracts hydrogen intramolecularly to form a carbon-based radical (Scheme 3a). This species then abstracts chlorine from another *N*-chloroamine ⟨60JA1657, 50JA2118⟩. The observed positional selectivity for hydrogen abstraction is a consequence of the preferred adoption of a six-membered transition state. A typical conversion achieved is indicated in Scheme 3b.



Scheme 3

4.2.1.2.4 Six-membered rings

These methods parallel the synthesis just described for the five-membered rings. As indicated in structures (**21**)–(**28**), standard reactions of aliphatic chemistry can be extended to the preparation of piperidines, tetrahydropyrans and pentamethylene sulfides (**23**; Z = N, O, S); glutarimides, glutaric anhydrides and glutaric thioanhydrides (**25**; Z = N, O, S); and δ-lactams, δ-lactones and δ-thiolactones (**28**; Z = N, O, S).



(21) (22) (23) (24) (25)

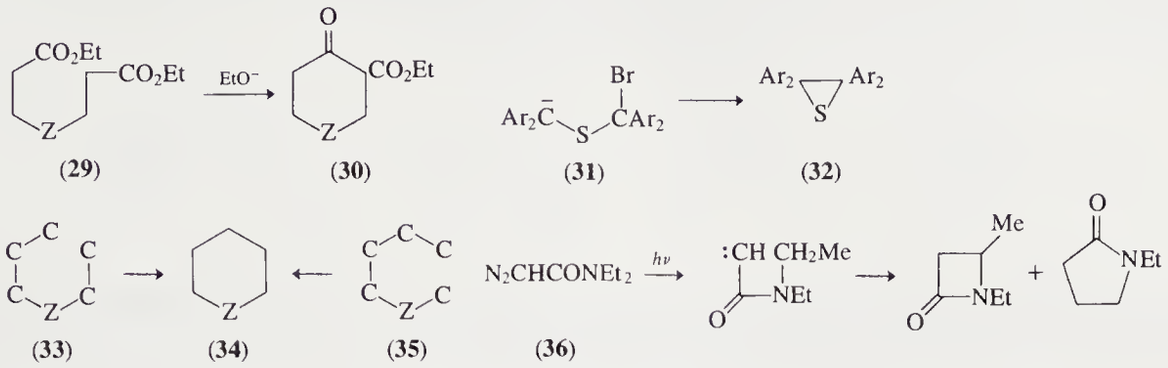
(26) (27) (28)

4.2.1.2.5 Larger rings

Similar methods can also be used for seven-membered and larger rings; however, high dilution techniques must often be utilized. Oxepane, for example, is obtained by the dehydration of hexane-1,6-diol ⟨80BCJ3031⟩.

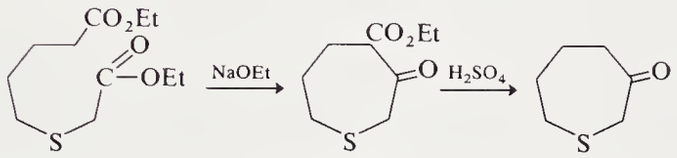
4.2.1.3 From Acyclic Compounds by Formation of One C—C Bond

Many of the standard methods of C—C bond formation in aliphatic systems can be extended to heterocyclic systems, *e.g.* the Dieckmann reaction (*cf.* **29**→**30**) and alkylation of active methylene compounds (*e.g.* **31**→**32**).



Of the syntheses involving C—C bond formation, those in which the C(3)—C(4) bond is formed (**33**→**34**) are more important than those involving C(2)—C(3) bond formation (**35**→**34**). However, carbenic insertions of type (**36**) have been used to make β-lactams ⟨72JA1634⟩.

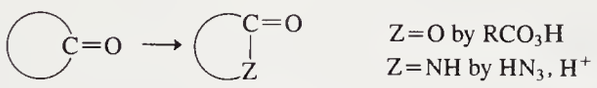
An example of the application of the Dieckmann reaction to the preparation of 3-thiepanone is shown in Scheme 4 ⟨52JA917⟩.



Scheme 4

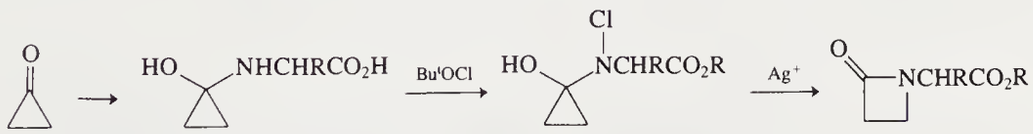
4.2.1.4 From Carbocyclic Compounds

Reactions which insert an O or NH group next to a carbonyl can be used to form heterocycles (Scheme 5). The Schmidt reaction or the Beckmann rearrangement can accomplish this for nitrogen, the Baeyer–Villiger oxidation does it for oxygen. For example cyclohexanone is converted in this way into 2-azepinone and into 2-oxepinone; cycloheptanone yields the corresponding eight-membered heterocycles.



Scheme 5

While these rearrangements are used most often to prepare large rings, the expansion of cyclopropane derivatives to azetidines is also practical (Scheme 6; CHEC 5.09.3.3.3).



Scheme 6

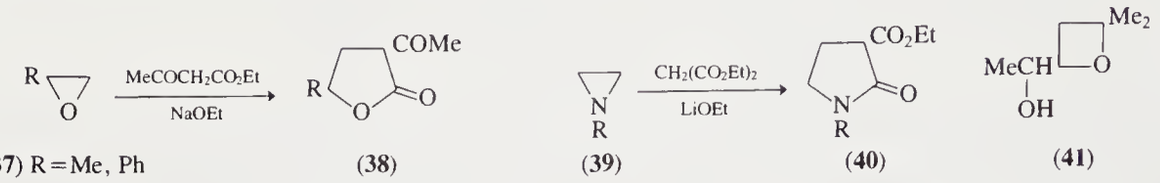
4.2.1.5 From Other Heterocyclic Compounds

Such syntheses are also considered as reactions of the corresponding starting heterocycles in the relevant reactivity chapter.

4.2.1.5.1 Reactions involving ring expansion

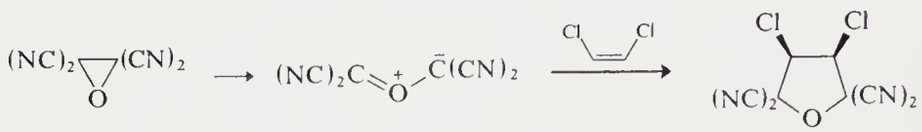
The facility with which oxiranes may be prepared and the ease with which they undergo ring opening with nucleophiles or electrophiles make them useful synthons.

Examples of ring-opening reactions with carbanions leading to five-membered heterocyclic ring formation are shown in (**37**)→(**38**) ⟨50JA4368⟩ and (**39**)→(**40**) ⟨66CB2556⟩. 3,4-Epoxyalcohols give hydroxymethyloxetanes (*e.g.* **41**) by ring expansion ⟨80BCJ2895⟩.



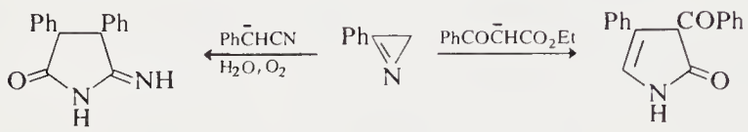
(**37**) R = Me, Ph (**38**) (**39**) (**40**) (**41**)

Certain oxiranes undergo ring opening to carbonyl ylides, and the addition to alkenes, leading to formation of tetrahydrofurans, is stereospecific (Scheme 7).



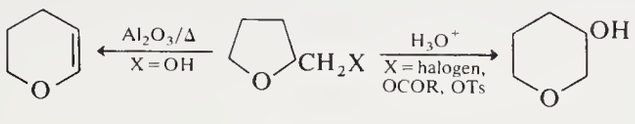
Scheme 7

Azirines can give pyrrolidine derivatives (Scheme 8) ⟨67BCJ2936⟩.

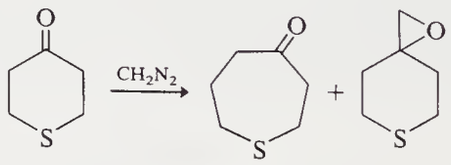


Scheme 8

2-Hydroxymethyltetrahydrofuran is converted into 5,6-dihydro-4*H*-pyran and the acid-catalyzed rearrangement of other 2-substituted tetrahydrofurans forms 3-hydroxytetrahydropyrans (Scheme 9). Thiepan-4-one results from ring expansion of tetrahydrothiopyran-4-one (Scheme 10).



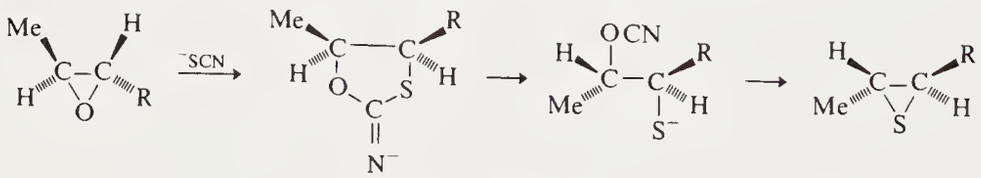
Scheme 9



Scheme 10

4.2.1.5.2 Reactions without change in ring size

A classic prototype of these reactions is the conversion of oxiranes into thiiranes by thiocyanate ion (Scheme 11; CHEC 5.06.4.3). Inversion at both ring carbons makes the reaction stereospecific with respect to the *E*/*Z* relation of the substituents on the oxirane carbons.



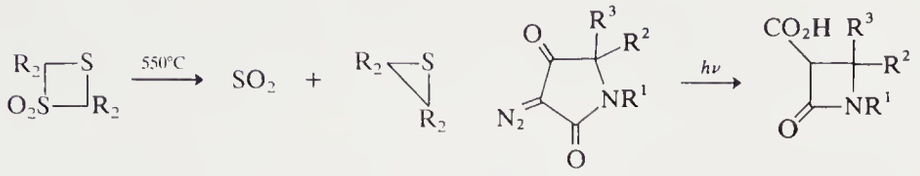
Scheme 11

Aziridines are obtained in one step from oxiranes with iminophosphoranes ⟨76CB814⟩ or phosphoramidate esters ⟨76TL4003⟩.

Many Diels–Alder reactions of furan give addition products containing dihydrofuran rings (Section 3.3.1.8.1).

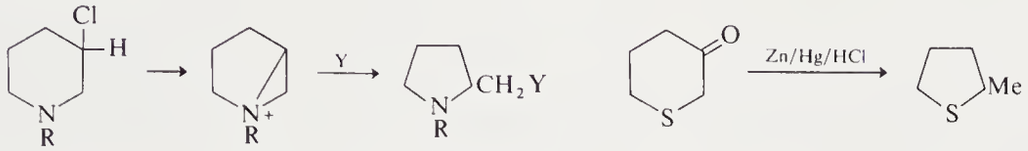
4.2.1.5.3 Ring contractions

The loss of CO, S, SO, SO_2 and N_2 by thermolysis or photolysis has been used to make three- and four-membered rings, for example thiiranes (**43**) are obtained from (**42**) (CHEC 5.06.4.4). Δ^2-1,2,3-Triazolines give aziridines and Wolff rearrangement of (**44**) gives (**45**).



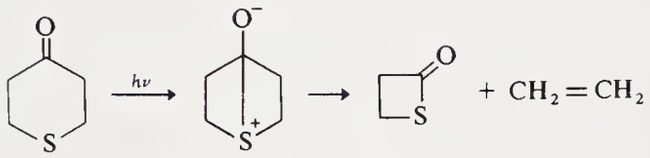
(**42**) (**43**) (**44**) (**45**)

The solvolytic ring contraction of 3-chloropiperidines (**46**) to pyrrolidines proceeds through intramolecular displacement of chloride by the nitrogen, forming an aziridinium ion (**47**); subsequent ring opening by a nucleophile gives (**48**) ⟨69AG(E)962⟩. Abnormal Clemmensen reduction can also give a ring contraction as in the conversion (**49**)→(**50**).



(**46**) (**47**) (**48**) Y = R^1NH, OH, CN (**49**) (**50**)

Many photo-induced ring contractions are known. An illustrative example is the isomerization of tetrahydrothiin-4-one into a zwitterion before loss of ethylene (Scheme 12) ⟨70JOC584⟩; pyrazolidinones give β-lactams (Section 3.4.2.3.4).



Scheme 12

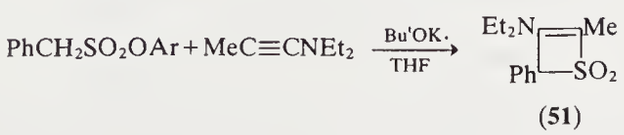
The photo-rearrangements of certain pyridines and azines into azaprismanes and azabenzvalenes are discussed in Section 3.2.1.2.3.

4.2.2 RINGS CONTAINING ONE ENDOCYCLIC DOUBLE BOND

Most monoheterocycles with one cyclic double bond have been prepared by C—Z bond formation in which the Z atom acts as the nucleophile. However, for six-membered rings of this type, Diels–Alder reactions are especially important. Three-membered rings are also atypical: azirines are often made by C—N bond formation from precursors in which N is electrophilic or has nitrene character, and oxirenes are but fleeting intermediates (CHEC 5.05.6.3).

4.2.2.1 From Acyclic Compounds by Concerted Formation of Two Bonds

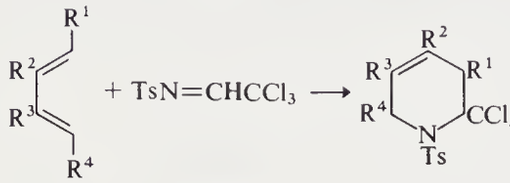
(i) Thiete 1,1-dioxides (*e.g.* **51**) result from sulfenes and ynamines ⟨73S534⟩.



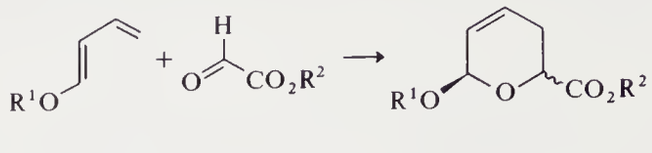
(**51**)

(ii) However, by far the most important reactions of this type are [4 + 2] heterocyclization analogues of the Diels–Alder reaction which present a versatile route to six-membered rings. The

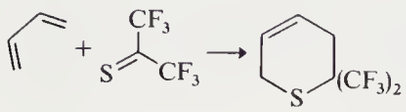
heteroatom can originate from the dienophile (*e.g.* Schemes 13–15) or from the diene (*e.g.* Schemes 16 and 17). Whereas α,β-unsaturated carbonyl compounds react best with electron-rich alkenes (Scheme 16), enaminothiones prefer electron-deficient dienophiles (Scheme 17).



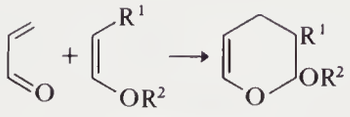
Scheme 13



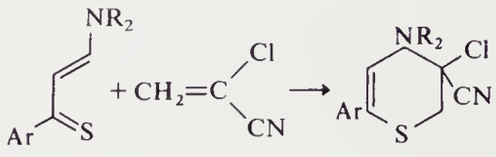
Scheme 14



Scheme 15



Scheme 16



Scheme 17

4.2.2.2 From Acyclic Compounds by Formation of One or Consecutive Formation of Two C—Z Bond(s)

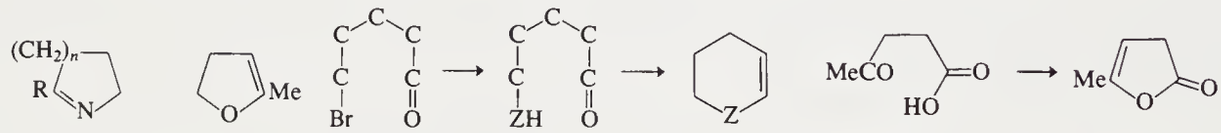
4.2.2.2.1 Z Atom component acting as nucleophile

The appropriate reactions of aliphatic chemistry are applicable, and take place particularly readily for the formation of five- and six-membered rings. For example:

(i) 4- and 5-Oxo primary amines yield Δ¹-pyrrolines and Δ¹-tetrahydropyridines, respectively (**52**; $n = 1, 2$).

(ii) Cyclic enol ethers and their thio analogues are formed from keto alcohols and thiols: $Ac(CH_2)_3OH$ gives the dihydrofuran (**53**) on distillation; *cf.* (**54**)→(**55**)→(**56**) for the preparation of Δ²-dihydro-pyrans and -thiins (Z = O or S).

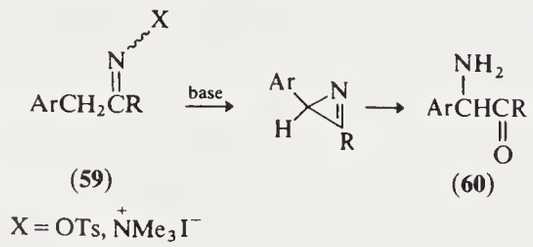
(iii) Unsaturated lactones are prepared from keto acids, *e.g.* (**57**)→(**58**).



(**52**) (**53**) (**54**) (**55**) (**56**) (**57**) (**58**)

4.2.2.2.2 Z Atom component acting as electrophile

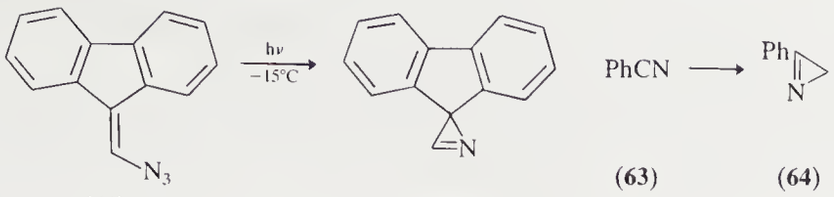
1-Azirines are prepared by base-catalyzed cycloelimination of imine derivatives, *e.g.* as isolable intermediates in the Neber rearrangement (**59**→**60**) ⟨77JA1514⟩.



(**59**) (**60**)

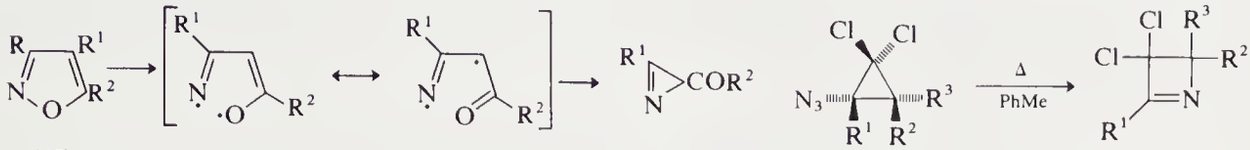
$X = OTs, \overset{+}{N}Me_3I^-$

1-Azirines are also made by thermal or photochemical ⟨68JA2869⟩ elimination of N_2 from vinyl azides (*e.g.* **61**→**62**), and by carbene addition to nitriles (**63**→**64**).



(61) (62) (63) (64)

Thermal ring contraction of 3,5-disubstituted isoxazoles (**65**) gives 1-azirines (**66**).



(65) Scheme 18 (66) (67) (68) 50–75%

4.2.2.3 From Carbocycles

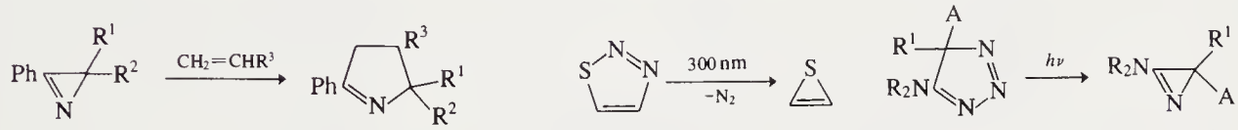
Most of the methods of Section 4.2.1.4 apply.

Thermal ring expansion of cyclopropyl azides provides a general route (**67**→**68**) to alkyl- and aryl-1-azetines ⟨79CB3914⟩.

4.2.2.4 From Heterocycles

The photolytic ring opening of 2*H*-azirines yields nitrile ylides which can be trapped as pyrrolines (**69**) ⟨73JA1945⟩.

Nitrogen extrusion has been used to make fragile molecules: 2-thiirene (**71**) has been obtained by matrix photolysis of 1,2,3-thiadiazole (**70**), and azirines from 4*H*-triazoles (**72**→**73**).



R^3=CN, CO_2Me (69) (70) (71) (72) A = ester 85–92% (73)

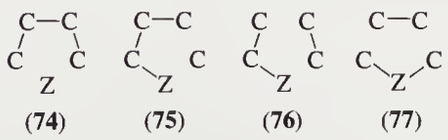
The photo-isomerization of certain pyridines to Dewar pyridines is described in Section 3.2.1.2.2, and the formation of bridged ring 6*H*-1,2-dihydro-3-pyridones in Section 3.2.1.9.5.iv.

4.2.3 RINGS CONTAINING TWO ENDOCYCLIC DOUBLE BONDS

4.2.3.1 Overview

The only four-membered heterocycles with two endocyclic double bonds are the highly reactive azetes; approaches to their synthesis are discussed in CHEC 5.09.5.3.1.

Very importantly, this section also includes the pyrroles, furans and thiophenes. We deal with their preparation by cyclization methods of type (**74**; Section 4.2.3.3.1), (**75**; Section 4.2.3.3.2), (**76**; Section 4.2.3.3.3) and (**77**; Section 4.2.3.3.4), successively, but precede this by a discussion of their preparation by substituent introduction or modification.



(74) (75) (76) (77)

The most important methods of synthesis for these ring systems and the sections in which they are considered are:

(i) Pyrroles: Paal–Knorr (4.2.3.3.1.i), Knorr (4.2.3.3.3.i), Hantzsch (4.2.3.3.3.ii).
(ii) Furans: Paal–Knorr (4.2.3.3.1.i), Feist–Benary (4.2.3.3.3.ii).
(iii) Thiophenes: Paal–Knorr (4.2.3.3.1.i), Hinsberg (4.2.3.3.4).

We then consider methods for the synthesis of pyrans, dihydropyridines and their oxo derivatives, and finally methods for compounds with larger ring sizes.

4.2.3.2 Synthesis of Pyrroles, Furans and Thiophenes by Substituent Introduction or Modification

For detailed discussion of this topic for pyrroles (CHEC 3.06.7), furans (CHEC 3.12.6) and thiophenes (CHEC 3.15.9) see the chapters given. Some important routes to substituted derivatives are summarized in Table 1.

Table 1 Routes to Substituted Pyrroles, Furans and Thiophenes

Substituent	*Method*[a]	*See Section*
Aldehyde	S (Vilsmeier–Haack)	3.3.1.5.5
Alkyl	R, Li	3.3.3.8.2
	S (pyrrole anion)	3.3.1.3.1.ii
Acyl	S (Friedel–Crafts)	3.3.1.5.5
	S (pyrrole anion)	3.3.1.3.1.ii
Amino	Reduce NO_2 or NO	3.3.3.4.1
Aryl	S	3.3.1.7.2
	Pd	3.3.3.8.8
Azo	S (pyrrole anion)	3.1.5.9
Carboxylic acid	R, Li–CO_2, S (pyrrole anion)	3.3.1.3.1.ii
Chloromethyl	S	3.3.1.5.7.iii
Halogen	S	3.3.1.5.4
	Li	3.3.3.8.6
	Hg	3.3.3.8.8
Hydroxy (alcoholic)	S	3.3.1.5.7.i
	Li	3.3.3.8.2
Nitro	S	3.3.1.5.2
	Li	3.3.3.8.5
Sulfonic acid	S	3.3.1.5.3
Ring carbonyl	R, S	3.3.1.5
	Li	3.3.8.3
Substituted methyl	From CH_2Cl	3.3.3.3.3
	From CH_2NMe_2	3.3.3.3.5

[a]R, preparation usually by ring synthesis; S, preparation by substitution; Li, *via* lithio derivative; Pd, *via* palladio derivative; Hg, *via* mercuration.

All these rings undergo easy electrophilic substitution at the 2-position. Particularly for pyrrole and furan the high reactivity often leads to low yields and sometimes it is useful to incorporate deactivating substituents such as CO_2H which can later be removed.

N-Substituted pyrroles, furans and thiophenes can be 2-lithiated, and these lithio derivatives are important synthetic intermediates (Section 3.3.3.8). 2-Mercuri and 2-palladio derivatives are also important (Section 3.3.3.8.8).

The preparation of β-substituted derivatives is more difficult and different methods have been used in the various series.

2-Tritylpyrrole undergoes electrophilic substitution selectively at the 3-position (Section 3.3.1.4.3) and the trityl group can then be removed. Again, in the pyrrole series the selective hydrolysis of α-CO_2Et in alkali and of β-CO_2Et in acid, followed by decarboxylation, allows the introduction of β-substituents into compounds such as 2,4-dialkylpyrrole-3,5-dicarboxylic esters to afford 3-substituted 2,4-dialkylpyrroles (Section 3.3.3.3.6).

2,4-Disubstituted furans can be prepared by the 3-lithiation of 2-phenylthio-5-alkylfurans, followed by reaction with an electrophile and then desulfurization with Raney nickel (Section 3.3.3.8.4). 3-Furylmercuri acetate can be obtained from furan-2-carboxylic acid (CHEC 3.11.3.9) and transformed to other 3-substituted furans *via* the lithio compound.

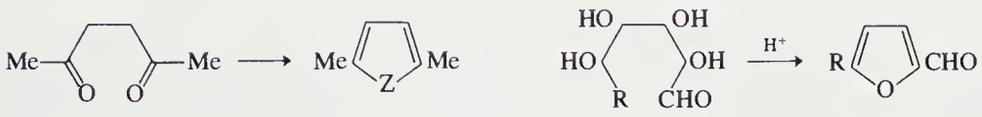
3-Lithiothiophene is a key to the synthesis of many 3-substituted thiophenes. It is prepared from 3-bromothiophene, itself obtained from 2,3,4-tribromothiophene by selective Zn reduction (CHEC 3.14.3.8), or by rearrangement of 2-bromothiophene with $NaNH_2$–NH_3 (CHEC 3.15.9.6.3).

4.2.3.3 Synthesis of Pyrroles, Furans and Thiophenes from Acyclic Precursors

4.2.3.3.1 From C_4 units

(i) The versatile Paal–Knorr synthesis is the most important preparative method for furans and thiophenes; it is also extensively used for pyrroles. The common starting materials are 1,4-diketones (*e.g.* **78**) which yield:

(a) pyrroles (**79**; Z = NH or NR) by reaction with NH_3 or RNH_2;
(b) furans (**79**; Z = O) on treatment with H_2SO_4, P_2O_5 or $ZnCl_2$;
(c) thiophenes (**79**; Z = S) by distilling with P_4S_{10}.

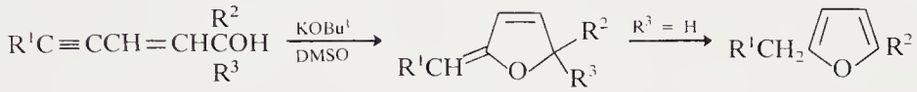


(**78**) (**79**) (**80**) (**81**)

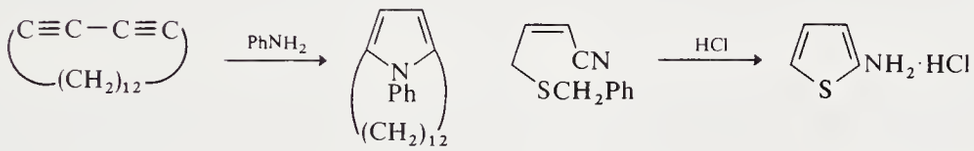
(ii) 1,2,3,4-Tetrahydroxy compounds are used in further reactions of the same general type. Thus, hexoses (**80**; R = CH_2OH) and pentoses (**80**; R = H) give 5-hydroxymethylfurfural (**81**; R = CH_2OH) and furfural (**81**; R = H), respectively.

Pyrolysis of butane with sulfur gives thiophene; this reaction is probably the source of thiophene in coal-tar benzene.

Triple bonds are susceptible to nucleophilic addition which can take place in an intra- (Scheme 19) or inter-molecular fashion (*e.g.* **82**→**83**).



Scheme 19

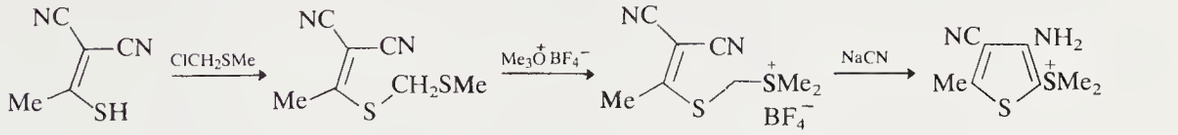


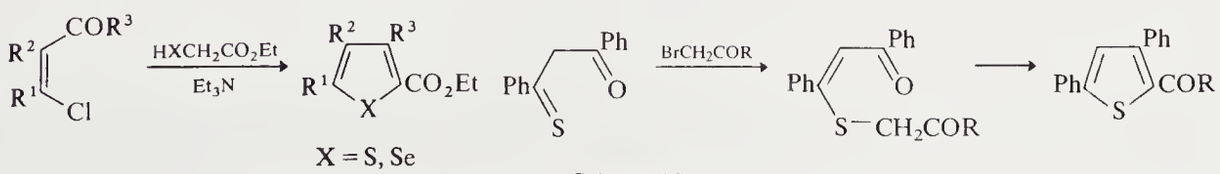
(**82**) (**83**) (**84**) (**85**)

Cyclization reactions effected by intramolecular attack of a heteroatom on a nitrile group provide a useful source of 2-amino heterocycles, *e.g.* (**84**)→(**85**), and numerous syntheses employ this strategy (*vide infra*).

4.2.3.3.2 From C_3ZC or C_3 and CZ units

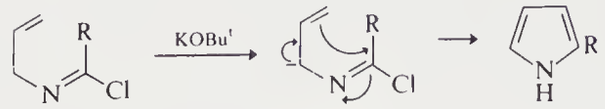
Many variations of this route involve the formation of the 2,3-bond of a thiophene by the 2-carbon atom acting as a nucleophilic center. Examples are shown in Scheme 20.





Scheme 20

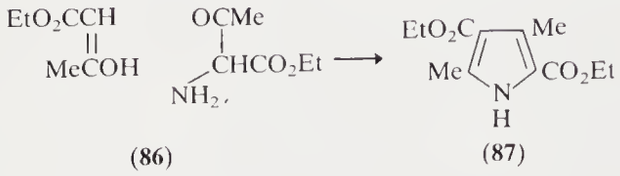
Electrocyclization of a suitable carbanion can also occur as illustrated in Scheme 21 ⟨78AG(E)676⟩.



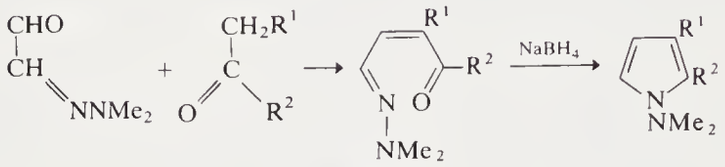
Scheme 21

4.2.3.3.3 From C_2 and ZCC units

(i) The versatile Knorr pyrrole synthesis is the most important route to pyrroles: it involves the condensation of a β-keto ester with an α-amino ketone, *e.g.* (**86**)→(**87**). The β-keto ester can be replaced by a β-diketone; simple ketones give poor yields. The amino ketone is frequently prepared *in situ* by nitrosation and reduction (*e.g.* with Zn–AcOH) of a second molecule of the β-keto ester.



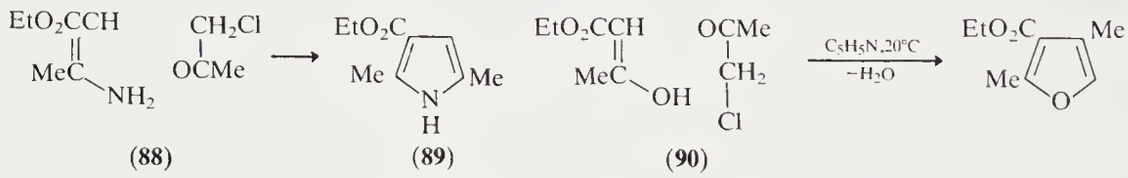
(**86**) (**87**)



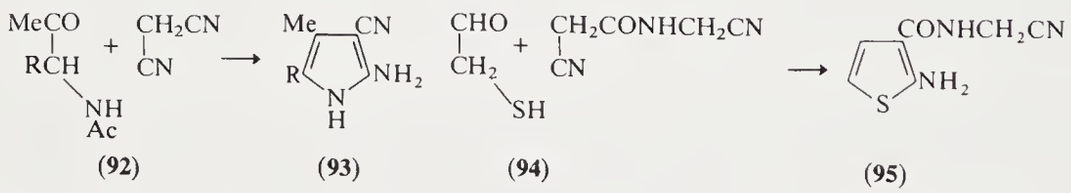
Scheme 22

α-Phenylazo ketones may be used in place of α-oximino ketones ⟨57CB79⟩. Other variations include the use of α-aminoaldimines ⟨78S590⟩, and glyoxal mono-*N*,*N*-dimethylhydrazone which yields 2,3-disubstituted pyrroles ⟨77CB491⟩ (Scheme 22). α-Aminonitriles afford 3-aminopyrroles ⟨74AG(E)807⟩.

(ii) α-Halo ketones react with enamines to form pyrroles, and with β-keto esters to give furans. The orientation in the Hantzsch pyrrole synthesis (*e.g.* **88**→**89**) differs from that in the Feist–Benary furan synthesis (*e.g.* **90**→**91**). The employment of activated cyanomethylene derivatives (**92**) for condensation with α-amino ketones provides 2-aminopyrroles (**93**). In comparable fashion, the condensation of α-mercapto carbonyl compounds with malononitrile derivatives provides 2-aminothiophenes (**94**→**95**) ⟨79LA328⟩.



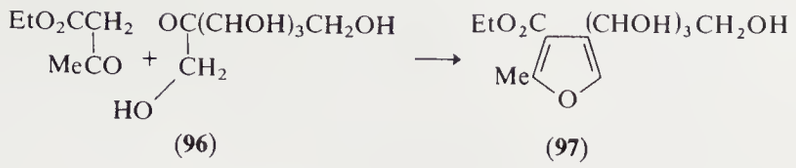
(**88**) (**89**) (**90**)



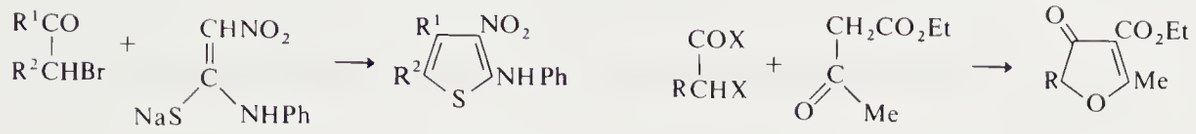
(**92**) (**93**) (**94**) (**95**)

The synthesis of furans from α-hydroxycarbonyl compounds frequently utilizes aldoses or ketoses as readily available sources of this functional grouping (**96**→**97**); the resulting polyhydroxyalkyl side chain can be removed easily by oxidative degradation ⟨56MI30300⟩.

Reactions of the Feist–Benary type have been applied to the synthesis of thiophenes (**98**→**99**) ⟨75ZC100⟩. The use of α-halocarbonyl halides provides an entrée to 3-furanones (**100**→**101**) ⟨73RTC731⟩.

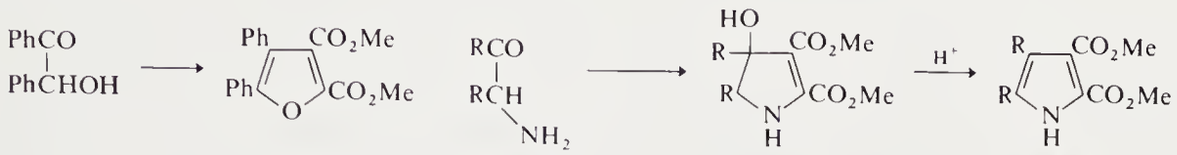


(96) (97)



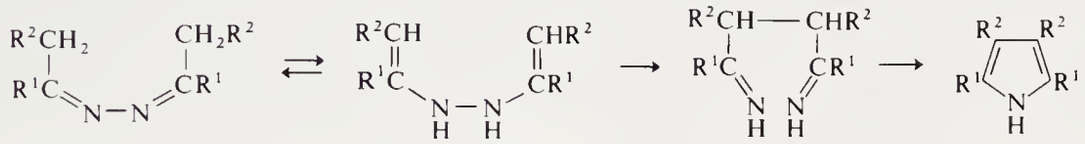
(98) (99) (100) (101)

(iii) Additions to conjugated triple bonds as in dimethyl acetylenedicarboxylate occur with facility. Thus base-catalyzed addition of benzoin to DMAD provides a route to furans (**102**→**103**) ⟨64JA107⟩, and pyrroles result from an analogous addition of α-amino ketones (**104**→**105**→**106**) ⟨64JA107⟩.



(102) (103) (104) (105) (106)

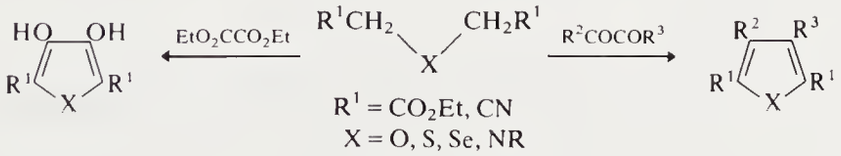
(iv) The Piloty–Robinson pyrrole synthesis (Scheme 23) is the monocyclic equivalent of the Fischer indole synthesis. The conversion of ketazines into pyrroles under strongly acidic conditions proceeds through a [3,3] sigmatropic rearrangement of the tautomeric divinylhydrazine ⟨74JOC2575⟩. The cyclization of *N*-substituted azines provides 1-substituted pyrroles ⟨71LA(744)81⟩. The reaction can be conducted under relatively mild conditions by converting the azine into the *N,N'*-dibenzoyl derivative prior to thermal (~140 °C) rearrangement ⟨82CC624⟩.



Scheme 23

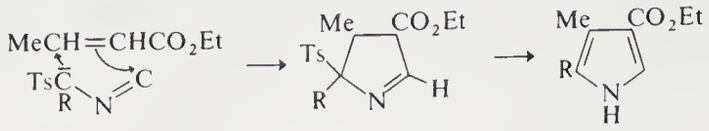
4.2.3.3.4 From C_2 and CZC units

Ring syntheses based on the combination of $C_\beta C_{\beta'}$ and $C_\alpha X C_{\alpha'}$ fragments depend upon the latter reacting either as a carbanion or as a 1,3-dipole. An example of the former is the Hinsberg thiophene synthesis in which ethyl thiodiglycollate is condensed with a 1,2-dicarbonyl compound under basic conditions (Scheme 24) ⟨79JHC1147⟩. Other carbanion stabilizing groups such as cyano can be used in place of the ethoxycarbonyl group. The same basic method has been used for the synthesis of furans ⟨40RTC423⟩, selenophenes ⟨40RTC423⟩ and pyrroles ⟨65JOC859⟩.



Scheme 24

A useful synthesis of pyrroles depends upon the addition of the anion of *p*-toluenesulfonylmethyl isocyanide (TOSMIC) to α,β-unsaturated ketones or other Michael acceptors ⟨72TL5337⟩ (Scheme 25).

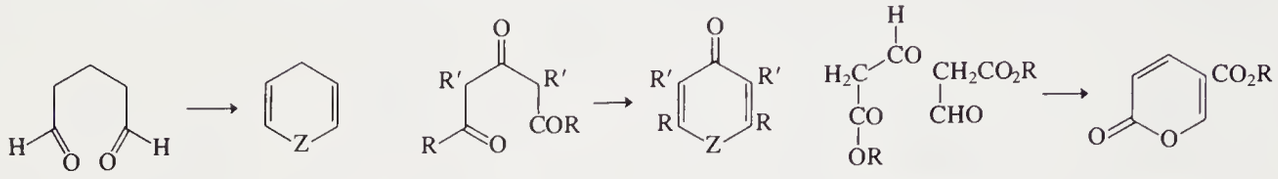


Scheme 25

4.2.3.4 Synthesis of Pyrans, Dihydropyridines and their Thio and Oxo Derivatives from Acyclic Precursors

4.2.3.4.1 From C_5 units

The degree of unsaturation of the heterocyclic product depends on the nature of the five-carbon starting material: pentane-1,5-diones yield dihydro compounds (**107**→**108**) (which are sometimes oxidized *in situ*); pentane-1,3,5-triones (**109**) give γ-pyrones (**110**; Z = O) by dehydration, and γ-pyridones (**110**; Z = NH) by the action of ammonia.

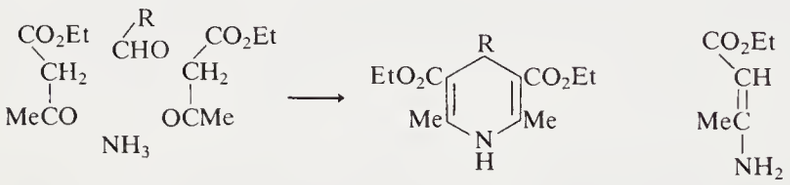


(**107**) (**108**) (**109**) (**110**) (**111**) (**112**)

Pent-2-ene-1,5-diones may be formed *in situ* (usually by an aldol-type reaction) and subsequently cyclized. Thus, malic acid (*i.e.* hydroxysuccinic acid) with sulfuric acid gives carboxyacetaldehyde (**111**) which cyclizes spontaneously to coumalic acid (**112**).

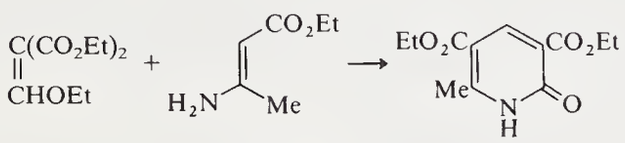
4.2.3.4.2 With C—C bond formation

(i) The Hantzsch pyridine synthesis affords 1,4-dihydropyridines, although spontaneous oxidation to pyridines often occurs. In its simplest form it involves the condensation of two molecules of a β-keto ester with an aldehyde and ammonia (*cf.* **113**→**114**). Compounds resulting from the condensation of ammonia with one of the carbonyl components can be used in the Hantzsch synthesis. Thus β-aminocrotonic ester (**115**) can replace the ammonia and one mole of acetoacetic ester in (**113**).

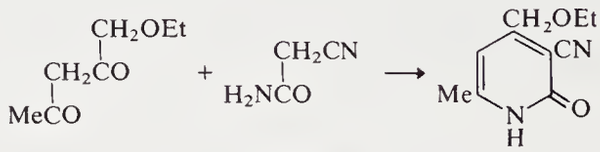


(**113**) (**114**) (**115**)

(ii) Related preparations of 2-pyridones involve condensation of enamines and enamides with 1,3-bielectrophiles, *e.g.* Schemes 26 and 27.

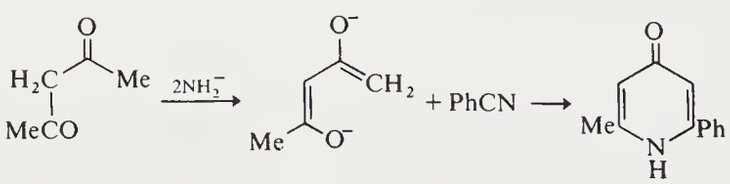


Scheme 26



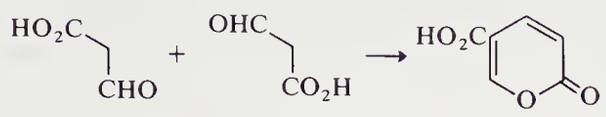
Scheme 27

(iii) 4-Pyridones can be made from β-diketone dianions and nitriles (Scheme 28).



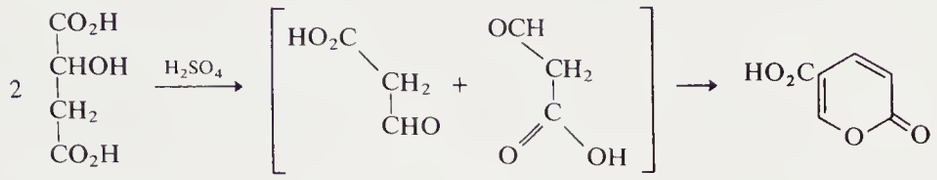
Scheme 28

(iv) Routes to α-pyrones are illustrated in Schemes 29, 30 and 31.



Scheme 29

Scheme 30

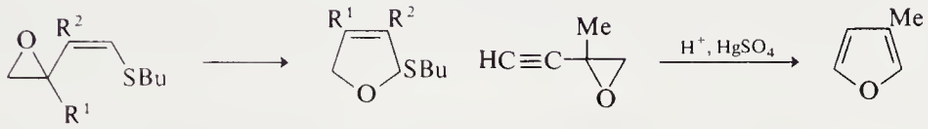


Scheme 31

4.2.3.5 Synthesis of Five- and Six-membered Rings from Heterocyclic Precursors

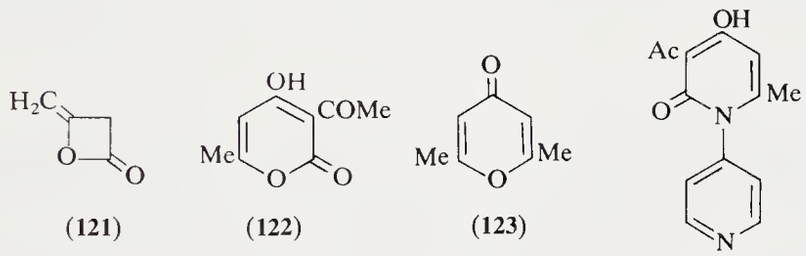
4.2.3.5.1 With ring expansion

The isomerization of vinyl- or ethynyl-oxiranes is a frequently exploited source of dihydrofurans or furans, as illustrated by (**117**)→(**118**) ⟨73JA250⟩ and (**119**)→(**120**) ⟨69JCS(C)12⟩. Vinylazirine similarly gives pyrrole (Section 3.5.2.2).



(**117**) (**118**) (**119**) (**120**)

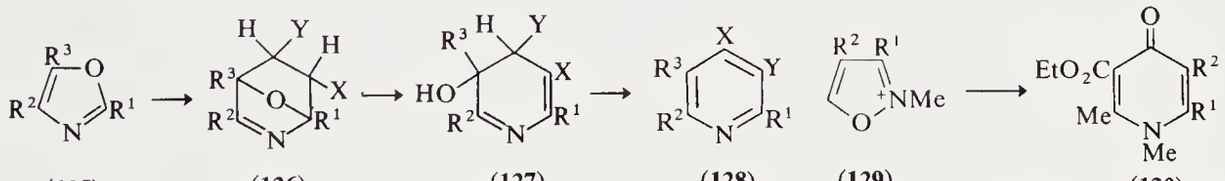
Base-catalyzed dimerization of diketene (**121**) efficiently yields dehydroacetic acid (**122**); treatment of diketene with aqueous triethylamine gives 2,6-dimethyl-4-pyrone (**123**).



(**121**) (**122**) (**123**) (**124**)

Diketene reacts as a masked form of acetoacetic ester with a variety of mono- and di-nucleophiles. Aromatic and heteroaromatic amines give acetoacetanilides which with more diketene cyclize to dioxopyridines, *e.g.* (**124**) is formed from 4-aminopyridine.

Ring opening of the cycloadducts (**126**) from oxazoles (**125**) and dienophiles (XCH=CHY) gives dihydropyridines (**126**→**127**→**128**); entities such as XR^3, HR^3 or XOH can also be lost in the aromatization of intermediate (**127**).



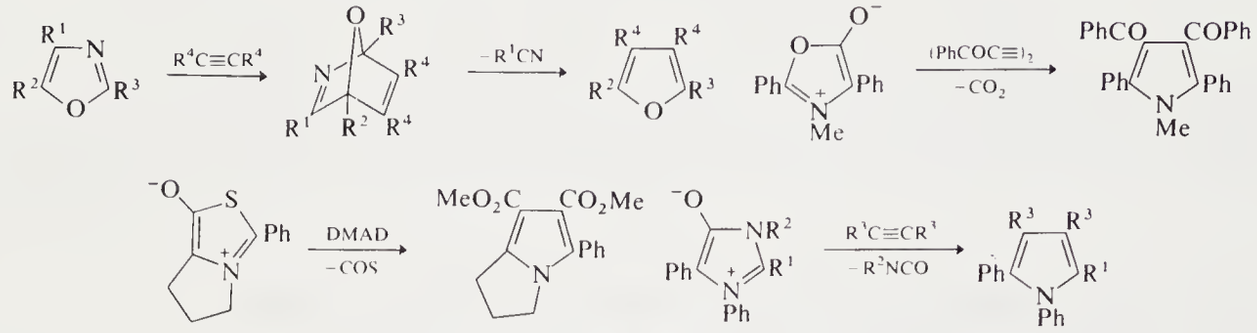
(**125**) (**126**) (**127**) (**128**) (**129**) (**130**)

Isoxazolium salts with active methylene compounds can undergo ring expansion: thus (**129**) + $MeCOCH_2CO_2Et$ gives the 4-pyridone (**130**).

See the sections quoted for ring expansion of 2,3-dihydrothiophenes to thiophene derivatives (3.3.2.3.3) and 1,2-dithiolium cations to thiinthiones (3.4.1.6.5.i).

4.2.3.5.2 No change in ring size

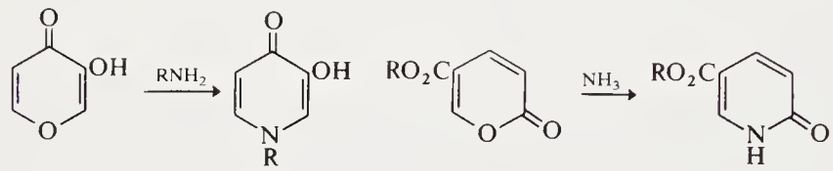
Furans, thiophenes and pyrroles have all been obtained by addition of alkyne dienophiles to a variety of other five-membered heterocycles, as illustrated in Scheme 32 (see also Section 3.4.1.9.1). As the alkyne moiety provides carbons 3 and 4 of the resulting heterocycle, this synthetic approach provides an attractive way of introducing carbonyl-containing substituents at these positions, especially as many of the heterocyclic substrates are readily available. A similar conversion of an oxadiazinone to a pyrone is described in Section 3.2.1.9.5.iii.



Scheme 32

The conversion of furans into the corresponding thiophenes or pyrroles entails passage of the furan with hydrogen sulfide or ammonia over an alumina-based catalyst at elevated temperatures ⟨B-73MI30300⟩. Conversions of furans into thiophenes are also achieved with hydrogen sulfide and hydrogen chloride at 80–100 °C ⟨80DOK(255)1144⟩.

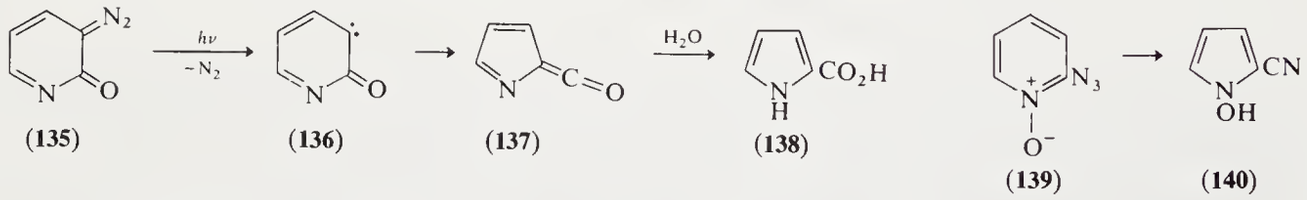
Aminolysis of α- and γ-pyrones is important for the preparation of 2- and 4-pyridones, *e.g.* (**131**)→(**132**) and (**133**)→(**134**) (see also Section 3.2.1.6.4).



(**131**) (**132**) (**133**) (**134**)

4.2.3.5.3 With ring contraction

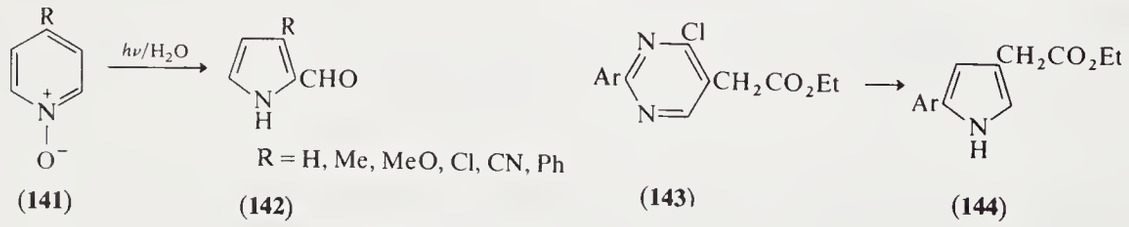
The photolytic Wolff ring contraction of diazopyridones (**135**) is a synthesis of pyrrole-2-carboxylic acids *via* carbene (**136**) and ketene (**137**) intermediates ⟨76S754⟩.



(**135**) (**136**) (**137**) (**138**) (**139**) (**140**)

The thermolysis of 2-azidopyridine *N*-oxides leads to *N*-hydroxy-2-cyanopyrroles (**139**→**140**) ⟨73JOC173⟩ (see also Section 3.4.3.11).

Photolysis of pyridine 1-oxides (**141**) affords a versatile route to a variety of pyrroles (**142**).

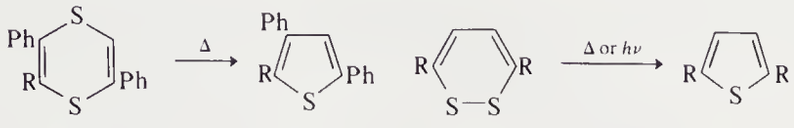


(**141**) (**142**) R = H, Me, MeO, Cl, CN, Ph (**143**) (**144**)

Reduction of appropriate 2-arylpyrimidines with zinc in acetic acid provides pyrrolylacetic acids (**143**→**144**) ⟨70JCS(C)1658⟩.

Related reactions include preparations of furans from pyrylium cations (Section 3.2.1.6.3.v) and from bromopyrroles (3.2.1.6.3.vi).

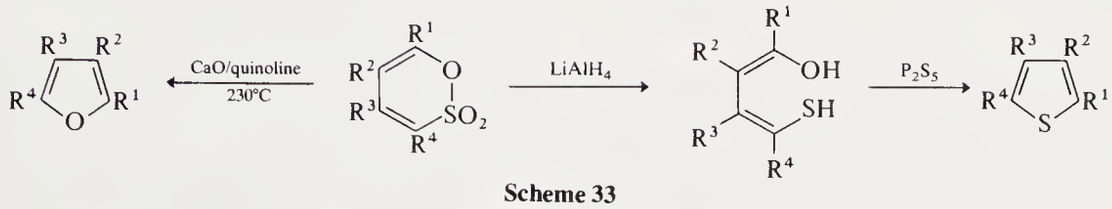
1,4-Dithiins readily lose sulfur on heating, yielding the corresponding thiophene (**145**→**146**) ⟨56JA850⟩. Ring contraction is also effected by treatment with hydrogen peroxide; a mixture of isomeric thiophenes can result ⟨55JA68⟩ (see also Section 3.2.2.1.1).



(145) **(146)** **(147)** **(148)**

1,2-Dithiins behave similarly on thermolysis or photolysis, again forming thiophenes (**147**→**148**) ⟨67AG(E)698⟩.

Similar transformations are based upon 1,2-oxathiin 2,2-dioxides (δ-sultones), which can be converted subsequently into furans ⟨51RTC35⟩, thiophenes ⟨60LA(630)120⟩ (Scheme 33) or pyrroles ⟨61LA(646)32⟩.

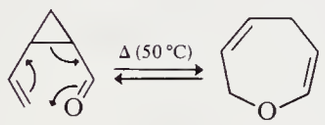


Scheme 33

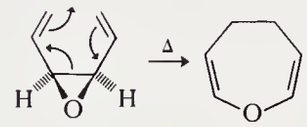
For a triazepine into pyrrole ring contraction see Section 3.5.2.1.

4.2.3.5 Synthesis of Seven- and Eight-membered Rings

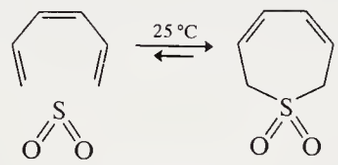
cis-2-Vinylcyclopropanecarboxaldehyde and 2,5-dihydrooxepin interconvert at 50 °C (Scheme 34) ⟨69JA2813⟩ and *cis*-1,2-divinyloxirane thermally yields 4,5-dihydrooxepin (Scheme 35) ⟨63JOC1383⟩. Reversible 1,6-addition of SO_2 to *cis*-hexatriene affords 2,7-dihydrothiepin 1,1-dioxide (Scheme 36) ⟨67JA1281⟩.



Scheme 34



Scheme 35



Scheme 36

4.2.4 RINGS CONTAINING THREE ENDOCYCLIC DOUBLE BONDS

4.2.4.1 Synthetic Methods for Substituted Pyridines

There are several significant ring syntheses for pyridines, of which the most important is the Hantzsch synthesis (Section 4.2.3.3.2). However, the majority of substituted pyridines are prepared from pyridine itself or from a simple alkyl derivative.

Frequently used methods for introducing substituents into the various positions of the pyridine nucleus include the following.

(i) *Substituents in the 2-position* are often introduced *via* the Chichibabin reaction, which gives 2-aminopyridines (Section 3.2.1.6.4). These can be converted into 2-halopyridines and 2-pyridones (Section 3.2.3.5.3); all are versatile intermediates.

(ii) *Substituents in the 4-position* are most frequently introduced by further transformations of the readily available 4-nitropyridine 1-oxides (Section 3.2.1.4.4).

(iii) *Substituents in the 3-position.* Pyridines can be halogenated (Section 3.2.1.4.7) and sulfonated (Section 3.2.1.4.5) in the 3-position. Yields are better if an activating substituent (which

can subsequently be removed) is present in the 2-position and in this case nitration is also feasible. The resulting 3-nitro- and 3-halo-pyridines and pyridine-3-sulfonic acids can be converted into other compounds by the usual methods of benzenoid chemistry.

Methods for obtaining various types of functionally substituted pyridine are summarized in Table 2.

Table 2 Routes to Substituted Pyridines: Cross References to Relevant Sections

Substituent group	*Direct introduction of substituent (R)*[a]	*Obtainable indirectly by or starting from*
Acyloxy	—	Hydroxy compounds (3.2.3.7.3), *N*-oxides (3.2.3.12.5)
Aldehyde	—	Oxidation (3.2.3.3.1), halo compounds (3.2.3.4.4)
Alkoxy	—	Nitro (3.2.3.6.1), hydroxy (3.2.3.7.3) and halo compounds (3.2.3.10.6)
Alkyl	3.2.1.6.8, R	—
Alkylthio	—	Halo (3.2.3.10.6) and thio-carbonyl compounds (3.2.3.9.2)
Amino	3.2.1.6.4, R	Halo (3.2.3.10.6), amido (3.2.3.4.2) and nitro compounds (3.2.3.6.1)
Aryl	3.2.1.6.8, R	—
Arylamino	—	Amines (3.2.3.5.2)
Azo	—	Nitro (3.2.3.6.1) and amino compounds (3.2.3.5.2)
Carboxyl, alkoxycarbonyl, *etc*	R	Oxidation (3.2.3.3.1, 3.2.3.4.3), halo compounds (3.2.3.10.6)
Cyano	—	Carboxylic acids (3.2.3.4.2), sulfonic acids (3.2.3.9.4), halo compounds (3.2.3.10.6), vinyl compounds (3.2.3.4.5), Reissert compounds (3.2.1.6.8)
Halo	3.2.1.4.7, 3.2.1.6.7	*N*-Oxides (3.2.1.6.7), nitro compounds (3.2.3.6.1), pyrones and pyridones (3.2.3.7.4), amines (3.2.3.5.3)
Hydrazino	—	Nitramines (3.2.3.6.2), halo (3.2.3.10.6) and nitro compounds (3.2.3.6.1)
Hydroxy (alcoholic)	—	Alkyl (3.2.3.3.1) and vinyl compounds (3.2.3.4.5), carboxylic acids (3.2.3.4.2)
Hydroxy (phenolic)	—	Halo compounds (3.2.3.10.6), sulfonic acids (3.2.3.9.4)
Imino	—	Amines (3.2.1.3.6)
Keto	R	Alkyl compounds (3.2.3.3.3), esters (3.2.3.4.2)
Mercapto	—	Halo compounds (3.2.3.10.6)
Nitro	3.2.1.4.4	Amines (3.2.3.5.2)
Nitroso	3.2.1.4.10	—
Sulfonic acid	3.2.1.4.5	Halo (3.2.3.10.6), thio carbonyl (3.2.3.9.2) and vinyl compounds (3.2.3.4.5)
Thiocarbonyl	—	Halo compounds (3.2.3.10.6), pyrones and pyridones (3.2.3.7.3)
Vinyl	—	Alkyl (3.2.3.3.4) and hydroxy compounds (3.2.3.4.4)

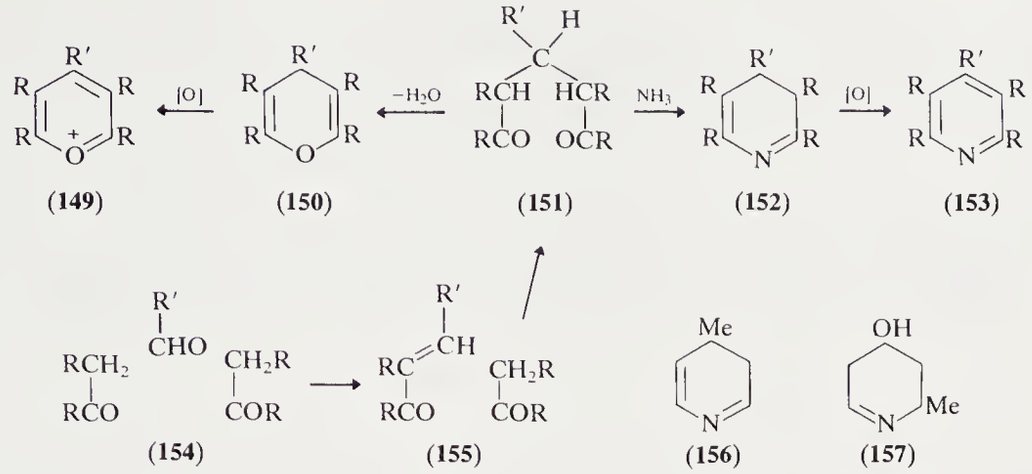
[a]R in this column signifies that compounds containing these substituents are commonly prepared by ring synthesis.

4.2.4.2 Synthesis of Six-membered Rings from Acyclic Compounds

4.2.4.2.1 From or via *pentane-1,5-diones*

As discussed in Section 4.2.3.2, pentane-1,5-diones (**151**) can undergo ring closure to give a

pyran (**150**), or, in the presence of ammonia, a dihydropyridine (**152**). Oxidative aromatization of these products occurs so easily (*cf.* Section 4.2.3.4.2) that it frequently takes place prior to isolation, giving a pyrylium salt (**149**) or a pyridine (**153**). The Hantzsch pyridine synthesis is described in Section 4.2.3.3.2.



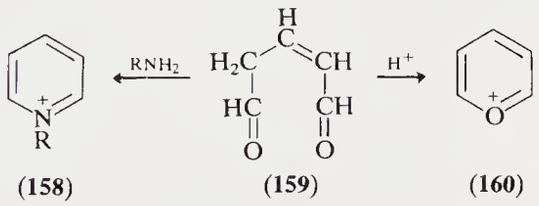
(**149**) (**150**) (**151**) (**152**) (**153**)

(**154**) (**155**) (**156**) (**157**)

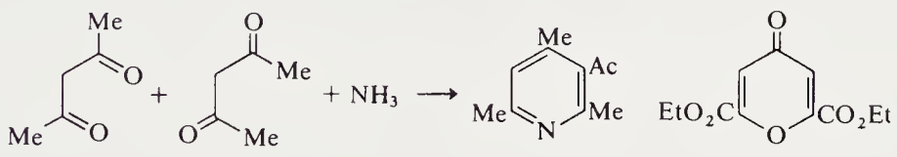
The pentane-1,5-dione is usually formed *in situ* by aldol- or Michael-type reactions (**154**→**155**→**151**). Thus, acetaldehyde (**154**; R = H, R′ = Me) and ammonia give 4-picoline and 3-ethyl-4-methylpyridine by formation of the intermediate (**156**), condensation with another molecule of MeCHO, and subsequent dehydrogenation. The same reaction also yields 2-picoline and 5-ethyl-2-methylpyridine *via* the intermediate (**157**). Such reactions are used industrially.

4.2.4.2.2 From pent-2-ene-1,5-diones

Ring closure of glutaconic dialdehyde (**159**) with ammonia gives pyridine, hydroxylamine forms pyridine 1-oxide, while primary amines yield pyridinium (**158**) and acids afford pyrylium cations (**160**). Substituted glutaconic dialdehydes and related diketones react similarly. If one of the carbonyl groups is incorporated in a carboxyl group or a modified carboxyl group, α-pyridones and α-pyrones are formed. Pent-2-ene-1,5-diones or nitrogen analogues can be built up from components and subsequently cyclized, *e.g.* $NH_3 + (\mathbf{161}) \rightarrow (\mathbf{162})$, and $Me_2CO + 2(CO_2Et_2)_2 \rightarrow (\mathbf{163})$. A recent route to pent-2-ene-1,5-diones involves the conjugate addition of the potassium enolate of methyl ketones to α-oxoketene dithioacetals; ring closure with ammonium acetate in hot acetic acid affords excellent yields of 2,6-disubstituted 4-(methylthio)pyridines.



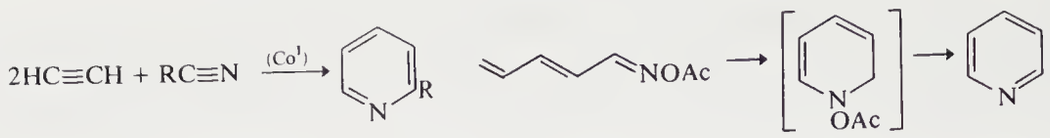
(**158**) (**159**) (**160**)



(**161**) (**162**) (**163**)

4.2.4.2.3 Other methods

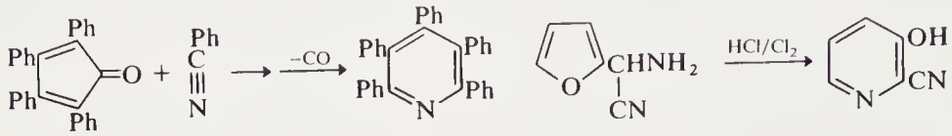
The cobalt(I)-catalyzed condensation of nitriles (1 mole) or isocyanates (1 mole) with alkynes (2 moles) gives pyridines and 2-pyridones, often in excellent yield (Scheme 37).



Scheme 37 **(164)** **(165)**

The oxime acetate (**164**) readily undergoes electrocyclization to the dihydropyridine (**165**), from which pyridine is derived by loss of acetic acid.

Cycloadducts from cyclopentadienones and nitriles spontaneously lose CO to form a pyridine (Scheme 38).

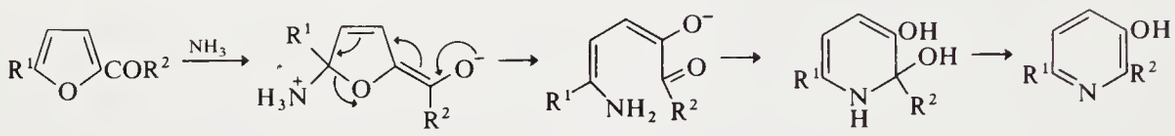


Scheme 38 **(166)** **(167)**

4.2.4.3 Synthesis of Six-membered Rings from Other Heterocycles

4.2.4.3.1 From five-membered rings

Aminomethylfurans are converted into 3-hydroxypyridines by acid and an oxidizing agent, *e.g.* (**166**)→(**167**). 2-Hydroxymethylfurans with chlorine in aqueous methanol give 3-hydroxy-4-pyrones. 3-Hydroxypyridines can conveniently be prepared by reaction of 2-acylfurans with ammonia (Scheme 39). Pyrrole and dichlorocarbene give some 3-chloropyridine (Section 3.3.1.7.1).



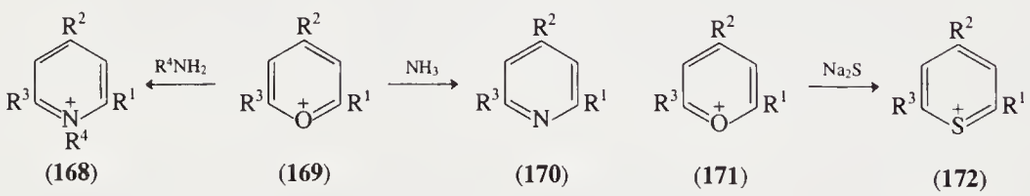
Scheme 39

Oxazoles and dienophiles give pyridines in good yield as discussed in Section 3.4.1.9.1.

4.2.4.3.2 From other six-membered rings

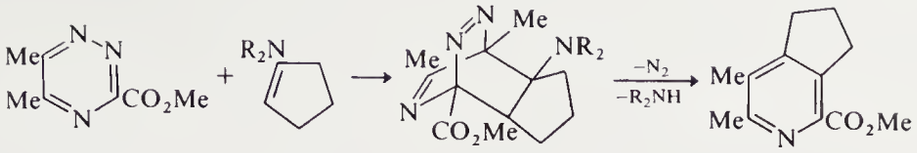
For the thermal conversion of pyridazines to pyrimidines see Section 3.2.1.2.2.

Nucleophilic addition at the 2-position of pyrylium salts (**169**) occurs readily under mild conditions and when ammonia or primary amines are used the subsequent ring-opening/ring-closure sequences give pyridines (**170**) and pyridinium salts (**168**) respectively (Section 3.2.1.6.4.ii). The process is most useful for the synthesis of 2,4,6-trisubstituted pyridine derivatives. Thiinium salts (**172**) are conveniently prepared from pyrylium salts (**171**) by treatment with sodium sulfide (Section 3.2.1.6.5). Thiinium salts (**172**) react with ammonia and amines similarly to their pyrylium analogues.



(168) **(169)** **(170)** **(171)** **(172)**

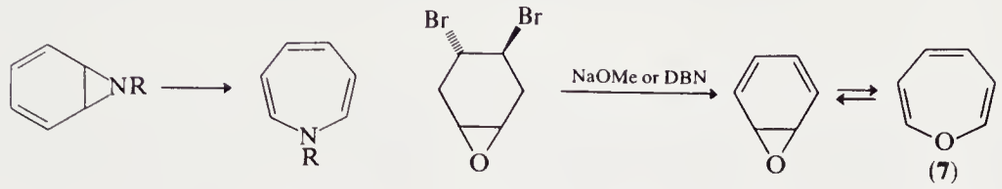
'Inverse electron demand' Diels–Alder/retro-Diels–Alder-type reactions, of di- and especially poly-azines with electron-rich dienophiles, interconvert six-membered rings. 1,2,4-Triazines react with enamines and enol ethers to give pyridines (Scheme 40).



Scheme 40

4.2.4.4 Synthesis of Seven-membered and Larger Rings

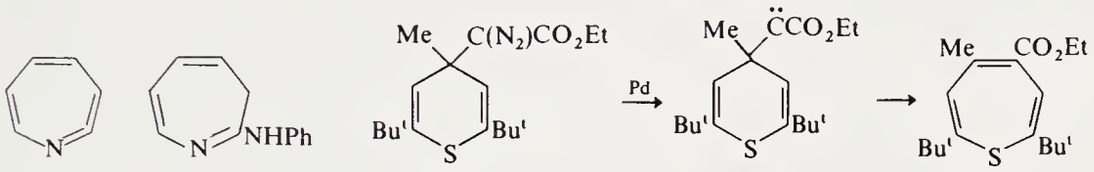
1*H*-Azepines (**174**) result from spontaneous valence-bond isomerization of azanorcaradienes (**173**) which are themselves made by reaction of arenes with nitrenes (see CHEC 5.16.4.1.3). Oxepins are prepared by an analogous method (**176**→**177**); the starting material is made from (**175**) ⟨64AG(E)510⟩.



(**173**) (**174**) (**175**) (**176**) (**177**)

Photolysis of PhN_3 in an argon matrix gives 1-aza-1,2,4,6-cycloheptatetraene (**178**) ⟨79RTC334⟩; in aniline the photoproduct is the 3*H*-azepine (**179**) ⟨81AHC(28)231⟩.

For related preparations of azepines from pyridines (Section 3.2.3.4.4.iii) and indazole derivatives (Section 3.4.3.2.4) see the sections indicated.



(**178**) (**179**) (**180**) (**181**) (**182**)

Ring expansion of thiinium salts has been used for the preparation of various thiepins: intermediate (**180**) is prepared using $N_2C(Li)CO_2Et$, and decomposes *via* the carbene (**181**) to afford (**182**) (see CHEC 5.17.3.4.2.ii).

[2 + 2] Cycloaddition of DMAD to 1,2-dihydropyridines ⟨77JOC2903⟩ is a fairly general route to 1,2-dihydroazocines which proceeds *via* a bicyclic intermediate as described in Section 3.2.2.3.8.

4.3

Synthesis of Monocyclic Rings with Two or More Heteroatoms

4.3.1 SUBSTITUENT INTRODUCTION AND MODIFICATION

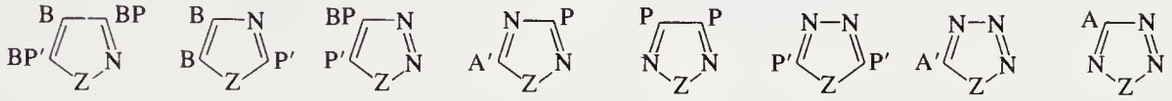
4.3.1.1 Overview

In this chapter, synthetic methods are classified by the ring that is being formed. We deal successively with rings containing two, three and four or more heteroatoms. Within each category, classification is first by the relative orientation of the heteroatoms, and then by the ring size.

However, we commence with two sections dealing with preparative methods involving substituent introduction and modification for the two large and important classes of monocyclic compounds: those with five and six members and with various heteroatoms.

4.3.1.2 Substituent Introduction and Modification in Azoles

The azoles encompass a very wide range of reactivity (see Chapter 3.4) and possibilities of substituent introduction and modification are very varied. Scheme 1 gives a classification in terms of reactivity type for each position in the various rings.



(1) (2) (3) (4) (5) (6) (7) (8)

Scheme 1 Character of azole ring positions (Z=NR, O or S)

(i) Positions marked B show reactivity comparable to that of ring carbons in benzene. Substituents can be introduced by electrophilic substitution reactions (Section 3.4.1.4) and show reactivity similar to those of the analogous benzene. Thus, amino groups can be diazotized (Section 3.4.3.5.3) and halogens are unreactive.

(ii) Positions marked P show reactivity similar to those of the 2- and 4-positions in pyridine. The substituents can be introduced by very strong nucleophiles (Section 3.4.1.6); OH compounds exist in the oxo form and can be converted (Section 3.4.3.7) into chloro compounds which are reactive (Section 3.4.3.9.1). Alkyl groups can be deprotonated into anions which undergo many substitution reactions (Section 3.4.3.3).

(iii) Positions marked BP have reactivity intermediate between benzene and pyridine and can be compared to the 3-position of pyridine.

(iv) Positions marked A resemble azines and have the reactivity of the 2-position of pyrimidine, *i.e.* comparable to P but more marked.

(v) Positions marked with a prime (B′, P′, A′) additionally can be lithiated and the lithium replaced in a wide variety of synthetically interesting ways.

4.3.1.3 Substituent Introduction and Modification in Azines

As explained in Chapter 3.2, the reactivity of six-membered rings containing two heteroatoms bears the same relationship to six-membered rings containing one heteroatom as do the latter to

benzene. Hence many of the methods listed for the preparation of pyridines by substituent introduction and modification in Table 1 of Section 4.2.4.1 are also applicable to the preparation of analogous azines.

4.3.2 TWO HETEROATOMS IN THE 1,2-POSITIONS

4.3.2.1 Three-membered Rings

(i) Oxaziridines (**9**) are formed by oxidation ($MeCO_3H$, CH_2Cl_2 at 20 °C) of Schiff's bases $R_2C{=}NR'$.

(ii) Diaziridines (**10**) are prepared by the reaction $R_2CO + R'NH_2 + NH_2OSO_3H \rightarrow$ (**10**).

(iii) Diazirines (**11**) are produced by the oxidation of *N*-unsubstituted diaziridines: (**10**; $R' = H$) + $Ag_2O \rightarrow$ (**11**).

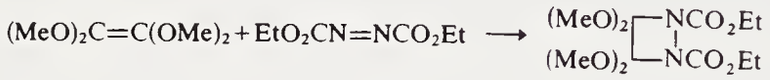
(**9**) (**10**) (**11**) (**12**) (**13**)

(iv) Diaziridinones can be obtained by nucleophilic displacement (**12** → **13**); bulky substituents are required to obtain stable products.

4.3.2.2 Four-membered Rings

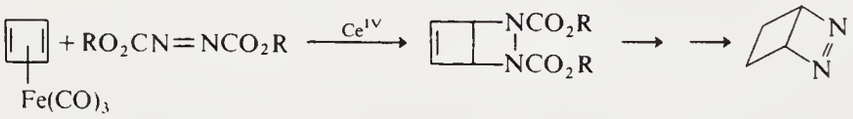
4.3.2.2.1 1,2-Diazetidines

Azodicarboxylates undergo [2 + 2] additions to alkenes activated by alkoxy ⟨71CB873⟩, alkylthio ⟨72TL4713⟩ or dialkylamino ⟨66AG416⟩ substituents to give substituted 1,2-diazetidines (Scheme 2).



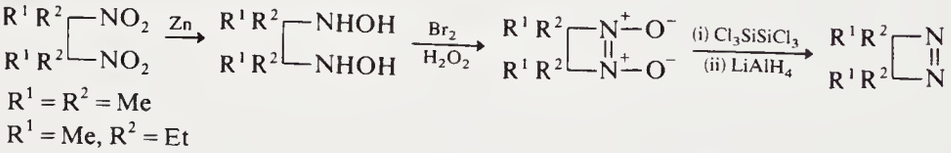
Scheme 2

Cyclobutadiene adds ⟨79AJC2659⟩ in this reaction to give fused diazetines (Scheme 3).



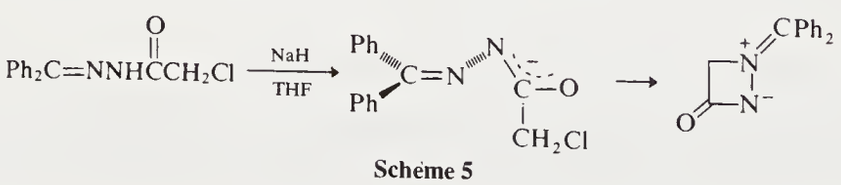
Scheme 3

Oxidative closure of β-dihydroxylamines leads to diazetine dioxides which can be further reduced in two steps to Δ^1-1,2-diazetines (Scheme 4) ⟨75JOC1409⟩.



Scheme 4

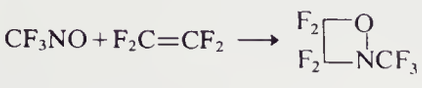
Diazetidinum betaines are prepared by displacement (Scheme 5) ⟨81JA7743⟩.



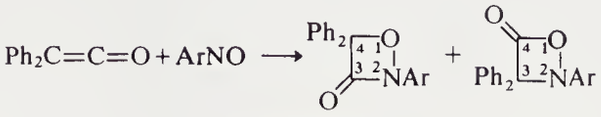
Scheme 5

4.3.2.2.2 1,2-Oxazetidines

Oxazetidines have been obtained by [2 + 2] addition of nitroso compounds to appropriate alkenes. The trifluoromethylnitroso compound reacts with polyhalogenated ethylenes ⟨69JCS(C)2119⟩, with styrene ⟨65JGU855⟩ or with allenes ⟨73JCS(P1)1561⟩ to give oxazetidines (*e.g.* Scheme 6).



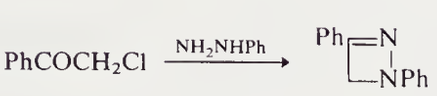
Scheme 6



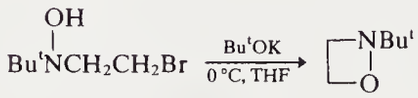
Scheme 7

The addition of nitrosobenzenes to diphenylketene gives two products. The 4-one predominates with *p*-dimethylamino- and the 3-one with *p*-methoxycarbonyl-nitrosobenzene (Scheme 7) ⟨74JOC2552⟩.

The 4*H*-1,2-oxazete *N*-oxide ring has been prepared by cyclization (Scheme 8) ⟨75AG(E)69, 75AG(E)70⟩.



Scheme 8

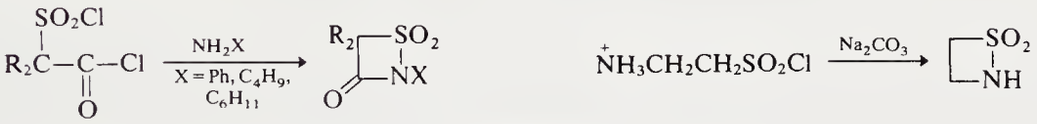


Scheme 9

β-Haloalkylhydroxylamines can be converted into oxazetidines (Scheme 9) ⟨71JA4082⟩ and similar cyclizations give *N*-substituted 4,4-diaryl-1,2-oxazetidin-3-ones ⟨68JOC3619⟩.

4.3.2.2.3 1,2-Thiazetidines

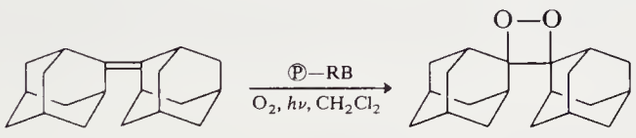
1,2-Thiazetidines are made by nucleophilic displacement (Scheme 10) ⟨75BSF(2)807⟩.



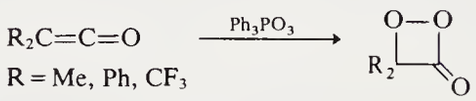
Scheme 10

4.3.2.2.4 1,2-Dioxetanes

The addition of singlet oxygen to alkenes gives dioxetanes: bisadamantylidene forms an unusually stable dioxetane (Scheme 11) ⟨75JA7110⟩.



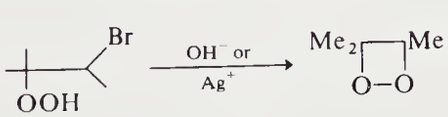
Scheme 11



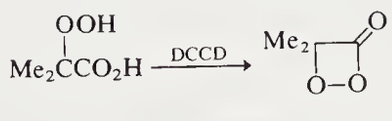
Scheme 12

Ketenes have been converted into 1,2-dioxetan-3-ones by triphenylphosphine ozonide (Scheme 12) ⟨77JA5836, 80CC898⟩.

Dioxetanes and dioxetanones have been prepared ⟨80CJC2089⟩, *e.g.* by cyclization of the β-bromohydroperoxide of 2-methyl-2-butene (Scheme 13).



Scheme 13

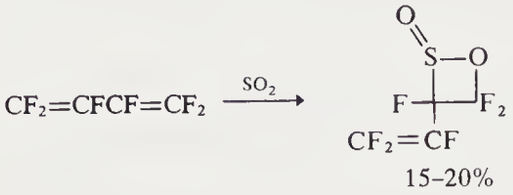


Scheme 14

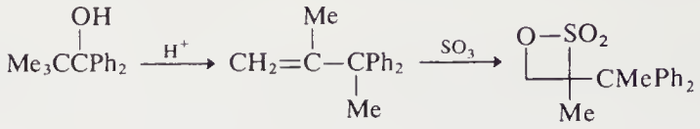
α-Peroxylactones or 1,2-dioxetan-3-ones are prepared from α-hydroperoxy acids which are cyclized with dicyclohexylcarbodiimide (Scheme 14) ⟨77JA5768⟩.

4.3.2.2.5 1,2-Oxathietanes

Polyhalogenated alkene addition to sulfur dioxide ⟨60JA6181, 66JCS(C)1171⟩ gives 1,2-oxathietane 2-oxide adducts (Scheme 15) ⟨78BAU142, 79BAU106⟩.



Scheme 15

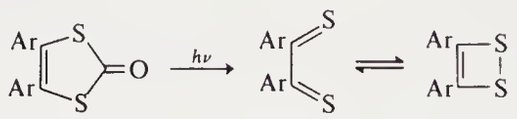


Scheme 16

Acid-catalyzed rearrangement of 1,1-diphenyl-2,2-dimethylpropanol in presence of sulfur trioxide forms a stable 1,2-oxathietane 2,2-dioxide (Scheme 16) ⟨77JCS(P1)247⟩.

4.3.2.2.6 1,2-Dithietanes

Photochemically induced extrusions of carbon monoxide generate 1,2-dithietanes in equilibrium with their valence bond tautomers, dithiones (Scheme 17) ⟨74JA3502⟩.



Scheme 17

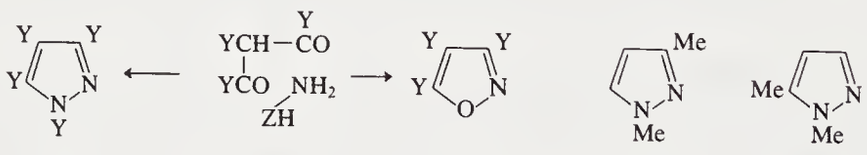
4.3.2.3 Five-membered Rings: Pyrazoles, Isoxazoles, Isothiazoles, *etc.*

Five-membered rings with two adjacent heteroatoms are most frequently made using a hydroxylamine or hydrazine derivative. However, dipolar cycloadditions are also significant. Methods forming a Z—Z bond are important particularly for sulfur-containing derivatives.

4.3.2.3.1 *Synthesis from hydrazine, hydroxylamine and hydrogen disulfide derivatives*

(i) Pyrazoles and isoxazoles from 1,3-diketones

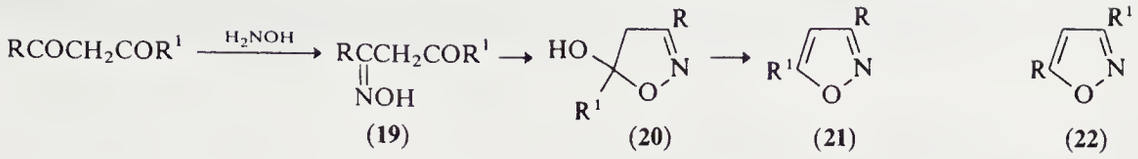
The standard syntheses for pyrazoles (**14**) and isoxazoles (**16**) involve the reactions of β-dicarbonyl compounds (**15**) with hydrazines and hydroxylamine, respectively. These reactions take place under mild conditions and are of very wide applicability; the substituents Y can be H, R, Ar, CN, CO_2Et, *etc.*



(14) (15) (16) (17) (18)

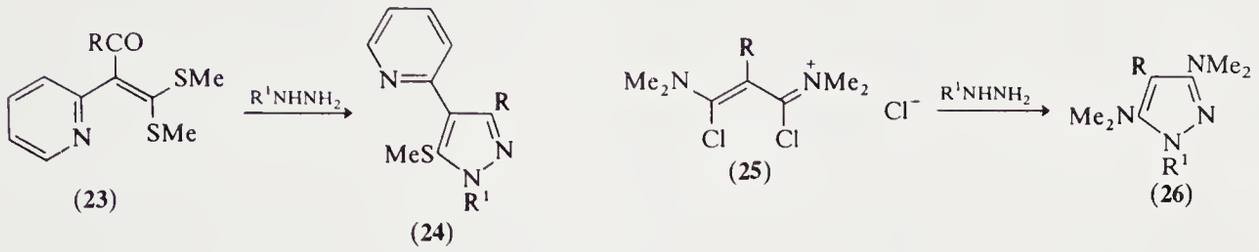
A monosubstituted hydrazine such as methylhydrazine can give two products, *e.g.* 1,3-dimethylpyrazole (**17**) and 1,5-dimethylpyrazole (**18**) ⟨77BSF1163⟩. Details regarding orientation are given in CHEC 4.04.

Reaction of a 1,3-diketone with hydroxylamine gives, *via* the isolable monoxime (**19**) and 5-hydroxydihydroisoxazole (**20**), the isoxazole (**21**). Unsymmetrical 1,3-diketones result in both possible isomers (**21**) and (**22**), but the ratio of the isomeric products can be controlled by the right combination of the 1,3-dicarbonyl component and the reaction conditions used, as described in CHEC 4.16.



(19) (20) (21) (22)

The scope of the possible modifications to the 1,3-dioxo component is illustrated by the following examples. The β-oxoketene dithioacetal (**23**) with a monosubstituted hydrazine gives the pyrazole (**24**) ⟨76BCJ398⟩. The iminium salt (**25**) with monosubstituted hydrazines gives the 3,4-bis(dimethylamino)pyrazole (**26**) ⟨68T4217, 69T3453⟩. β-Ketocyanides yield amino-pyrazoles or -isoxazoles (*e.g.* **27**→**28**).



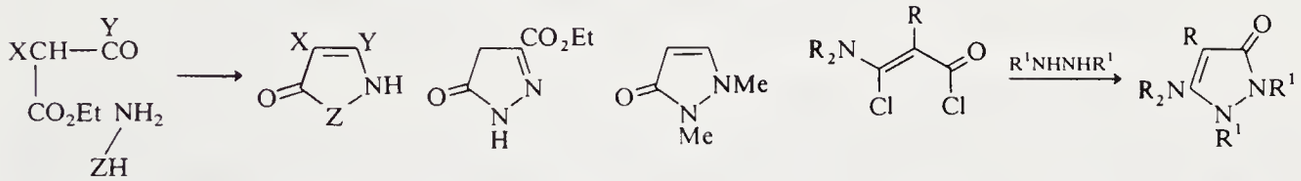
(23) (24) (25) (26)

(27) (28) (29) (30)

The dianion (**29**) of acetophenone methylhydrazone reacts with acid chlorides to give pyrazoles (**30**; see also CHEC 4.04).

(ii) Pyrazolinones and isoxazolinones

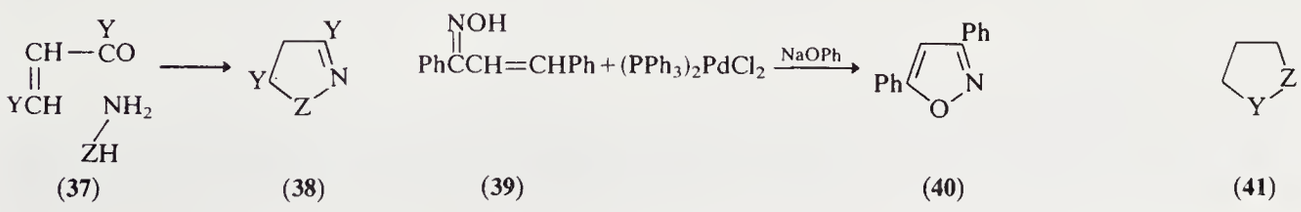
Pyrazolinones and isoxazolinones are prepared from β-keto esters and hydrazine or hydroxylamine by reactions such as (**31**→**32**) similar to those in (*i*) above. Diketene behaves as a masked β-keto ester. Acetylenecarboxylic esters can be used in place of β-keto esters to give pyrazolinones such as (**33**) and (**34**) and the corresponding isoxazolinones. β-Chloro α,β-unsaturated acid chlorides react similarly (*cf.* **35**→**36**).



(31) (32) (33) (34) (35) (36)

(iii) Pyrazolines, isoxazolines, pyrazolidines, isoxazolidines and 1,2-dithiolanes

α,β-Unsaturated ketones form pyrazolines and isoxazolines (**37**→**38**) and the intermediate hydrazones and oximes are often isolated. α,β-Unsaturated ketoximes such as (**39**) undergo oxidative ring closure with bis(triphenylphosphine)palladium dichloride to give 3,5-diphenyl-isoxazole (**40**) ⟨73TL5075⟩.

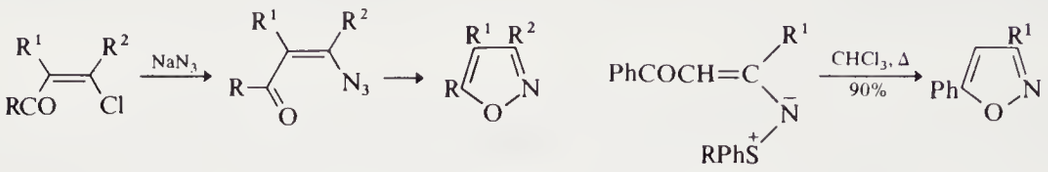


(37) (38) (39) (40) (41)

Tetrahydro compounds (**41**) can be obtained from 1,3-dibromides (with N_2H_4, NH_2OH, S_2^{2-}, *etc.*).

4.3.2.3.2 Synthesis by Z—Z bond formation

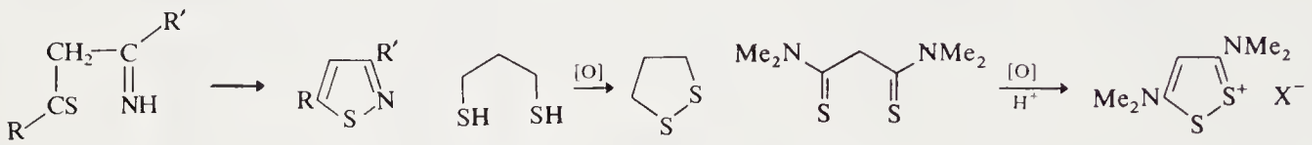
The β-acyl vinylazides (**42**) lose N_2 forming the isoxazole (**43**) in an anchimerically assisted concerted reaction ⟨75AG(E)775, 78H(9)1207⟩. The imine (**44**) on heating undergoes cyclization to isoxazoles (**45**).



(**42**) (**43**) (**44**) (**45**)

Isothiazoles (**47**) may be obtained by the cyclization of β-thioxoimines (**46**; see CHEC 4.17).

A general route to 1,2-dithiolanes (**49**) involves oxidation of the 1,3-dithiol (**48**) with hydrogen peroxide at 75 °C in acetic acid containing potassium iodide. β-Dithio compounds such as (**50**) undergo oxidation in acid to the 1,2-dithiolylium salts (**51**) ⟨76JCS(D)455⟩.



(**46**) (**47**) (**48**) (**49**) (**50**) (**51**)

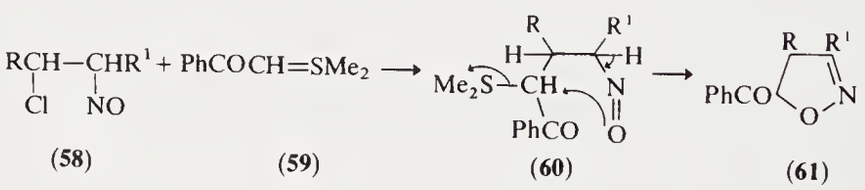
4.3.2.3.3 Other methods from acyclic precursors

Alkynes add nitrile oxides and diazoalkanes to give isoxazoles (**52**) and pyrazoles (**53**), respectively, in 1,3-dipolar cycloadditions. If an alkene is used instead of an alkyne the non-aromatic analogues (**54**; Z = NH, O) result; yields are best when the alkene contains an electron-withdrawing substituent.

(**52**) (**53**) (**54**) (**55**) (**56**) (**57**)

In a convenient route to Δ^2-isoxazoline *N*-oxides (**57**), the ylide (**56**) adds to the nitrostyrene (**55**) in the presence of copper(I) salts ⟨76JOC4933⟩.

Dimethylsulfonium phenacylide (**59**) undergoes *C*-alkylation with α-chloronitroso compounds (**58**): intermediates (**60**) cyclize to the isoxazolines (**61**) ⟨72T3845⟩.

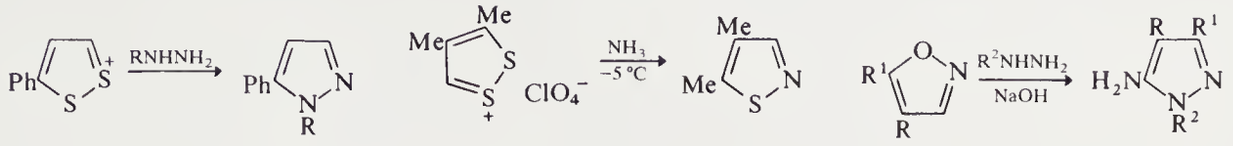


(**58**) (**59**) (**60**) (**61**)

4.3.2.3.4 From other heterocycles

1,2-Dithiolylium salts (**62**) may be converted into pyrazoles, pyrazolium salts and isothiazoles (see Section 3.4.1.6.2.ii). For example, 4-phenyl-1,2-thiolylium salt (**62**) with hydrazine,

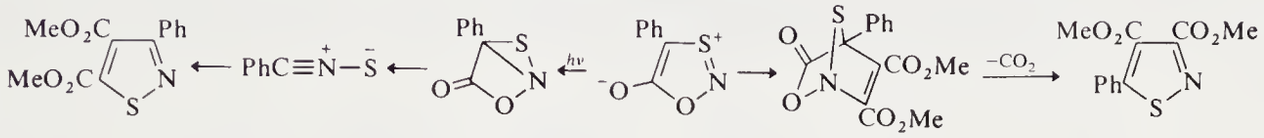
methylhydrazine or phenylhydrazine yielded the corresponding pyrazoles (**63**). 3,4-Dimethyl-1,2-dithiolylium perchlorate (**64**) with ammonia gave 4,5-dimethylisothiazole (**65**).



(**62**) (**63**) (**64**) (**65**) (**66**) (**67**)

Isoxazoles (**66**) in the presence of base undergo ring opening to α-ketonitriles. In the presence of hydrazines, 5-aminopyrazoles (**67**) are obtained.

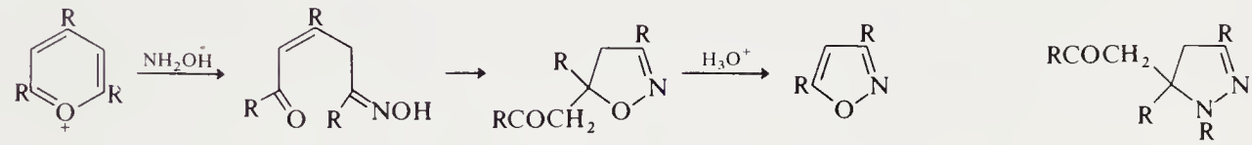
The anhydro-5-hydroxy-1,3,2-oxathiazolylium hydroxide system (**71**) and DMAD thermally yielded an intermediate 1:1 cycloadduct (**72**) which lost CO_2 forming dimethyl 2-phenylisothiazole-3,4-dicarboxylate (**73**) ⟨72CB196⟩. Irradiation of (**71**) in neat DMAD formed the valence tautomer (**70**) which lost CO_2 to give the nitrile sulfide dipole (**69**) captured by DMAD to form dimethyl 3-phenylisothiazole-4,5-dicarboxylate (**68**) ⟨75JA6197⟩ (see also CHEC 4.17). Anhydro-4-hydroxy-1,2,3-triazolium hydroxide reacts with DMAD similarly to give (**71**).



(**68**) (**69**) (**70**) (**71**) (**72**) (**73**)

With hydroxylamine, the pyrylium salt (**74**) undergoes ring opening to an intermediate 1,5-enedione oxime (**75**); conjugate addition of the α,β-unsaturated ketone gives (**76**), which in the presence of acid forms the isoxazole (**77**).

Reaction of (**74**) with a hydrazine resulted in the pyrazoline (**78**). A similar transformation of chromone is described in Section 3.2.1.6.4.iv.



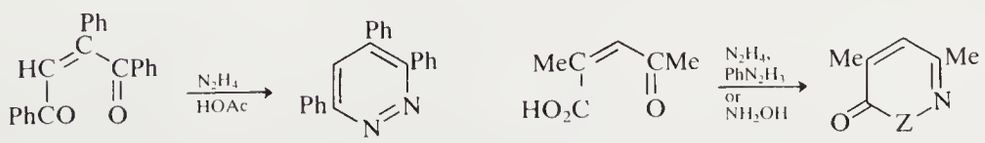
(**74**) (**75**) (**76**) (**77**) (**78**)

4.3.2.4 Six-membered Rings: Pyridazines, 1,2-Oxazines, *etc.*

The most important synthetic methods involve condensation of hydrazine, hydroxylamine or hydrogen peroxide with a 1,4-oxygenated carbon chain, and these procedures are particularly useful for the preparation of pyridazines and 1,2-oxazines. Other methods include Diels–Alder reactions of a diene with an azo or nitroso compound.

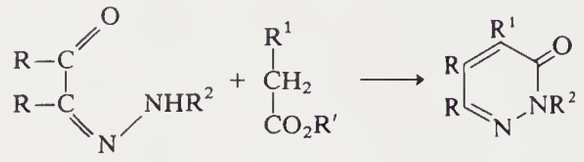
4.3.2.4.1 Synthesis from hydrazine or hydroxylamine derivatives

1,4-Dicarbonyl compounds with a double bond in the 2,3-position condense with hydrazine to give pyridazines (*e.g.* **79**→**80**). If one of the carbonyl groups in the starting material is part of a carboxyl group or a potential carboxyl group, then reactions with hydrazines or hydroxylamine lead to pyridazinones or 1,2-oxazinones (*e.g.* **81**→**82**; Z = NH, NPh, O). Similarly a cyano group leads to an amino or imino product.



(**79**) (**80**) (**81**) (**82**)

Saturated 1,4-dicarbonyl compounds give 1,4-dihydro-pyridazines or -pyridazinones, *etc.*, which are easily oxidized. 1,2-Diketone monohydrazones and esters containing a reactive CH_2 group give 3-pyridazinones (**83**→**84**) ⟨54HCA1467⟩.

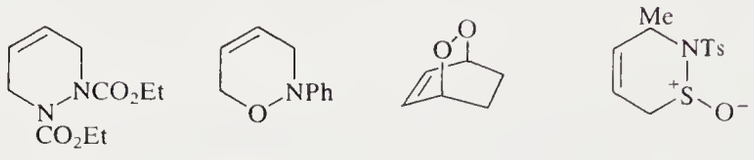


(**83**) (**84**)

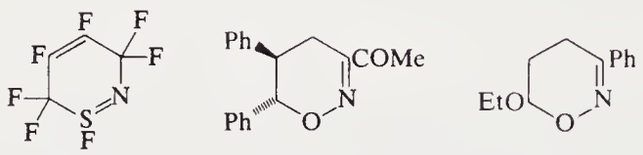
4.3.2.4.2 By cycloaddition reactions

Reduced pyridazines, 1,2-oxazines, 1,2-dioxins and 1,2-thiazines can be prepared by Diels–Alder-type reactions. Butadiene condenses with $EtO_2CN{=}NCO_2Et$ and nitrosobenzene to yield (**85**) and (**86**), respectively. Cyclohexadiene and singlet oxygen form (**87**) and pentadiene with TsNSO gives (**88**). For dihydropyridazines, diimine generated *in situ* has been used ⟨79TL1333⟩.

Perfluoro-1,2-thiazine (**89**) is prepared by the cycloaddition of thiazyl fluoride (FSN) and perfluoro-1,3-butadiene $CF_2{=}CFCF{=}CF_2$ ⟨79CC35⟩.



(**85**) (**86**) (**87**) (**88**)



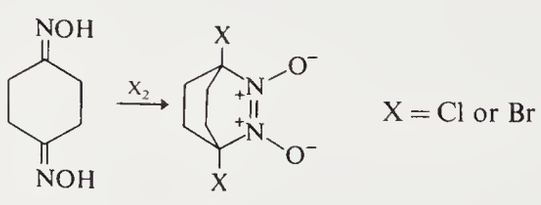
(**89**) (**90**) (**91**)

5,6-Dihydro-4*H*-1,2-oxazines are prepared by the cycloaddition of nitrosoalkenes and alkenes: $CH_2{=}C(NO)COMe$ with *trans*-stilbene gives (**90**) ⟨78CC847⟩.

Tetrahydro-1,2-oxazines are accessible by cycloaddition of nitrosoalkanes with electron-rich alkenes, *e.g.* $EtOCH{=}CH_2 + CH_2{=}CPh{-}N{=}O$→(**91**).

4.3.2.4.3 Other methods from acyclic precursors

The pyridazine dioxide derivative (**92**) was made by intramolecular nitroso compound dimerization as shown (Scheme 18). 1,2-Oxathiin 2,2-dioxides are obtained by the addition of sulfuric acid to α,β-unsaturated ketones, *e.g.* (**93**)→(**94**) ⟨66HC(21-2)774⟩. 1,2-Dithiins are synthesized from conjugated diynes using benzyl thiol: reductive debenzylation of intermediate (**95**) by sodium in liquid ammonia at −70 °C gives, after aerial oxidation, the 1,2-dithiin (**96**) ⟨67AG(E)698⟩.



(**92**)

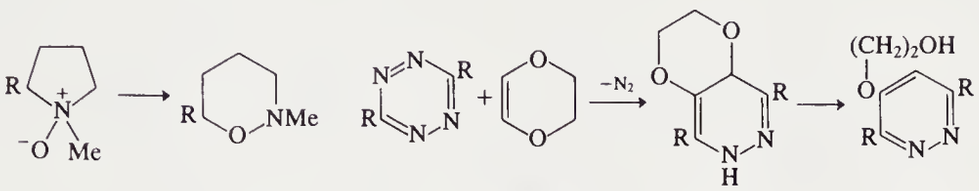
Scheme 18

(93) (94) (95) (96)

4.3.2.4.4 From other heterocycles

The Meisenheimer-type rearrangement of 1-substituted pyrrolidine 1-oxides gives tetrahydro-2*H*-1,2-oxazines (**97**→**98**).

1,4-Dihydropyridazines (**101**) result from Diels–Alder addition of *s*-tetrazines (**99**) with electron-rich alkenes (*e.g.* **100**). Frequently the products aromatize, as in (**101**)→(**102**).



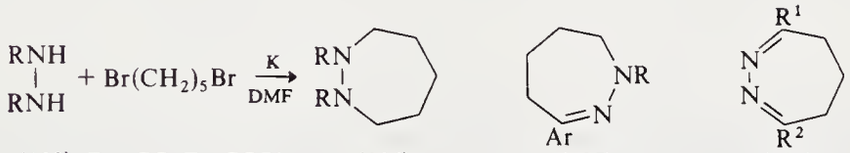
(97) (98) (99) (100) (101) (102)

4.3.2.5 Seven-membered Rings

4.3.2.5.1 1,2-Diazepines

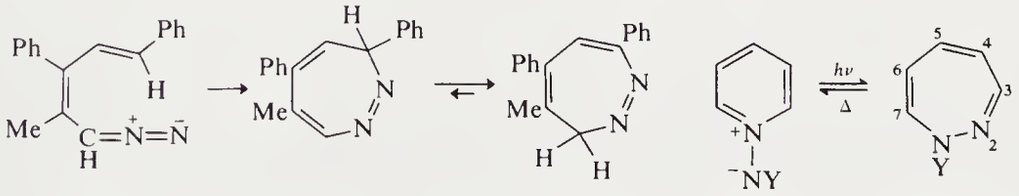
1,5-Dihalides and 1,5-ditosylates have been used for the preparation of fully saturated monocyclic systems, *e.g.* (**103**→**104**).

5-Halo-aldehydes and -ketones react with a wide range of substituted hydrazines to give 4,5,6,7-tetrahydro-1,2-diazepines (**105**) ⟨76H(4)1509⟩. The reaction of 1,5-diketones with hydrazine has been much used as a source of 5,6-dihydro-4*H*-1,2-diazepines (**106**) ⟨67AHC(8)21⟩.



(**103**) R = CO_2Et, COPh (**104**) (**105**) (**106**)

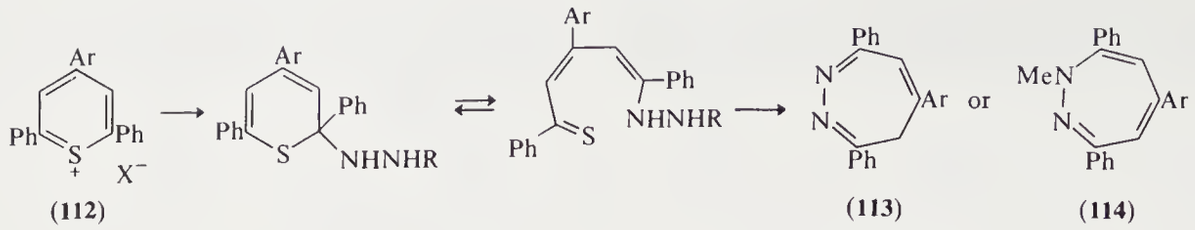
1,7-Electrocyclization of dienyldiazoalkanes, *e.g.* (**107**), provides a general route to 3*H*-1,2-diazepines, *e.g.* (**109**). In the example shown the eight-π-electron cyclization is followed by a 1,5-sigmatropic hydrogen shift of (**108**) ⟨82UP51800⟩. Such hydrogen shifts are rapid at room temperature and the isomer ratio reflects thermodynamic stability.



(107) (108) (109) (110) (111)

Photochemical conversion of pyridine *N*-imides, *e.g.* (**110**), gives 1*H*-1,2-diazepines (**111**) ⟨81ACR348⟩ (see Section 3.2.3.12.4.iii).

Reactions of hydrazine and methylhydrazine with pyrylium or thiinium salts, *e.g.* (**112**), provide major routes to 4*H*-1,2-diazepines (**113**) and 1*H*-1,2-diazepines (**114**) ⟨76H(4)1509, 80CJC494⟩.

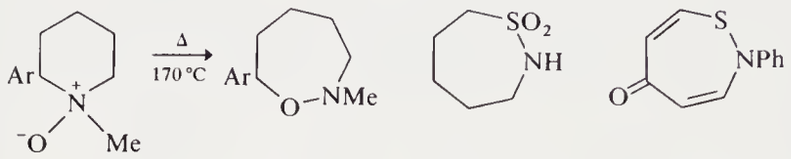


(112) (113) (114)

4.3.2.5.2 1,2-Oxazepines and 1,2-thiazepines

The Meisenheimer rearrangement of *t*-amine *N*-oxides has been applied to the synthesis of monocyclic 1,2-oxazepines, *e.g.* (**115**) ⟨82H(19)173⟩.

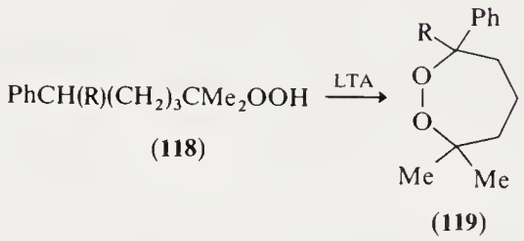
The cyclic sulfonamide (**116**) can be prepared by heating 5-aminopentanesulfonyl chloride. The ketone HC≡CC(O)CH=CHSCN reacts with amines to give the 1,2-thiazepin-5-one system (**117**) ⟨61CB1606⟩.



(115) (116) (117)

4.3.2.5.3 1,2-Dioxepins and 1,2-dithiepins

The monocyclic saturated peroxides (**119**; R = H, Me) have been prepared by the treatment of the hydroperoxides (**118**) with LTA ⟨81S633⟩.



(118) (119)

Simple 1,2-dithiepanes are prepared by the oxidation of α,ω-alkanedithiols using hydrogen peroxide, iodine or oxygen. Another useful general route involves the reaction of 1,5-dibromo compounds with sodium disulfide.

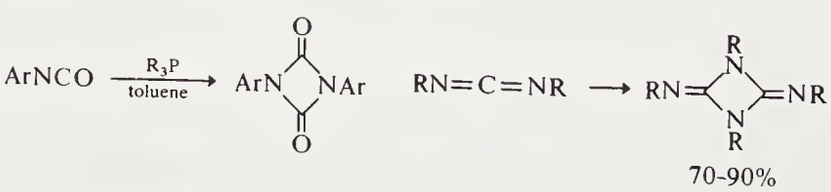
4.3.3 TWO HETEROATOMS IN THE 1,3-POSITIONS

4.3.3.1 Four-membered Rings

4.3.3.1.1 1,3-Diazetidines

Aromatic isocyanates readily dimerize to 1,3-diazetidine-2,4-diones when catalyzed by trialkylphosphines (Scheme 19) ⟨66JA3582, 76JGU799⟩.

Arylcarbodiimides also dimerize with alkyl phosphite catalysis ⟨68CB174⟩ to the bis(imino)-1,3-diazetidines (Scheme 20) ⟨72LA(762)167⟩.

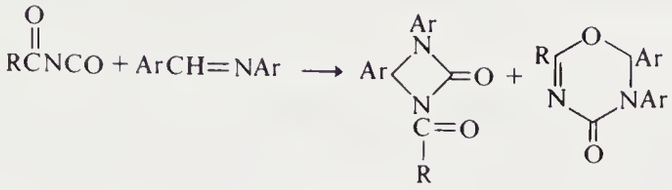


Scheme 19

70-90%

Scheme 20

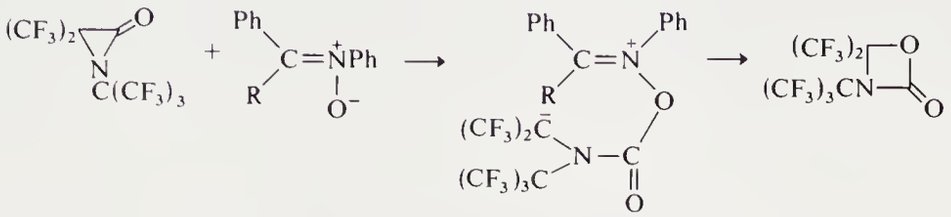
Imines and isocyanates ⟨80CC313⟩ form 1,3-diazetidinones (Scheme 21).



Scheme 21

4.3.3.1.2 1,3-Oxazetidines

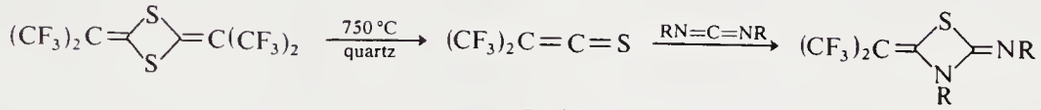
Nitrones transfer oxygen to α-lactams, giving 1,3-oxazetidin-2-ones (Scheme 22) ⟨80DOK(253)886⟩.



Scheme 22

4.3.3.1.3 1,3-Thiazetidines

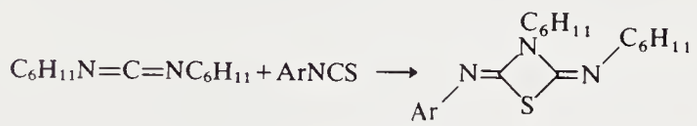
Thioketene dimers crack at high temperatures into monomers, which then undergo [2 + 2] additions (Scheme 23) ⟨70JOC3470⟩.



70%

Scheme 23

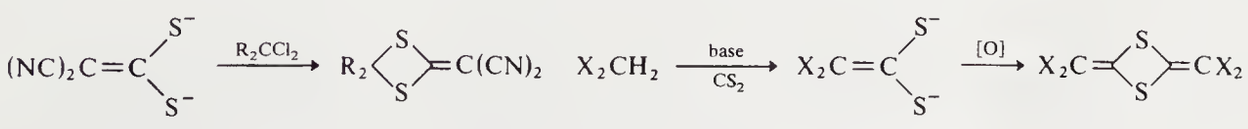
Isothiocyanates add carbodiimides across the carbon–sulfur bond (Scheme 24). The reaction works best for aryl isothiocyanates with electron-withdrawing groups ⟨75JCS(P2)1475⟩.



Scheme 24

4.3.3.1.4 1,3-Dithietanes

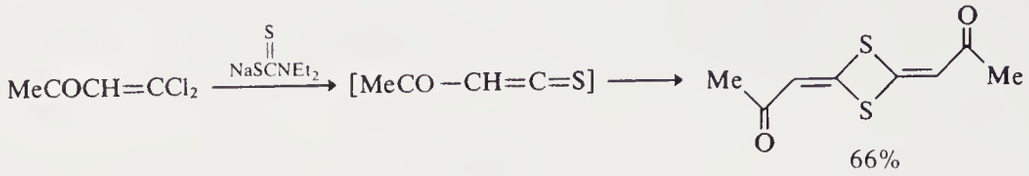
Active methylene compounds with carbon disulfide and base form reactive salts which undergo [3 + 1] additions to a variety of alkylating agents, even *gem*-dihaloethylenes (Scheme 25) ⟨77CC207, 80S907⟩. The salts can be oxidized to symmetrical 'desaurin' derivatives (Scheme 26) ⟨62CB2861⟩.



X = CO_2R or CN

Scheme 25 **Scheme 26**

Some thiones dimerize to 1,3-dithietanes ⟨75BSF(2)1670⟩. Thioketenes dimerize spontaneously; α-keto thioketenes give 'desaurins' (*cf.* Scheme 27) ⟨76BAU1913⟩.

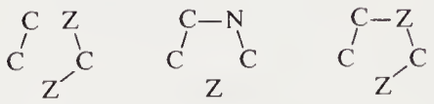


Scheme 27

4.3.3.2 Five-membered Rings: Oxazoles, Thiazoles, Imidazoles, Dithiolium Salts and Derivatives

4.3.3.2.1 Overview

We consider successively the synthesis of fully conjugated derivatives by ring closures of type (**120**; Section 4.3.3.2.2), (**121**; Section 4.3.3.2.3) and (**122**; Section 4.3.3.2.4). This is followed by a consideration of methods involving C—C bond formation and/or 1,3-dipolar cycloadditions (Section 4.3.3.2.5), and syntheses of oxo-containing and reduced rings from acyclic precursors (Section 4.3.3.2.6). Finally transformations from other heterocycles are described (Section 4.3.3.2.7).



(**120**) (**121**) (**122**)

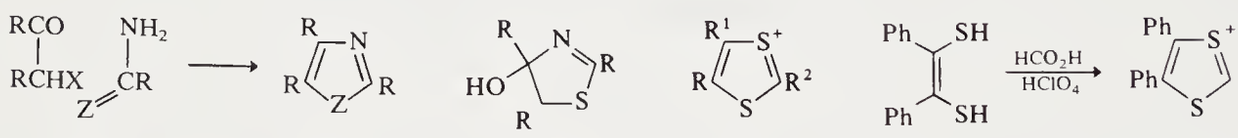
4.3.3.2.2 Synthesis from $C_2 + ZCZ'$ components

α-Halo ketones react with amides (100°C, no solvent), thioamides (reflux in EtOH) and amidines to give oxazoles, thiazoles and imidazoles (**123**→**124**; Z = O, S, NH), respectively. This is the most important thiazole synthesis, and both the thioamide and the halo ketone components can be varied widely (see CHEC 4.19). Intermediates of type (**125**) can sometimes be isolated.

Guanidines with α-halo ketones form 2-aminoimidazoles. α-Hydroxy ketones also react with amidines to form imidazoles, and a variety of substituents can be introduced into the imidazole nucleus (CHEC 4.08).

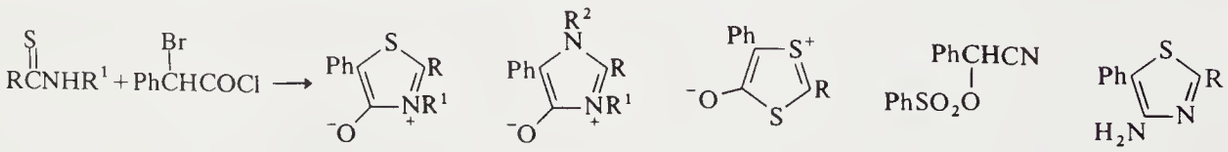
The reaction of α-halo ketones with primary amides is appropriate for oxazoles containing one or more aryl groups. Formamide may be used resulting in a free 2-position in the oxazole. Ureas form 2-aminooxazoles (*cf.* CHEC 4.18).

α-Halo ketones react with thioacids to form 1,3-dithiolylium salts (**126**) which are also obtained from α-dimercaptoethylenes (**127**→**128**; *cf.* CHEC 4.32).



(**123**) (**124**) (**125**) (**126**) (**127**) (**128**)

α-Haloacyl halides are used for the synthesis of mesoionic rings. The secondary thioamide (**129**) with α-bromophenylacetyl chloride (**130**) gave the 4-oxidothiazolium hydroxide (**131**). Similarly substituted amidines and dithioic acids with the same reagents formed the corresponding imidazolium (**132**) and dithiolylium (**133**) mesoionic systems ⟨77JOC1633, 77JOC1639⟩.



(**129**) (**130**) (**131**) (**132**) (**133**) (**134**) (**135**)

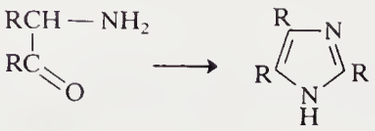
Replacement of the α-halo ketone by a cyano analogue can lead to amino derivatives. The benzenesulfonyl ester of mandelonitrile (**134**) with a primary thiomide, $RCSNH_2$, gives the 4-aminothiazole (**135**).

4.3.3.2.3 Synthesis of imidazoles, oxazoles and thiazoles from acylamino ketones

α-Acylamino ketones on heating with ammonium acetate are converted into imidazoles. 2,4,5-Triarylimidazoles (**137**) were prepared in this way from (**136**) ⟨73CB2415⟩, and the reaction is capable of numerous variations.

Oxazoles may be similarly prepared in good yields. Thus, 5-ethoxy-4-methyloxazole (**139**) was obtained by treating ethyl 2-formamidopropionate (**138**) with phosphorus pentoxide in chloroform at 55 °C ⟨72JCS(P1)909, 914⟩. Known collectively as the Robinson–Gabriel synthesis, these cyclodehydrations can be effected by sulfuric acid or anhydrous hydrogen fluoride (*cf.* CHEC 4.18).

(**136**) (**137**) (**138**) (**139**) (**140**)



(**141**) (**142**)

α-Acylamino ketones also provide a convenient synthesis of thiazoles on treatment with phosphorus pentasulfide (Gabriel's method). Substituents are usually restricted to alkyl, aryl and alkoxy derivatives. Thus, the α-acylamino ketone (**136**) with P_4S_{10} gave the thiazole (**140**).

In a related reaction α-amino ketones (**141**) with iminoesters RC(NH)OMe give imidazoles (**141** → **142**).

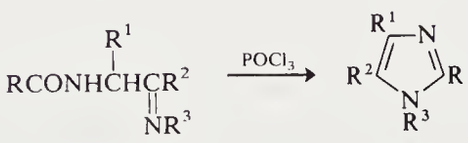
4.3.3.2.4 Other syntheses of imidazoles, oxazoles, thiazoles, dithiolyliums and oxathiolyliums by cyclization of C_2ZCZ' components

Reactions of this type include the following:

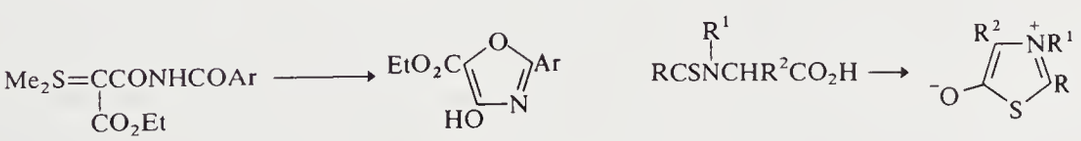
(i) α-Acylamino Schiff's bases (**143**) with phosphoryl chloride give the 1-substituted imidazoles (**144**) ⟨78LA1916⟩.

(ii) The dimethylsulfonium ylide and aroyl isocyanate addition product (**145**) on heating cyclized to the 4-hydroxyoxazole (**146**) ⟨73T1983⟩. The diazoimide $PhCONMeCOCN_2C_6H_4NO_2$ thermolyzes to a keto carbene which cyclizes to a mesoionic 4-oxidooxazolium system ⟨75CL499⟩.

(iii) Ring closure of (**147**) under acid cyclodehydration conditions gave the mesoionic 5-oxidothiazolium system (**148**).



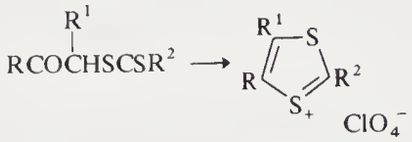
(**143**) (**144**)



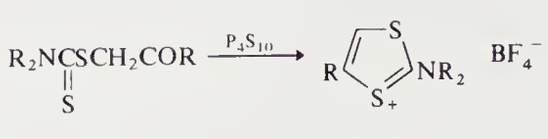
(**145**) (**146**) (**147**) (**148**)

(iv) α-Oxoalkyl dithioesters (**149**) are cyclized by perchloric acid to dithiolylium salts (**150**) ⟨80AHC(27)151⟩. Similarly dithiocarbamate (**151**) with phosphorus pentasulfide and tetrafluoroboric acid gives the 2-amino-1,3-dithiolylium tetrafluoroborate (**152**) ⟨69CPB1924⟩. The dithiol (**153**) with $Cl_2C{=}X$ (X = O or S) gives (**154**) ⟨76S489⟩.

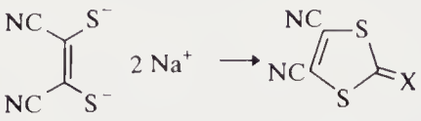
(v) 2,5-Diaryl derivatives of the 1,3-oxathiolylium system (**155**) are prepared by acid-catalyzed cyclization of the β-keto thioesters, $ArCOSCH_2COPh$.



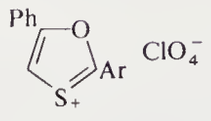
(**149**) (**150**)



(**151**) (**152**)



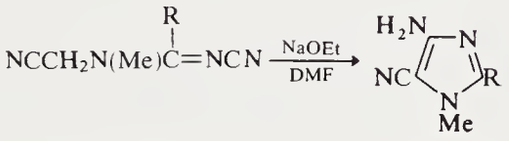
(**153**) (**154**)



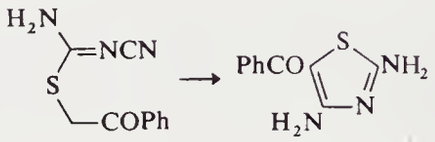
(**155**)

4.3.3.2.5 Synthesis of imidazoles, oxazoles and thiazoles by C—C bond formation or 1,3-dipolar addition

4-Aminoimidazoles (**157**; R = Me, SMe) are formed on base treatment of the appropriate precursors (**156**) ⟨75HCA2192⟩. Similarly the 4-aminothiazole (**159**) is obtained from the cyanoamidine (**158**) ⟨73JPR497⟩.

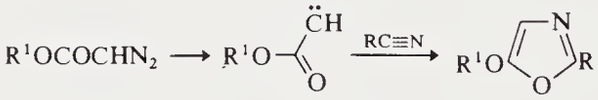


(**156**) (**157**)



(**158**) (**159**)

Decomposition of the diazoacetic ester (**160**) to the keto carbene (**161**) is promoted by copper(II) trifluoromethanesulfonate. In the presence of nitriles, (**161**) is captured by 1,3-dipolar addition giving the oxazole (**162**) ⟨75JOM(88)115⟩ (see also CHEC 4.03.8.1).



(**160**) (**161**) (**162**)

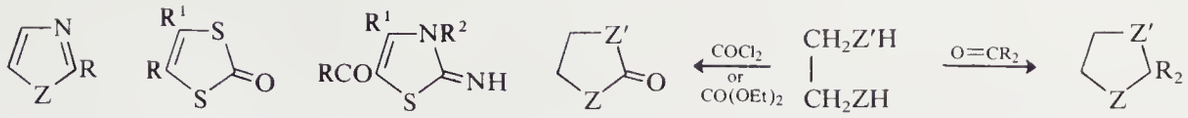
4.3.3.2.6 Synthesis of azolinones and reduced rings from acyclic precursors

(i) β-Hydroxy-, β-amino- and β-mercapto-acylamines ($HZCH_2CH_2NHCOR$; Z = O, NH, S) cyclize to give Δ^2-oxazolines, Δ^2-imidazolines and Δ^2-thiazolines (**163**).

(ii) 1,2-Difunctional ethanes (**165**; Z, Z′ = O, S, NH) react with carbonyl chloride and carbonate esters to give 2-oxazolidinones and analogous derivatives (**165**→**164**)

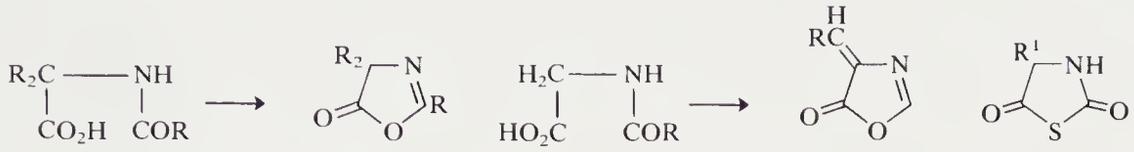
(iii) The 1,3-dithiol-2-one (**167**) is obtained by ring closure of $RCSCHR^1SCSOR$ ⟨76S489⟩ and treatment of $RCOCH{=}CR^1NHR^2$ with thiocyanogen effects cyclization to (**168**) ⟨83MI40300⟩.

(iv) 1,2-Difunctional ethanes (**165**; Z, Z′ = O, S, NH) react with aldehydes and ketones to form oxazolidines, *etc.* (**165**→**166**). Such reactions are used extensively to protect *cis* hydroxy groups (*e.g.* sugars + acetone→isopropylidene sugars) and carbonyl groups (*e.g.* steroidal ketones + ethylene glycol→ethylene ketals).



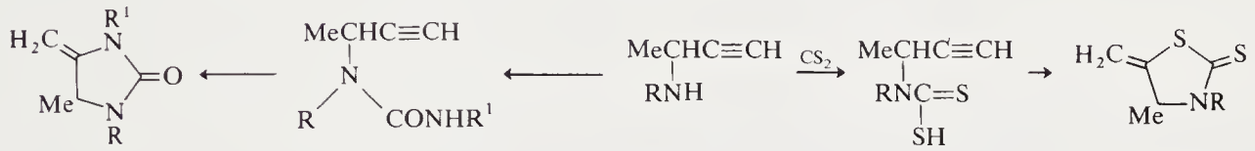
(163) (164) (165) (166) (167) (168)

(v) α-Acylaminocarboxylic acids are converted into 5(4*H*)-oxazolinones by acid anhydrides (**169**→**170**). In an extension of this reaction, *N*-acyl derivatives of glycine (**171**) react with aldehydes with concomitant cyclization to give azlactones (**172**); this is the basis of the Erlenmeyer synthesis of amino acids. Treatment of $ROCSNHCHR^1CO_2SiME_3$ with PBr_3 affords the thiazolidine-2,5-dione (**173**) ⟨71CB3146⟩.



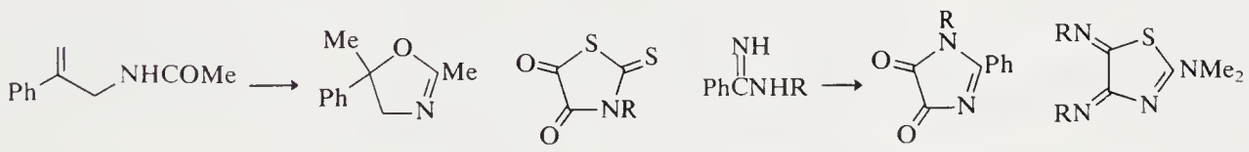
(169) (170) (171) (172) (173)

(vi) Nitrogen, oxygen and sulfur nucleophiles can add to unsaturated carbon–carbon systems. This synthetic approach is illustrated by the reaction of the propargylamine (**176**) with carbon disulfide. The intermediate dithiocarbamic acid (**177**) cyclizes to the thiazole (**178**) ⟨49JCS786⟩. The NH group of (**176**) adds isocyanates to give ureas (**175**) which are converted by sodium methoxide into 4-methylene-2-imidazolinones (**174**) ⟨63JOC991⟩. *N*-Allyl-amides, -urethanes, -ureas and -thioureas undergo intramolecular cyclization in 60–96% sulfuric acid to give 2-oxazolines and 2-thiazolines as illustrated by the conversion of *N*-2-phenylallylacetamide (**179**) into 2,5-dimethyl-5-phenyl-2-oxazoline (**180**) ⟨70JOC3768⟩ (see also CHEC 4.19).



(174) (175) (176) (177) (178)

(vii) Reaction of RNHCSSH with oxalyl chloride gives the thiazolidine-4,5-dione (**181**) (see CHEC 4.19), and the same reagent with *N*-alkylbenzamidine (**182**) at 100–140 °C formed the 1-alkyl-2-phenylimidazole-4,5-dione (**183**; see CHEC 4.08). Iminochlorides of oxalic acid react with *N,N*-disubstituted thioureas to give the 2-dialkylaminothiazolidine-4,5-dione bis-imides (**184**). Phenyliminooxalic acid dichloride likewise yielded thiazolidine derivatives on reaction with thioureas ⟨71KGS471⟩.

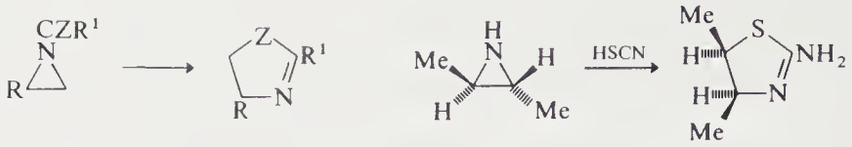


(179) (180) (181) (182) (183) (184)

4.3.3.2.7 Synthesis from heterocycles

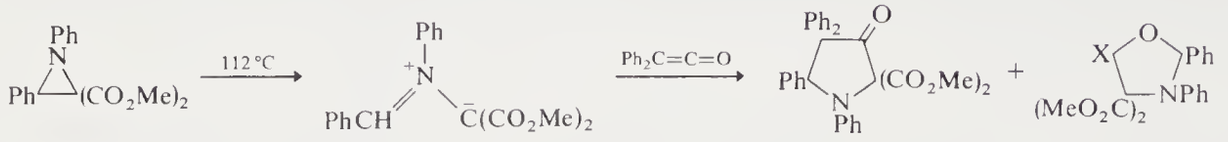
Aziridines (**185**; Z = O, S, NR) undergo a facile ring opening and subsequent closure on heating with sodium iodide in acetonitrile to give, for example, the oxazoline (**186**; Z = O). This aziridine ring-opening reaction is a particularly attractive route to imidazolines and ring-fused imidazolines (**186**; Z = NR) ⟨62JOC2943⟩ (see Section 3.5.2.2)

Aziridines also undergo ring enlargement on treatment with thiocyanic acid: *cis*- and *trans*-2,3-dimethylaziridine (**187**) thus gave *trans*- and *cis*-2-amino-4,5-dimethyl-2-thiazoline (**188**) stereospecifically ⟨72JOC4401⟩.



(185) (186) (187) (188)

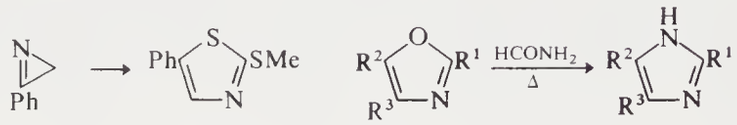
Thermolysis of the aziridine (**189**) with diphenylketene gave the pyrrolidone (**190**; minor product) and the oxazolidine (**191**; major product).



(189) (190) (191) X = CPh_2 (192) X = H, $CHPh_2$

The preferential addition to the C=O bond is explained in terms of steric effects ⟨72CC199⟩. Similar addition to diphenylacetaldehyde takes place with the same orientation to give the oxazolidine (**192**).

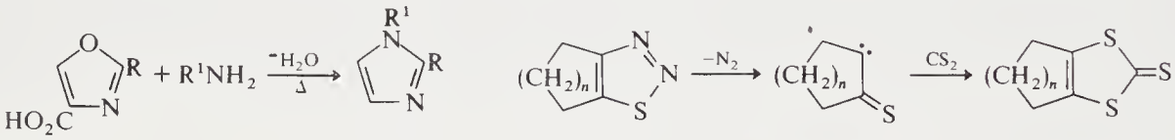
The thermal reaction of 2-phenyl-1-azirine (**193**) with carbon disulfide followed by methylation gave 2-methylthio-5-phenylthiazole (**194**).



(193) (194) (195) (196)

Photoisomerization of pyrazoles, isoxazoles and isothiazoles into imidazoles, oxazoles and thiazoles, respectively, is described in Section 3.4.1.2.4.

The oxazole (**195**) heated with formamide gave the imidazole (**196**); oxazolium cations undergo similar conversions. Primary amines convert oxazole-4-carboxylic acids (**197**) at 150 °C into imidazoles (**198**) with accompanying decarboxylation ⟨53CB88⟩ (see CHEC 4.07 and 4.18).

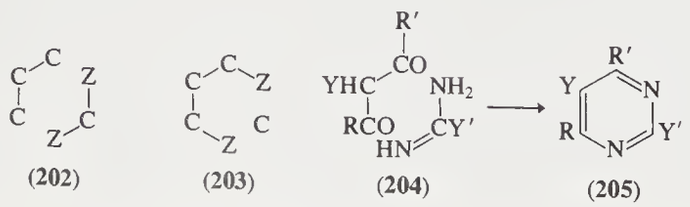


(197) (198) (199) (200) (201)

Thermolysis of the 1,2,3-thiadiazoles (**199**) in the presence of carbon disulfide leads *via* the thiocarbonyl carbene (**200**) to the ring-fused 1,3-dithiole-2-thione (**201**) ⟨76JOC730⟩.

4.3.3.3 Six-membered Rings

There are two major routes to six-membered rings, (**202**) and (**203**). For the preparation of pyrimidines, methods corresponding to types (**202**) are the most important. Saturated compounds, *i.e.* 1,3-dioxanes, 1,3-oxathianes and 1,3-dithianes, result from syntheses of type (**203**).



(202) (203) (204) (205)

R, R′ = H, Me, Ph, CO_2Et
Y = H, Me, Ph, Br, NO, NO_2
Y′ = H, Me, Ph, OMe, SMe, NH_2
Basic catalyst, *e.g.* NaOEt–EtOH

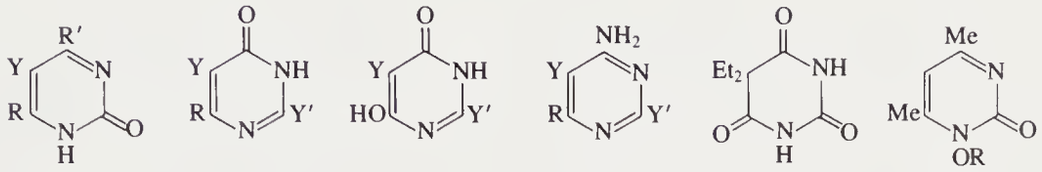
4.3.3.3.1 Pyrimidine syntheses: C—C—C + Z—C—Z and related types

Numerous pyrimidines have been synthesized by reaction of a 1,3-dicarbonyl compound, or a potential 1,3-dicarbonyl compound, with an amidine; representative substituents are shown in structures (**204**) and (**205**).

The following modifications are noteworthy (see CHEC 2.13 for a full discussion).

(i) The amidine can be replaced by urea, thiourea or guanidine when 2-pyrimidinones (**206**), thiones or 2-aminopyrimidines result.

(ii) If one or both of the carbonyl groups in the 1,3-dicarbonyl compound is in the form of an ester, 4-pyrimidinones (**207**) and their 6-hydroxy derivatives (**208**) are formed.



(**206**) (**207**) (**208**) (**209**) (**210**) (**211**)

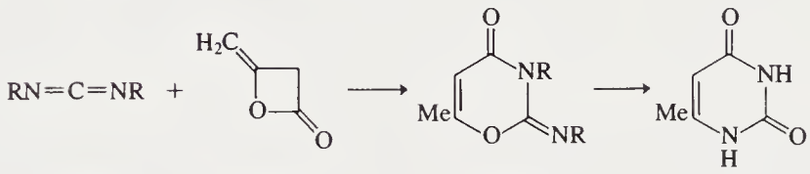
(iii) Replacement of one or both of the carbonyl groups by a cyano group leads to 4-amino- (**209**) or 4,6-diamino-pyrimidines.

(iv) If the central carbon atom of the carbonyl compound is tetrasubstituted, non-aromatic derivatives are produced, *e.g.* $Et_2C(CO_2Et)_2$ reacts with urea to yield veronal (**210**).

(v) Use of *N*-methoxyurea gives *N*-oxide derivatives such as (**211**).

(vi) Use of an α,β-unsaturated compound gives a dihydropyrimidine.

Amidines, ureas, thioureas, *S*-alkylisothioureas and carbodiimides (**212**) also react with diketene (**213**) to give pyrimidines (*e.g.* **215**). Amidines, *S*-alkylisothioureas and carbodiimides, however, initially form 1,3-oxazines (*e.g.* **214**) which are converted into pyrimidines on subsequent treatment with acid or base.



(**212**) (**213**) (**214**) (**215**)

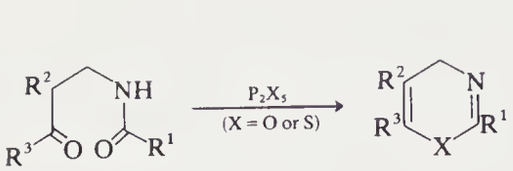
4.3.3.3.2 Other syntheses from acyclic precursors

1,3-Dioxins (**217**) are obtained from the acid-catalyzed condensation of diketene (**216**) with ketones $R^1R^2C{=}O$.

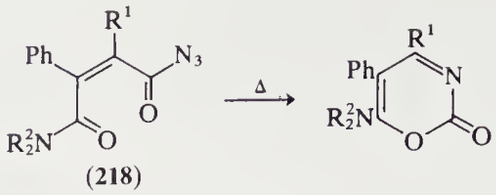
(**216**) (**217**)

The most important route to 1,3-dioxanes, 1,3-oxathianes and 1,3-dithianes is the acid-catalyzed condensation of an aldehyde or ketone with a 1,3-diol, a 3-mercaptoalcohol or a 1,3-dithiol, respectively (*cf.* **222**→**221** below); such reactions are used extensively for protection. The Prins reaction yields 1,3-dioxanes ⟨77S661⟩; it involves the acid-catalyzed condensation of alkenes with aldehydes with 1,3-diols as intermediates.

Routes to 4*H*-1,3-oxazines and -thiazines involve the cyclization of amides or thioamides with acidic reagents (Scheme 28) ⟨78AHC(23)1⟩.



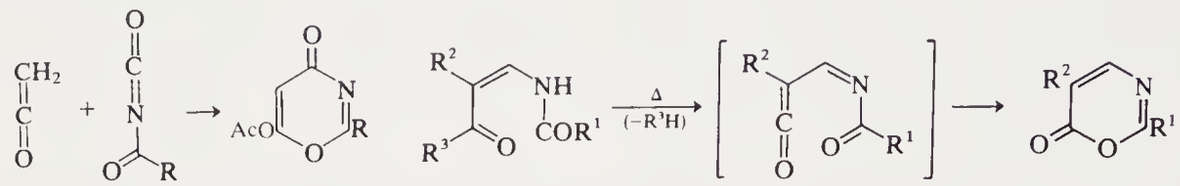
Scheme 28



(218)

Scheme 29

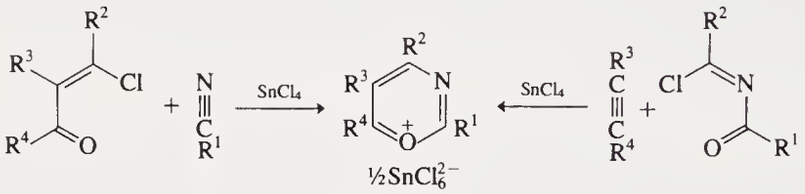
1,3-Oxazin-2-ones can be made by the thermolysis of carbonyl azides (**218**; Scheme 29) ⟨79CC719⟩. Oxazin-4-ones are obtained by cycloadditions between isocyanates and ketenes (Scheme 30).



Scheme 30 (219) (220)

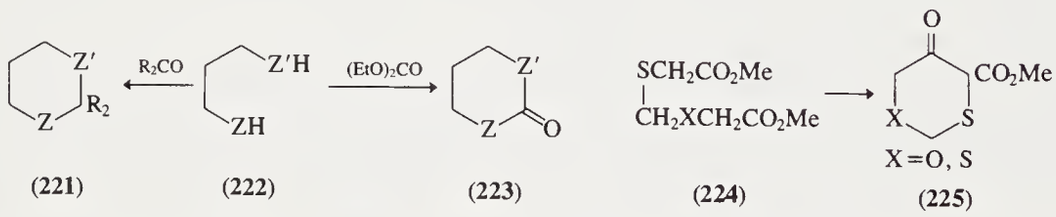
1,3-Oxazin-6-ones (**220**) are made by heating β-acylamino esters (**219**; $R^1 = Ar$, $R^3 = OMe$) ⟨74AG(E)533⟩.

Routes to 1,3-oxazinium salts consist of 1,4-cycloadditions either between α,β-unsaturated β-chlorocarbonyl compounds and nitriles or between *N*-acylimidoyl chlorides and alkynes. Tin(IV) chloride is an effective catalyst for both reactions (*cf.* Scheme 31). 1,3-Thiazinium perchlorates are synthesized by treating oxazinium salts with hydrogen sulfide in absolute acetonitrile and then with perchloric acid ⟨72S333⟩.



Scheme 31

The method $ZC_3Z + C$ is used for the preparation of reduced pyrimidines, oxazines and thiazines as well as for dioxanes, dithianes and oxathianes as mentioned above (*e.g.* **222**→**221**, **223**; Z, Z′ = NH, O, S).



(221) (222) (223) (224) (225)

Dieckmann cyclization has been used for the synthesis of non-aromatic heterocycles of this type (**224**→**225**).

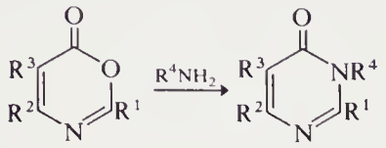
4.3.3.3.3 Syntheses from heterocycles

1,3-Oxazines and 1,3-thiazines are converted into pyrimidine derivatives by ammonia. For the conversion of 1,2,4-thiadiazoles into pyrimidines see Section 3.4.1.6.5.i.

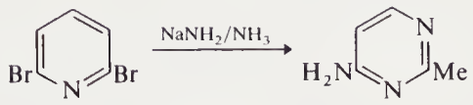
4,6-Diaryl-1,2,3,5-oxathiadiazines (**226**; from sulfur trioxide and aryl isocyanates) with β-diketones yield pyrimidines (**227**). *s*-Triazine reacts with RCH_2CN to give 4-aminopyrimidines (**228**; see Section 3.2.1.6.1.iii for a similar reaction), and with electron-rich alkenes and alkynes to yield pyrimidines such as (**229**) from EtC≡CMe (Section 3.2.1.9.5.ii).

(226) (227) (228) (229)

1,3-Oxazin-6-ones are converted by amines into 4-pyrimidinones (Scheme 32) and the ANRORC reaction (*e.g.* Scheme 33) can be used to prepare pyrimidines from 2-bromopyridines (*cf.* Section 3.2.3.10.5).



Scheme 32



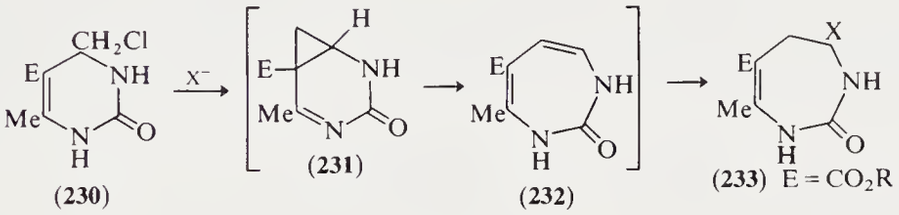
Scheme 33

4.3.3.4 Seven-membered Rings

4.3.3.4.1 1,3-Diazepines

The condensation of 1,4-diamines with a variety of carboxylic acid derivatives, *e.g.* imidate esters, orthoformic esters, *N*-ethoxycarbonylthioamides ⟨77JOC2530⟩, nitriles and ethoxyacetylene, produces the cyclic amidine linkage —N=C(R)NH— ⟨67AHC(8)21, p. 40⟩. Cyclic ureas, —NHC(O)NH—, have been similarly produced using carbonyl chloride, *N,N'*-carbonyldiimidazole, carbon monoxide, thiocarbonyl chloride or carbon disulfide ⟨67AHC(8)21, p. 38⟩.

4-Chloromethylpyrimidines such as (**230**), with bases, undergo ring expansion to 1,3-diazepin-2-ones (**233**; X = OR, CN, $CH(CO_2Et)_2$) ⟨77CJC895⟩ *via* (**231**) and (**232**).

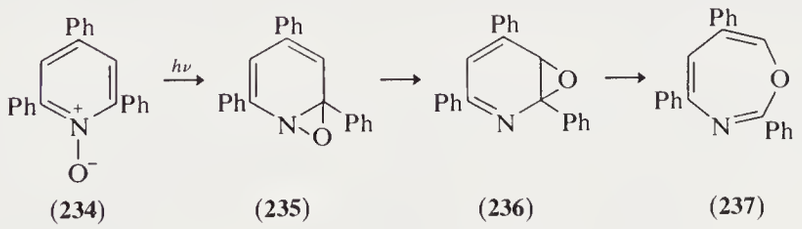


(230) (231) (232) (233) E = CO_2R

Fully unsaturated monocyclic 1,3-diazepines have been prepared by thermolysis of 1*H*-1,2-diazepines with electron-releasing groups in the 4- and 6-positions ⟨79JOC2683, 80CC444⟩.

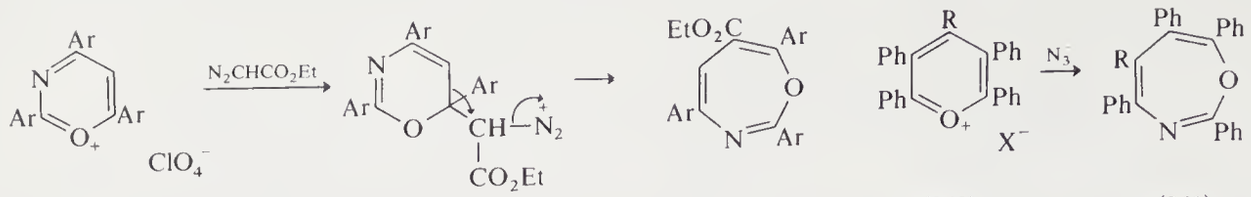
4.3.3.4.2 1,3-Oxazepines and 1,3-thiazepines

The photochemical rearrangement of aromatic *N*-oxides, *e.g.* (**234**), gives the fully unsaturated 1,3-oxazepine system, *e.g.* (**237**), *via* an oxaziridine intermediate (**235**) which rearranges by a 1,5-sigmatropic shift to (**236**) converted to the product by disrotatory ring opening ⟨76H(4)1391⟩.



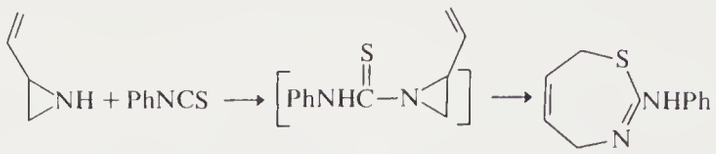
(234) (235) (236) (237)

Monocyclic 1,3-oxazepines (**239**) can be prepared by reaction of aliphatic diazo compounds with 1,3-oxazinium perchlorates (**238**) ⟨74S187⟩. Tetra- and penta-phenyl-1,3-oxazepines (**241**; R = H or Ph) have been obtained by the reaction of azide ion with pyrylium salts (**240**) ⟨78H(11)331⟩.



(238) (239) (240) (241)

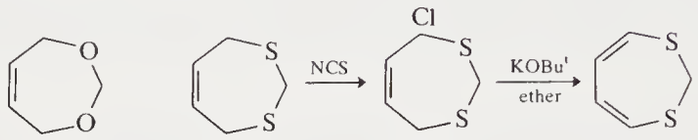
2-Vinylaziridine (**242**) with phenyl isothiocyanate or 4-chlorothiobenzoyl thioglycollate gives (**244**), presumably *via* the intermediate (**243**) ⟨71JOC3076⟩.



(242) (243) (244)

4.3.3.4.3 1,3-Dioxepins and 1,3-dithiepins

4,7-Dihydro-1,3-dioxepins (**245**) are prepared by the reaction of *cis*-butene-1,4-diols with aldehydes, and a similar route gave the dithia derivative (**246**) which was converted into the more unsaturated compound (**248**) *via* (**247**) ⟨76TL1251⟩.



(245) (246) (247) (248)

Fully saturated 1,3-dithiepins can be prepared by the Lewis acid-catalyzed exchange reactions of 1,4-butanedithiol with an appropriate diethyl acetal. 1,3-Dithiepan-2-one is obtained *via* the reaction of 1,4-dichlorobutane with alkali trithiocarbonates ⟨72HC(26)598, p. 616⟩.

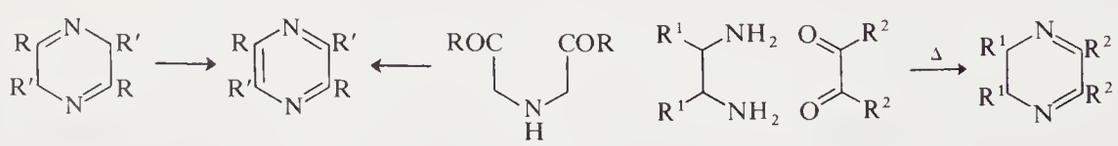
4.3.4 TWO HETEROATOMS IN THE 1,4-POSITIONS

4.3.4.1 Six-membered Rings

4.3.4.1.1 Pyrazines from acyclic compounds

An important preparation of pyrazines (**250**) is from α-amino ketones $RCOCH_2NH_2$ which spontaneously condense to give 2,5-dihydropyrazines (**249**). The α-amino ketones are often prepared *in situ* by reduction of isonitroso ketones, and the dihydropyrazines are usually oxidized to pyrazines before isolation (*cf.* Section 3.2.2.3.3). Catalytic reduction of α-azido ketones also leads to 2,5-dihydropyrazines ⟨80OPP265⟩. Similarly, α-nitro ketones may be reduced to the α-amino ketones which dimerize spontaneously ⟨69USP3453278⟩.

The condensation of an α-diketone with a 1,2-diaminoalkane gives 2,3-dihydropyrazines (Scheme 34), which like their 2,5-analogues can be oxidized by air, or better by MnO_2 in ethanolic KOH, to pyrazines ⟨78MI21400⟩.

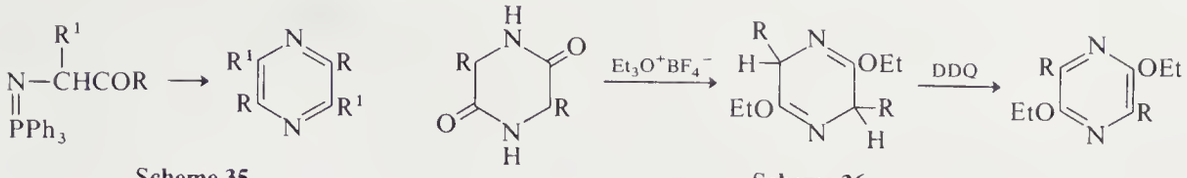


(249) (250) (251)

Scheme 34

Pyrazines are obtained by oxidative ring closure of bis(acylmethyl)amines (**251**) with ammonia.

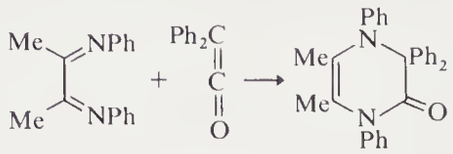
Conversion of α-azido ketones to pyrazines by treatment with triphenylphosphine in benzene (Scheme 35) proceeds in moderate to good yields ⟨69LA(727)231⟩.



Scheme 35 (252) Scheme 36

Cyclodimerization of α-amino acids [$RCH(NH_2)CO_2H$] gives 2,5-dioxopiperazines (**252**). Treatment of 2,5-dioxopiperazines with triethyl- or trimethyl-oxonium fluoroborate followed by oxidation with DDQ, chloranil or iodine results in pyrazine formation (Scheme 36) ⟨71JCS(P1)2494⟩.

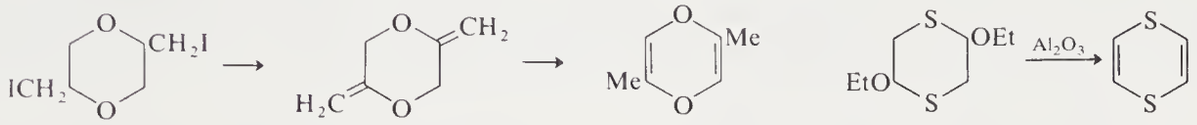
The cycloaddition of Scheme 37 yields tetrahydropyrazinones.



Scheme 37

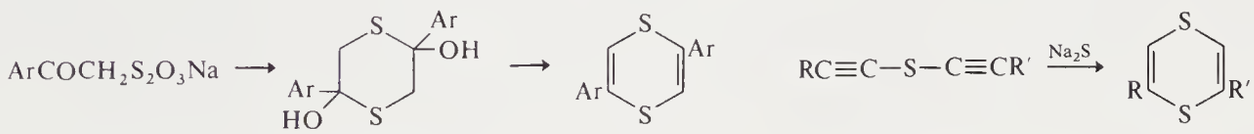
4.3.4.1.2 1,4-Dioxins, 1,4-dithiins, 1,4-oxazines and 1,4-thiazines

A two-step synthesis of 1,4-dioxin from dioxane is *via* 2,3,5,6-tetrachloro-1,4-dioxane which is dechlorinated using magnesium and iodine ⟨39JA3020⟩. The route to 2,5-dimethyl-1,4-dioxin uses 2,5-diiodomethyl-1,4-dioxane (diepiiodohydrin) as precursor (Scheme 38) ⟨57JA6219⟩.



Scheme 38 (253) (254)

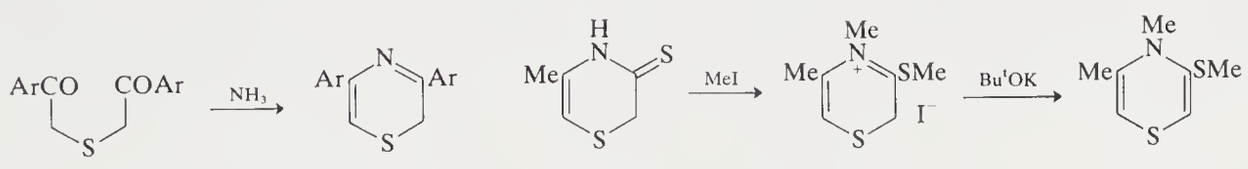
Dithiins are prepared by vapor phase dealkoxylation of 2,5-dialkoxy-1,4-dithianes (from $HSCH_2CH(OEt)_2 + H^+$) over alumina at 260–265 °C (**253**→**254**). 2,5-Diaryl derivatives, however, are best prepared from Bunte salts (**255**; Scheme 39) with acid *via* the intermediate diol (**256**). Addition of sodium sulfide to alkynyl sulfides (**257**) in DMF/methanol yields (**258**) ⟨75RTC163⟩.



(255) (256) (257) (258)

Scheme 39

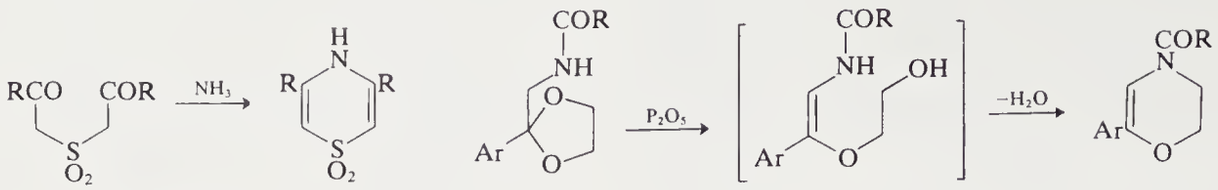
2*H*-1,4-Thiazines are formed when the sulfides (**259**) are reacted with ammonia (Scheme 40) ⟨67JMC591⟩. The 3,4-dihydrothiazine-3-thione (**260**) is converted by methyl iodide into the thiazinium salt (**261**), deprotonation of which yields a 4*H*-thiazine (**262**) ⟨69JHC247⟩. 1,4-Thiazine 1,1-dioxides are formed by the cyclodehydration of diacylsulfones and ammonia (Scheme 41) ⟨72OS(52)135⟩.



(259) (260) (261) (262)

Scheme 40

Dihydro-1,4-oxazines (**264**) are available through the treatment of acetals (**263**) with phosphorus pentoxide in pyridine ⟨79SC631⟩.

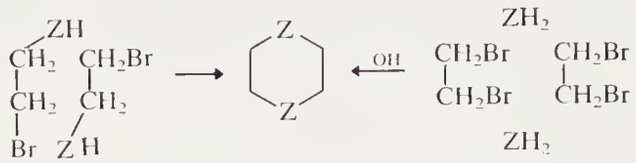


Scheme 41

(263) (264)

4.3.4.1.3 Non-aromatic rings from acyclic compounds

Piperazines, dioxanes and dithianes can be prepared as shown (**265**, **267**→**266**; Z = NH, O, S) from fragments CCZ + CCZ or $C_2 + C_2 + Z + Z$.

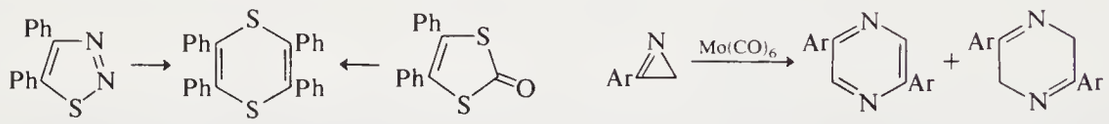


(265) (266) (267)

4.3.4.1.4 From heterocyclic precursors

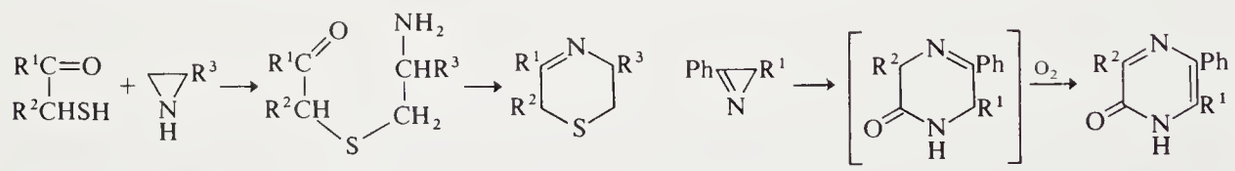
1,4-Dithiins are obtained upon photolysis of thiadiazoles, *e.g.* (**268**)→(**269**) ⟨81JA486⟩. Photolysis of the dithiocarbonate (**270**) also gives (**269**; 82%) ⟨73ZC424⟩.

Aziridine is converted into piperazine on NH_3 treatment; 1-substituted aziridines give 1,4-disubstituted piperazines when reacted with Grignard reagents. Azirines (**271**) with Group VI metal carbonyls give pyrazines (**272**) and dihydropyrazines (**273**).



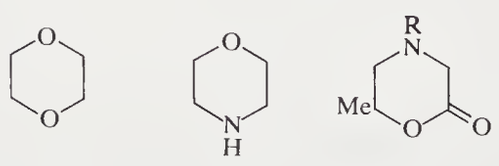
(268) (269) (270) (271) (272) (273)

A general type of [3 + 3] heterocyclization involves initial nucleophilic attack on the electrophilic three-membered heterocycle by a 1,3-electrophile–nucleophile. Aziridines (**275**) with either α-mercapto ketones (**274**) or with a mixture of a ketone and sulfur give 5,6-dihydro-1,4-thiazines (**275**→**276**→**277**). Azirines (**278**) can be used for the preparation of pyrazinones (**279**) from α-amino esters $R^2CH(NH_2)CO_2Et$ and of 1,4-oxazinones from α-hydroxy esters ⟨83TL1153⟩.



(274) (275) (276) (277) (278) (279)

1,4-Dioxanes (**280**) are produced in excellent yields from oxiranes and dilute sulfuric acid. 1,4-Dioxanes (**280**) are also conveniently obtained by acid-catalyzed condensation of oxiranes with glycols, while use of ethanolamine gives morpholine (**281**). Base-catalyzed reaction of oxiranes with α-amino acids and esters gives tetrahydro-1,4-oxazin-2-ones, *e.g.* propene oxide + $RNHCH_2CO_2H$→(**282**). 1,4-Dithianes have been prepared by the dimerization of thiiranes either in the vapor phase or in the presence of acid catalysts.

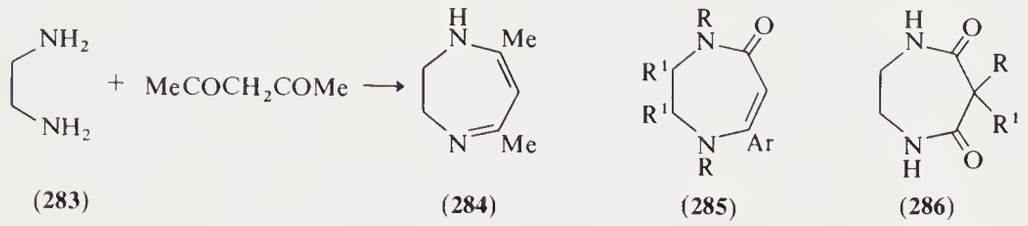


(280) (281) (282)

4.3.4.2 Seven-membered Rings

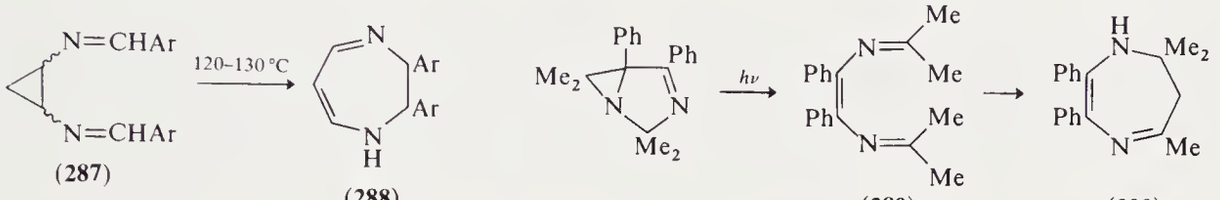
4.3.4.2.1 1,4-Diazepines

Ethylenediamine (**283**) and its *N*-substituted analogues with 1,3-dialdehydes or -diketones give 2,3-dihydro-1,4-diazepines, *e.g.* (**284**) ⟨78H(11)550⟩. 1,4-Diazepin-5-ones, *e.g.* (**285**), can be readily prepared by the reactions of 1,2-diamines with β-keto esters ⟨67AHC(8)21, p. 57⟩. Similarly reactions with malonic acids and esters give 1,4-diazepine-5,7-diones (**286**) ⟨67AHC(8)21, pp. 55, 69, 68CRV747, p. 781⟩.



(**283**) (**284**) (**285**) (**286**)

Bis-anils of 1,2-diaminocyclopropanes (**287**) undergo a thermal Cope rearrangement followed by hydrogen migration to give the 2,3-diaryldihydrodiazepines (**288**) ⟨78H(11)552⟩.



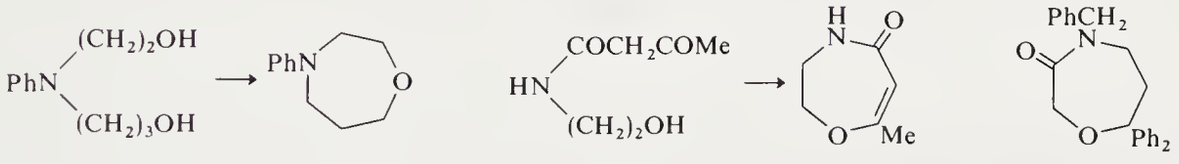
(**287**) (**288**) (**289**) (**290**)

The enediimine (**289**) underwent thermal transformation to (**290**) ⟨72CC1116⟩.

4.3.4.2.2 1,4-Oxazepines and 1,4-thiazepines

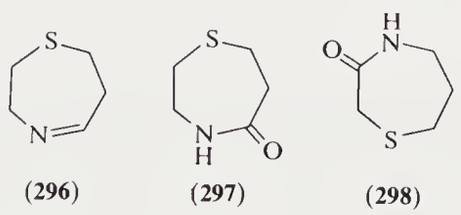
The monocyclic systems (**292**) and (**294**) have been obtained by the dehydrative cyclization of (**291**) and (**293**) respectively.

The use of α-haloacyl halides as the C—C fragment leads to 1,4-oxazepin-3-ones, *e.g.* (**295**) ⟨77USP4010166⟩.



(**291**) (**292**) (**293**) (**294**) (**295**)

2-Aminoethanethiol reacts with α,β-unsaturated or β-halo ketones to give (**296**). Similarly, reaction with α,β-unsaturated acids, esters or acid chlorides, and with 3-halopropionyl halides, yields 5-oxo derivatives such as (**297**). Thioglycollic acid ($HSCH_2CO_2H$) with 3-bromopropylamine gives (**298**).

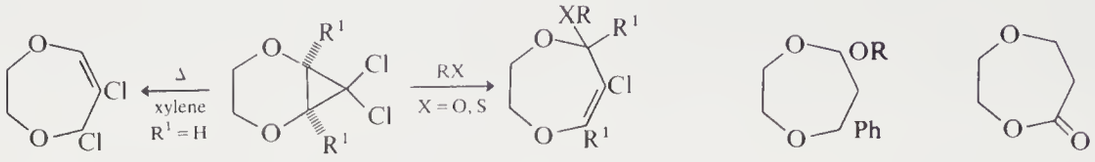


(**296**) (**297**) (**298**)

4.3.4.2.3 1,4-Dioxepins and 1,4-dithiepins

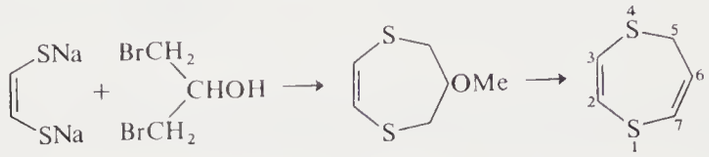
The 2,3-dihydro-5*H*-1,4-dioxepins (**299**) and (**301**) can be obtained from 1,4-dioxin–halocarbene adducts (**300**) ⟨77ZC331⟩. Saturated rings of type (**302**) have been prepared by the treatment of

cyclic acetals of ethane-1,2-diol with vinyl ethers in the presence of boron trifluoride. 1,4-Dioxepan-5-one (**303**) results from the reaction of bromoform and silver nitrate with aqueous dioxane ⟨60AG415⟩.



(**299**) (**300**) (**301**) (**302**) (**303**)

The unsaturated 5*H*-1,4-dithiepin (**305**) is synthesized by an elimination of the methyl ether (**304**) ⟨75TL1895⟩.



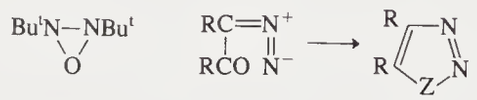
(**304**) (**305**)

The fully saturated 1,4-dithiepane system can be prepared by reactions of propane-1,3-dithiol with 1,2-dibromoethane, and of ethane-1,2-dithiol with 1,3-dihalopropanes ⟨72HC(26)598, p. 619⟩.

4.3.5 THREE HETEROATOMS IN THE 1,2,3-POSITIONS

4.3.5.1 Three- and Four-membered Rings

Valence isomerization is used in the formation of oxadiaziridines [$Bu^tN{=}N^+(O^-)Bu^t \rightarrow$ **306**] and triaziridines ⟨70JOC2482, 80CC1197⟩.



(**306**) (**307**) (**308**)

4.3.5.2 Five-membered Rings

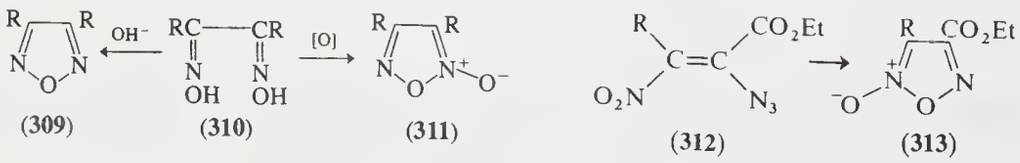
4.3.5.2.1 Formation of a bond between two of the heteroatoms

(i) 1,2,3-Triazoles and 1,2,3-thiadiazoles

Diazo ketones are converted by amines into 1,2,3-triazoles and by hydrogen sulfide into 1,2,3-thiadiazoles (**307**→**308**; Z = NR, S).

(ii) 1,2,5-Oxadiazoles

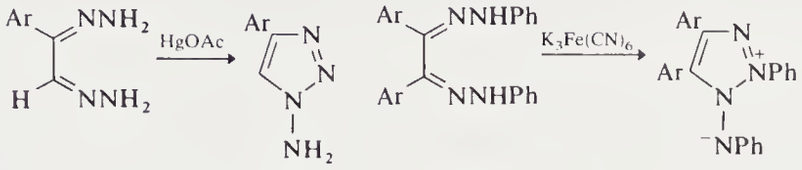
α-Dioximes (**310**) can be cyclized to furazans (**309**) and furoxans (**311**). β-Nitrovinylazides (**312**) spontaneously cyclize to the furoxan (**313**) with loss of N_2 ⟨75AG(E)775⟩.



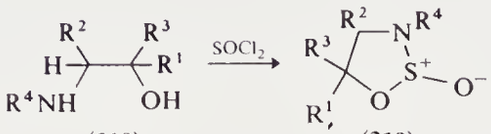
(**309**) (**310**) (**311**) (**312**) (**313**)

(iii) 1,2,3-Triazoles

Oxidative processes leading to N—N bond formation convert the bis-hydrazone (**314**) into the 1-amino-1,2,3-triazole derivative (**315**) [$Hg_2(OAc)_2$ or MnO_2] ⟨67TL3295, 71JPR882, 71ZC179⟩. The osazone (**316**) with potassium ferricyanide gives the zwitterionic 1,2,3-triazole (**317**) ⟨74T445⟩.



(**314**) (**315**) (**316**) (**317**)



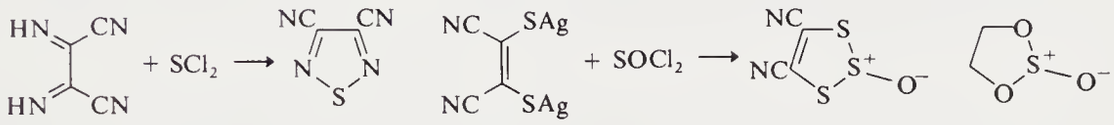
(**318**) (**319**)

(iv) 1,2,3-Oxathiazoles

1,2,3-Oxathiazole *S*-oxides are prepared by the reaction of thionyl chloride with suitable 1,2-disubstituted ethanes: the 2-aminoethanol (**318**) gives (**319**) (CHEC 4.34).

(v) 1,2,5-Thiadiazoles

An acyclic NCCN system in which the N—C links may be *sp*, sp^2 or sp^3 hybridized reacts with sulfur monochloride or sulfur dichloride to form the appropriate 1,2,5-thiadiazole ⟨68AHC(9)107, 67JOC2823⟩. Thus, *cis*-diaminomaleonitrile (**320**) gives 3,4-dicyano-1,2,5-thiadiazole (**321**) ⟨72JOC4136⟩. Tables 16 and 17 in CHEC 4.26 list the various substituted systems prepared in this fashion.



(**320**) (**321**) (**322**) (**323**) (**324**)

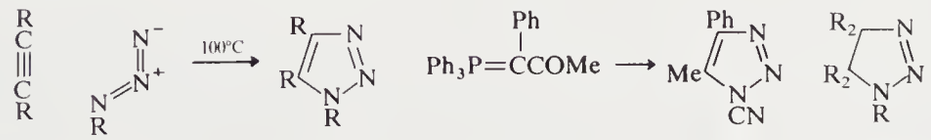
(vi) 1,2,3-Trithioles and 1,3,2-dioxathiolanes

4,5-Dicyano-1,2,3-trithiole 2-oxide (**323**) is prepared from the silver salt of 2,3-dimercapto-maleonitrile (**322**) and thionyl chloride ⟨66HC(21-2)1⟩. Similarly, ethylene glycol and $SOCl_2$ give 1,3,2-dioxathiolane 2-oxide (**324**), the parent saturated five-membered cyclic sulfite (see CHEC 4.33).

4.3.5.2.2 Other methods

(i) By dipolar cycloadditions

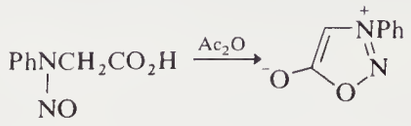
Alkynes react with alkyl and aryl azides to give 1,2,3-triazoles (**325**→**326**). Suitable phosphoranes behave similarly; thus (**327**) with cyanazide N_3CN provides the 1,2,3-triazole-1-carbonitrile (**328**). Alkenes which are activated by electron-withdrawing groups, or are strained, give 1,2,3-triazolines (**329**) with azides.



(**325**) (**326**) (**327**) (**328**) (**329**)

(ii) By cyclodehydration

Reaction of the *N*-nitrosoglycine (**330**) with acetic anhydride gives the anhydro-5-hydroxy-1,2,3-oxadiazolium hydroxide (**331**).



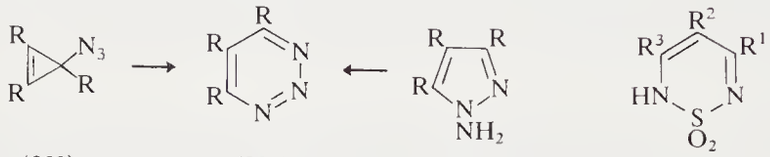
(**330**) (**331**)

(iii) From other heterocycles

See Sections 3.5.2.2 (ring expansion), 3.4.3.1.9 (monocyclic rearrangement) and 3.2.3.3.vi (ring contraction) for further preparations by the types of reaction indicated.

4.3.5.3 Six-membered Rings

The rearrangement of cyclopropenyl azides (**332**) is used for the synthesis of monocyclic 1,2,3-triazines (**333**) ⟨73JOC3149, 79CB1514⟩. However, the most general method is the oxidation of *N*-aminopyrazoles (**334**) with LTA or nickel peroxide ⟨81CC1174, 80CC1182⟩.

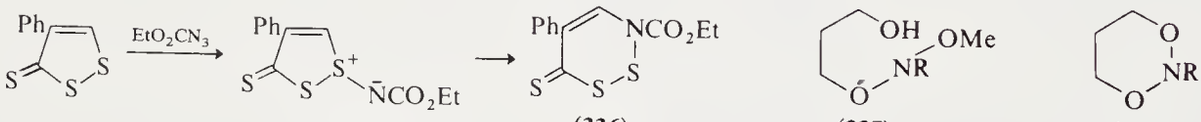


(**332**) (**333**) (**334**) (**335**)

The 1,2,6-thiadiazine (**335**) is prepared from the β-diketone $R^1COCHR^2COR^3$ and sulfamide $NH_2SO_2NH_2$.

Thermal decomposition of ethyl azidoformate in the presence of 4-phenyl-1,2-dithiole-3-thione leads to 1,2,3-dithiazine (**336**; Scheme 42) ⟨76CJC3879⟩.

Cyclization of (**337**) in CCl_4-NEt_3 gives a 1,3,2-dioxazine (**338**) ⟨80IZV2669⟩.



Scheme 42

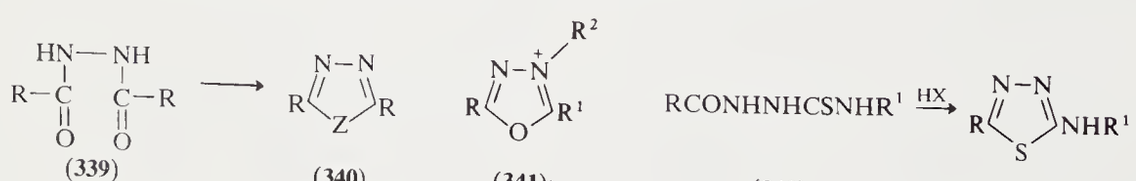
(**336**) (**337**) (**338**)

4.3.6 THREE HETEROATOMS IN THE 1,2,4-POSITIONS

4.3.6.1 Five-membered Rings

4.3.6.1.1 From acyclic intermediates containing the preformed Z—Z′ bond

(i) Diacylhydrazines (**339**) yield 1,3,4-oxadiazoles (**340**; Z = O) on heating or on treatment with $SOCl_2$, 1,3,4-thiadiazoles (**340**; Z = S) with P_2S_5 and 1,2,4-triazoles (**340**; Z = NR′) with primary amines. 1-Substituted 1,2-diacylhydrazines are cyclized by strong acid to 2,3,5-trisubstituted 1,3,4-oxadiazolium salts (**341**) ⟨70JCS(C)1397⟩. Cyclization of acyl thiosemicarbazides (**342**) with sulfuric acid or phosphorus halides gave 5-substituted 2-amino-1,3,4-thiadiazoles (**343**) ⟨80JHC607⟩.

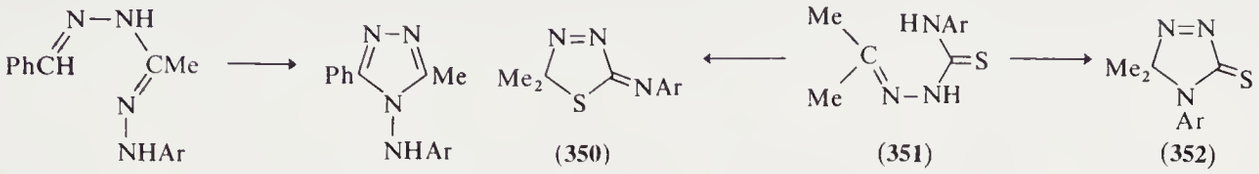


(**339**) (**340**) (**341**) (**342**) (**343**)

(ii) Similar ring closures can be carried out oxidatively. Lead tetraacetate causes hydrazone cyclization at a carbonyl oxygen atom as in the conversion of (**344**) into the 1,3,4-oxadiazolyl ether (**345**) ⟨76NKK782⟩. The semicarbazones (**346**) yield the 2-amino-5-benzoyl-1,3,4-oxadiazoles (**347**) ⟨72AC(R)11, 76MI40300⟩.

(**344**) (**345**) (**346**) (**347**)

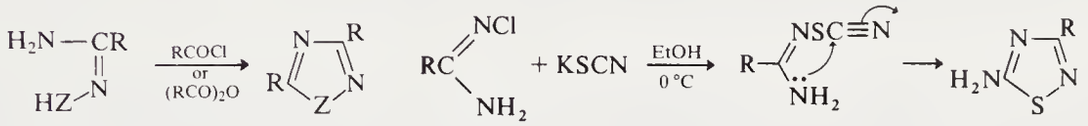
The conversion of the benzylidene hydrazidines (**348**) into the 4-arylamino-1,2,4-triazoles (**349**) was effected with mercury(II) oxide ⟨77BCJ953⟩.



(**348**) (**349**) (**350**) (**351**) (**352**)

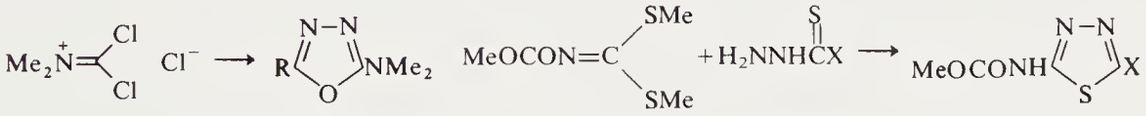
The direction of ring closure can often be influenced by the conditions. The substituted thiosemicarbazone (**351**) with $Al_2O_3/CHCl_3$ formed the 1,2,4-triazoline-3-thione (**352**) but MnO_2/C_6H_6 afforded the thiadiazoline (**350**) ⟨70JCS(C)63⟩.

(iii) Amidoximes and amidrazones (**353**; Z = O, NH) react with acid chlorides, *etc.*, to give 1,2,4-oxadiazoles and 1,2,4-triazoles (**354**; Z = O, NH). In a related reaction, conversion of an amidine into its *N*-chloro derivative (**355**) with sodium hypochlorite and addition of potassium thiocyanate yield 1,2,4-thiadiazoles (**357**); the intermediate (**356**) undergoes spontaneous ring closure.



(**353**) (**354**) (**355**) (**356**) (**357**)

(iv) Reaction of a hydrazide ($RCONHNH_2$) with phosgeneimonium chloride (**358**) led to the 2-dimethylamino-1,3,4-oxadiazole (**359**) ⟨75AG(E)806⟩. The 1,3,4-thiadiazole (**362**) was made by an analogous reaction from (**360**) and (**361**).



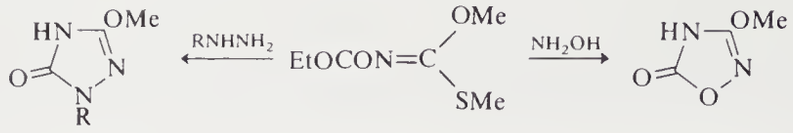
(**358**) (**359**) (**360**) (**361**) (**362**)

This approach is suited to the formation of mesoionic 1,3,4-thiadiazoles. The thiohydrazide (**363**) with phosgene, thiophosphene or an isocyanide dichloride leads to ready ring closure and formation of the mesoionic 1,3,4-thiadiazoles (**364**; X = O, S, NR, respectively) ⟨B-79MI40301⟩.

(**363**) (**364**) (**365**) (**366**) (**367**)

The isocyanide dichloride (**366**) with the *N*-hydroxythioamide (**365**) gives the 1,3,5-oxathiazole (**367**) ⟨71AP763⟩.

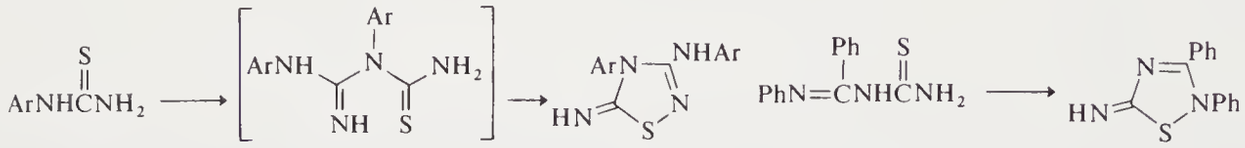
(v) Dimethyl *N*-ethoxycarbonylthiocarbonimidate (**369**) with a monosubstituted hydrazine gives the 1,2,4-triazolinone (**368**), and with hydroxylamine the 1,2,4-oxadiazolinone (**370**) ⟨73JCS(P1)2644⟩.



(368) (369) (370)

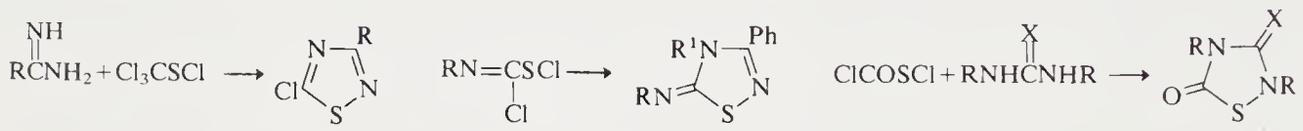
4.3.6.1.2 *From acyclic intermediates by formation of the Z—Z′ bond*

1,2,4-Thiadiazoles are conveniently prepared from thioamides or analogous substrates by oxidative dimerization which can be effected by halogens, hydrogen peroxide, sulfur halides, *etc.*; *cf.* the conversion of the thioamide (**371**) into (**372**; Hector's base) by hydrogen peroxide ⟨65AHC(5)119⟩. Commencing with the thiourea (**373**) gives the alternatively substituted product (**374**) ⟨72ZC130⟩.



(371) (372) (373) (374)

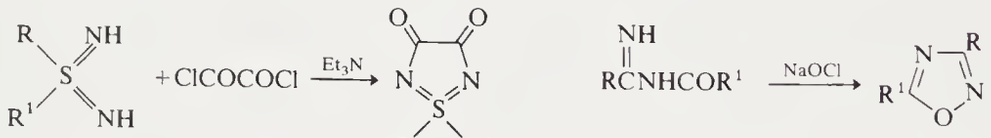
The reaction of trichloromethanesulfenyl chloride (**376**) with amidines (**375**) and mild base is a general preparation for 5-chloro-1,2,4-thiadiazoles (**377**) ⟨65AHC(5)119⟩. Iminochloromethanesulfenyl chlorides (**378**; from $RNCS+Cl_2$) react with amidines such as PhC(NH)NHR′ to give 1,2,4-thiadiazolines (**379**) ⟨71T4117⟩. Chlorocarbonylsulfenyl chloride (**380**) (prepared from trichloromethanesulfenyl chloride and sulfuric acid) reacts with ureas, thioureas and guanidines to give 1,2,4-thiadiazolidine derivatives (**381**) ⟨70AG(E)54, 73CB3391⟩.



(375) (376) (377) (378) (379) (380) (381)

R = aryl, ArCO

The reaction of *S,S*-disubstituted sulfur diimides (**382**) with oxalyl chloride (**383**) in the presence of triethylamine gives 1,2,5-thiadiazole-3,5-dione (**384**) ⟨72LA(759)107⟩.



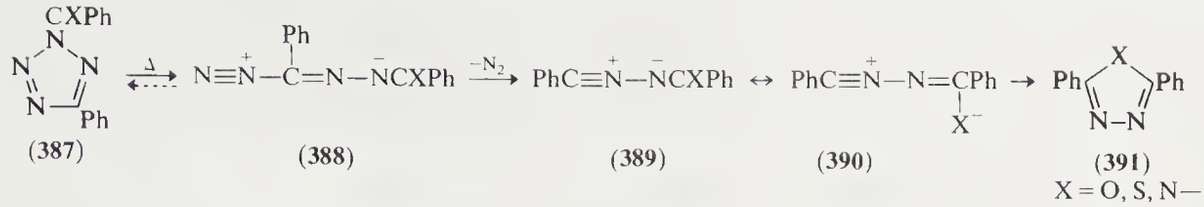
(382) (383) (384) (385) (386)

N—O bond formation by oxidative procedures has found less application. However, the 1,2,4-oxadiazole system (**386**) can be prepared by the action of sodium hypochlorite on *N*-acylamidines (**385**) ⟨76S268⟩.

4.3.6.1.3 *From heterocycles*

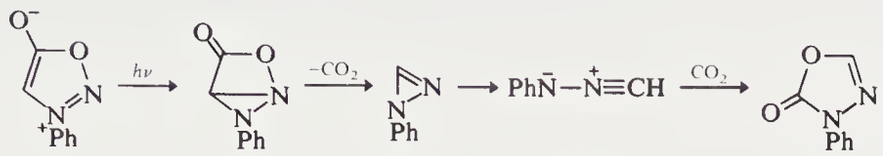
(i) By dipolar cycloadditions

The 2,5-disubstituted tetrazole (**387**; X = O, S, NR) undergoes thermal ring opening to the 1,5-dipolar species (**388**) which readily loses N_2 to give the conjugated nitrilimine (**389**↔**390**). 1,5-Dipolar cyclization of (**390**) leads to oxadiazoles, thiadiazoles and triazoles (**391**) ⟨70CB1918, 65CB2966⟩ (see also CHEC 4.13).



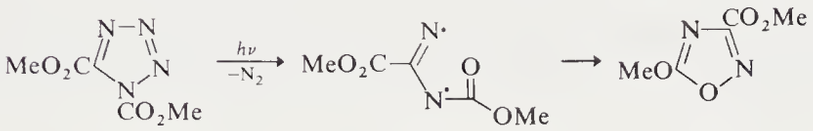
(387) (388) (389) (390) (391)
X = O, S, N—

N-Phenylsydnone (**392**) on irradiation gives 4-phenyl-1,2,4-oxadiazolin-5-one (**396**). When labelled carbon dioxide is passed through the solution during irradiation, it is incorporated into (**396**) ⟨66TL4043, 71JOC1589⟩. These results were rationalized in terms of an initial valence isomerization to (**393**) and loss of CO_2 to give (**394**), which underwent ring opening to the 1,3-dipole (**395**). This dipole subsequently reacted with carbon dioxide to give (**396**). For trapping with PhNCO see Section 3.4.1.9.1.



(392) (393) (394) (395) (396)

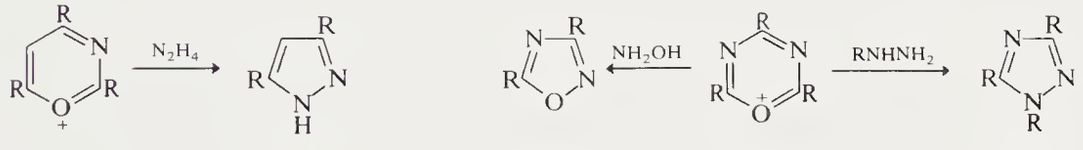
Intramolecular trapping of the intermediate (**398**) from the photolysis of methyl tetrazole-1,5-dicarboxylate (**397**) gave methyl 5-methoxy-1,2,4-oxadiazole-3-carboxylate (**399**) (see also Section 3.4.3.12.4).



(397) (398) (399)

(ii) By ring contraction

1,3-Oxazinium salts (**400**) and hydrazine give pyrazoles (**401**) ⟨69CB269, 65CB334, 62CB937⟩. 1,3,5-Oxadiazinium salts (**403**) with hydroxylamine give the 1,2,4-oxadiazoles (**402**) and with hydrazines form the 1,2,4-triazole derivatives (**404**). The substituents in these cationic species are usually aryl, restricting the appeal of these ring interconversions ⟨65CB334, 67CB3736⟩.



(400) (401) (402) (403) (404)

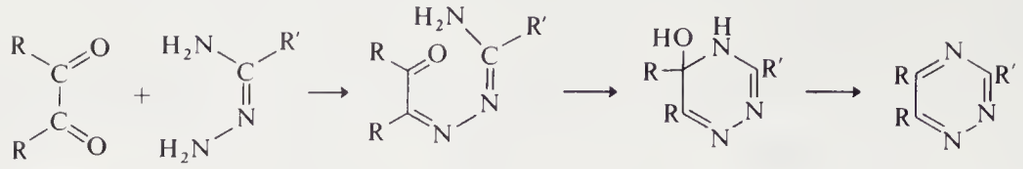
(iii) By the 'monocyclic rearrangements'

Section 3.4.3.1.9 gives details of ring interconversions involving three-atom side chain displacements at both N and S ring atoms.

4.3.6.2 Six-membered Rings

4.3.6.2.1 1,2,4-Triazines

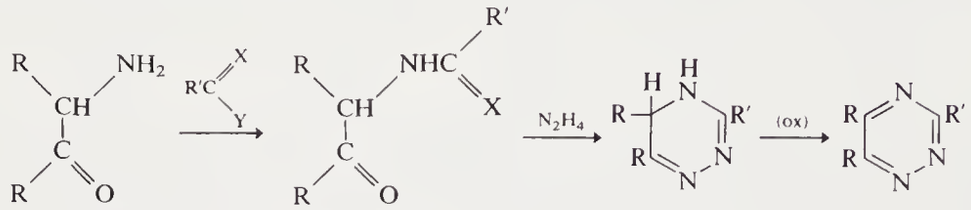
The reaction of 1,2-dicarbonyl compounds (**405**) with amidrazones (**406**) is the best method for the synthesis of alkyl-, aryl- or hetaryl-substituted 1,2,4-triazines (**409**) ⟨78HC(33)189⟩. Mixtures result unless the dione (**405**) is symmetrical.



(405) (406) (407) (408) (409)

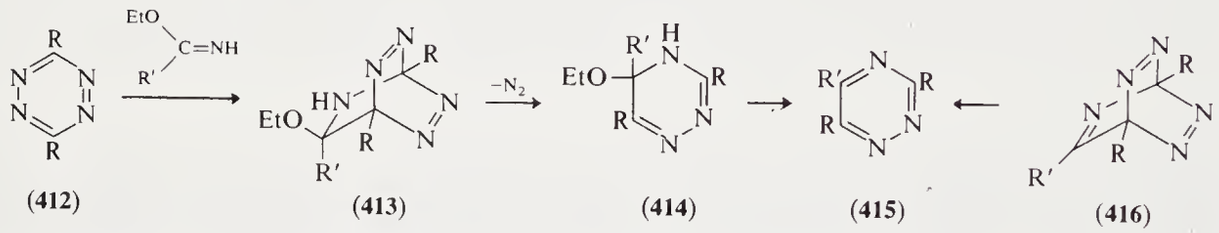
Various extensions are possible (see CHEC 2.19 for full details). Use of aminoguanidines, semicarbazide and thiosemicarbazide gives respectively the 3-amino-1,2,4-triazine, and the 3-one and 3-thione derivatives. Use of α-keto esters and α-keto cyanides gives 5-ones and 5-amino derivatives, respectively. α-Hydroxy ketones afford dihydro-1,2,4-triazines. Intermediates (**407**) and (**408**) can sometimes be isolated.

In another frequently used method for the synthesis of 1,2,4-triazines, α-acylamino and α-thioacylamino ketones (**410**; X = O, S) react with hydrazine to give dihydro derivatives (**411**) which can be oxidized to the 1,2,4-triazines ⟨78HC(33)189, p. 197⟩.



(410) (411)

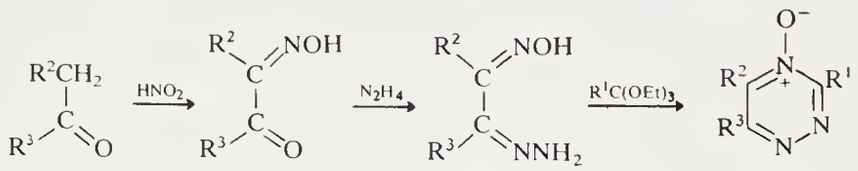
1,2,4,5-Tetrazines (**412**) undergo Diels–Alder reactions with C—N multiple bonds. Imidates thus afford 1,2,4-triazines (**415**) which are formed *via* intermediate bicycles (**413**) and dihydro-1,2,4-triazines (**414**) ⟨69JHC497⟩.



(412) (413) (414) (415) (416)

On reaction of tetrazines (**412**) with cyanamides, the bicyclic intermediates (**416**) lead directly to 3-amino-1,2,4-triazines (**415**; $R^1 = NR_2$) by elimination of nitrogen ⟨79CZ230⟩.

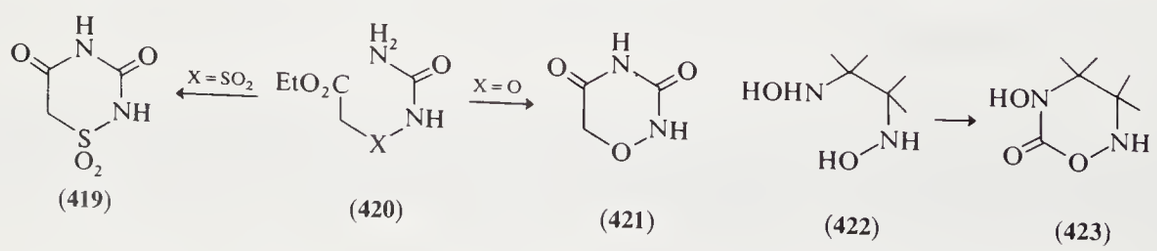
α-Hydrazono oximes (**417**) with ortho esters give triazine 4-oxides (**418**) ⟨77LA1713⟩.



(417) (418)

4.3.6.2.2 Rings containing O or S atoms

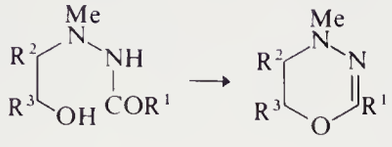
α-(Ethoxycarbonyl)methylsulfonylurea (**420**; X = SO_2) cyclizes to the 1,2,4-thiadiazine (**419**) on treatment with base ⟨59JA5655⟩, and a similar cyclization occurs with the oxygen analogue (**420**; X = O) to give (**421**) ⟨79JHC161⟩.



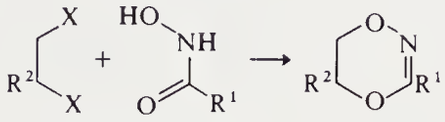
(419) (420) (421) (422) (423)

The 1,2-bishydroxylamine (**422**) with phosgene gives the 5-hydroxy-1,2,5-oxadiazine (**423**) ⟨80AP35⟩.

Acid-catalyzed dehydration of *N*-(2-hydroxyethyl)-*N'*-acylhydrazines (**424**) is a general route to 4,5-dihydro-1,3,4-oxadiazines (**425**) ⟨64JOC668⟩.



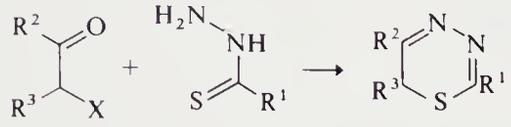
(**424**) (**425**)



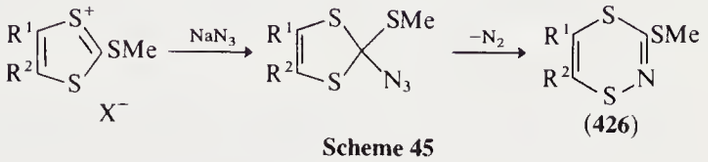
Scheme 43

1,4,2-Dioxazines are prepared by di-*O*-alkylation of hydroxamic acids (Scheme 43) using 1,2-dihalides or 1,2-dimesylates ⟨71JOC284, 75NKK1041⟩.

Condensation of α-halo ketones with thiohydrazides (Scheme 44) is a general route to 1,3,4-thiadiazines ⟨76JPR(318)971⟩.



Scheme 44



Scheme 45

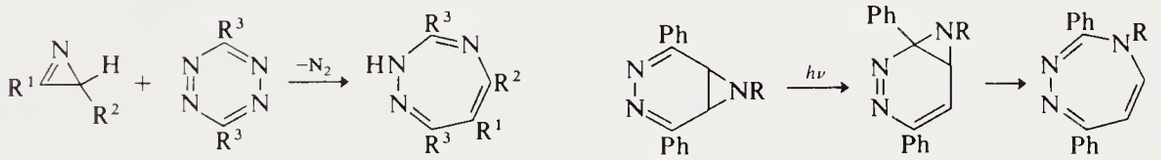
Preparation of 1,4,2-dithiazines (**426**) involves the ring expansion of 1,3-dithiolium salts with azide (Scheme 45) ⟨76JPR(318)127⟩.

4.3.6.3 Seven-membered Rings

4.3.6.3.1 Heteroatoms in the 1,2,4-positions

Fully unsaturated 2*H*-1,2,4-triazepines (**429**) are formed by the cycloaddition of 1-azirines (**427**) to 1,2,4,5-tetrazines (**428**). The initial product rearranges by a 1,5-hydrogen shift to give (**429**) ⟨74TL2303⟩.

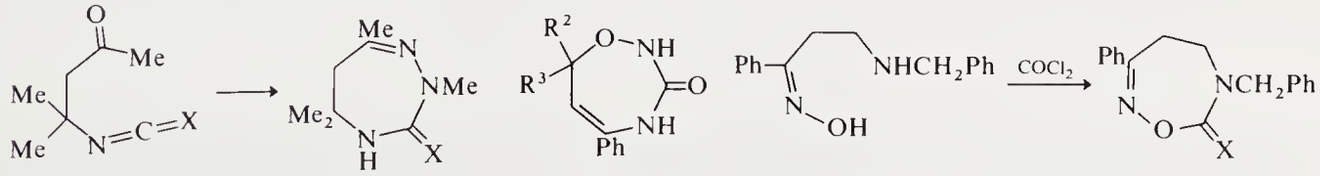
The 4*H*-1,2,4-triazepine system (**431**) can be prepared *via* a photochemical rearrangement of 3,4,7-triaza-2,4-norcaradienes (**430**) ⟨76TL2459⟩.



(**427**) (**428**) (**429**) (**430**) (**431**)

The β-functionalized isocyanate (**432**; X = O) reacts with methylhydrazine to give (**433**) ⟨77S756⟩, and (**432**; X = S) reacts with both alkylhydrazines and hydrazine itself to give the (**434**) ring system.

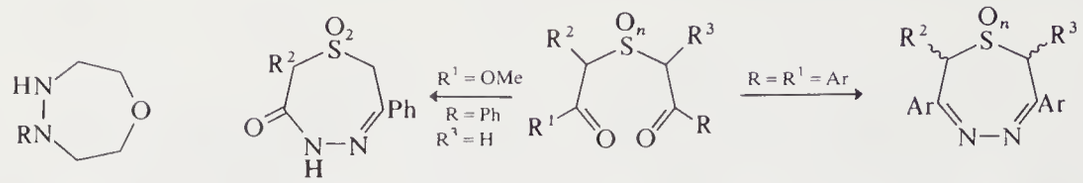
3-Oxo-1,2,4-oxadiazepines (**435**) have been prepared by the reaction of hydroxyurea with some α,β-unsaturated ketones ⟨75TL2979⟩. *syn*-ω-(Benzylamino)propiophenone oximes (**436**) react with phosgene to give the 7-oxo-1,2,6-oxadiazepines (**437**) ⟨75CB3387⟩, and with formaldehyde to give (**438**) ⟨80CB3373⟩.



(**432**) (**433**) X = O (**434**) X = S (**435**) (**436**) (**437**) X = O (**438**) X = H_2

4.3.6.3.2 *Seven-membered rings with heteroatoms in the 1,2,5-positions*

Hexahydro-1,4-5-oxadiazepines (**439**) are prepared by the reaction of monosubstituted hydrazines with $O(CH_2CH_2Cl)_2$ ⟨75MI51803⟩.



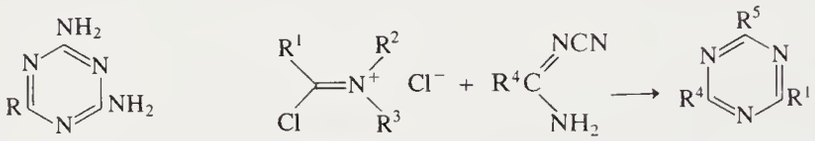
(**439**) (**440**) (**441**) (**442**)

The sulfides or sulfones (**441**) react with hydrazine to give (**440**) or (**442**) depending on R^1 ⟨70JHC431, 72T2307⟩.

4.3.7 THREE HETEROATOMS IN THE 1,3,5-POSITIONS

4.3.7.1 *s*-Triazines

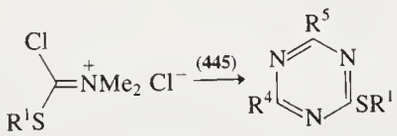
Biguanides $[H_2NC(=NH)NHC(=NH)NH_2]$ react with lactones, amides, ortho esters, esters, acid anhydrides and acid chlorides to produce a wide range of 6-substituted 2,4-diamino-1,3,5-triazines (**443**) ⟨59HC(13)1⟩. Biguanides with carbodiimides, isothiocyanates and ketones give corresponding melamines, thiones and dihydro derivatives, respectively.



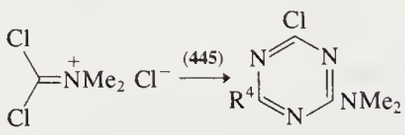
(**443**) (**444**) (**446**)

The condensation of *N*-cyanoamidines (**445**) with chloromethyliminium salts (**444**), prepared *in situ* from amides $R^1CONR^2R^3 + PCl_3$, provides an efficient, convenient route to many 1,3,5-triazines ⟨80S841, 81AJC623⟩. For R^2 and R^3 = alkyl, the chloro-1,3,5-triazines (**446**; R^5 = Cl) are produced. However, for R^2 = aryl, the amino derivative (**446**; $R^5 = NR^2R^3$) may become the major product.

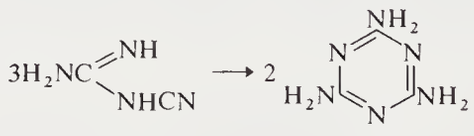
The condensation of *N*-cyanoamidines with thiocarbamate esters provides routes to 1,3,5-triazine thioethers (Scheme 46), and dimethylamino-1,3,5-triazines (Scheme 47). Melamine (**448**) can be prepared by fusing dicyandiamide (**447**) ⟨40MI22000⟩.



Scheme 46

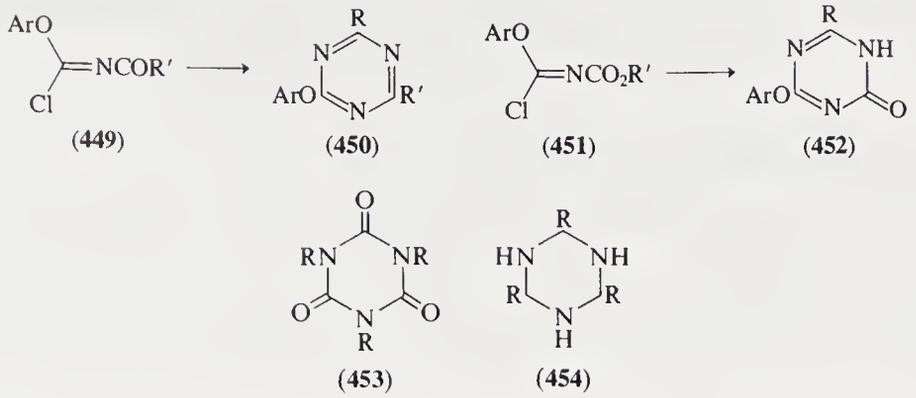


Scheme 47



(**447**) (**448**)

Amidines react with derivatives of cyanic esters to give a variety of 1,3,5-triazines with an aryloxy substituent. Typical examples are $RC(NH)NH_2$ + (**449**)→(**450**), and (**451**)→(**452**) ⟨72AG(E)949⟩.



(449) (450) (451) (452)

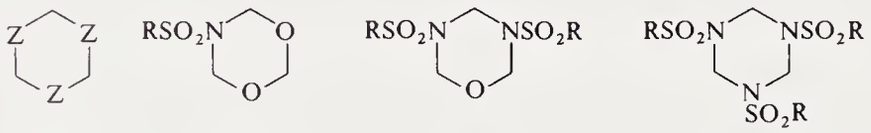
(453) (454)

Cyclotrimerization of nitriles is the best-known route to 1,3,5-triazines (for a detailed discussion see CHEC 2.18). The reaction is of value for preparing the symmetrical derivatives only. Nevertheless, many important triazines, such as cyanuric chloride, are made in this way. Other cyclotrimerization reactions are useful; thus, an easy route to 1,3,5-triazine involves heating ammonium acetate with ethyl orthoformate.

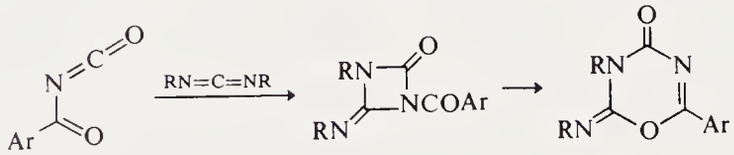
Trimerization of imidates is a valuable route to 1,3,5-triazines. Imidates can be considered as activated nitriles and cyclotrimerize more readily. Most symmetrical 2,4,6-trialkyl-1,3,5-triazines are easily formed, although large alkyl substituents may give rise to steric hindrance ⟨61JOC2778⟩. Symmetrical isocyanurates (**453**) are readily available from isocyanates, RNCO; catalysts include tertiary amines, phosphines and sodium methoxide. Aldehydes RCHO and ammonia give hexahydro-1,3,5-triazines (**454**), known as 'aldehyde ammonias' ⟨73JOC3288⟩.

4.3.7.2 Compounds Containing O or S Atoms

1,3,5-Trioxanes (**455**; Z = O) are trimers of aldehydes or ketones formed by acid-catalyzed condensations of the monomers. 1,3,5-Trithiane (**455**; Z = S) is prepared by passing H_2S through formaldehyde and hydrochloric acid ⟨43OSC(2)610⟩. Passage of H_2S through acetaldehyde in dilute hydrochloric acid affords not only the 1,3,5-trithiane but also the 1,3,5-oxadithiane and 1,3,5-dioxathiane analogues ⟨66HC(21-2)633⟩.



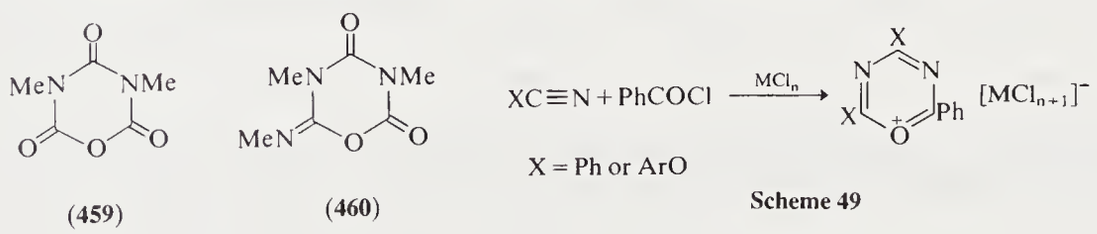
(455) (456) (457) (458)



Scheme 48

Sulfonamides RSO_2NH_2 react with formaldehyde to give *N*-sulfonyl-1,3,5-dioxazines (**456**), -1,3,5-oxadiazines (**457**) or -1,3,5-triazines (**458**) according to the relative quantities of reagents used ⟨75JCS(P1)772⟩. Aroyl isocyanates with carbodiimides give imino-1,3,5-oxadiazinones ⟨79BSF(2)499⟩ *via* the [2 + 2] adduct which rearranges (Scheme 48) ⟨79BSF(2)499⟩.

Trimerization of methyl isocyanate (MeNCO) in the presence of tri-*n*-butylphosphine gives a 1,3,5-oxadiazine (**459**) ⟨73CR(C)(277)795⟩. In the presence of carbon dioxide, the reaction leads to the 1,3,5-oxadiazinimine (**460**) derived from CO_2 (1 mol) and the isocyanate (2 mol) ⟨74BSF1497⟩.



(459) (460)

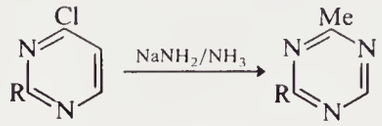
X = Ph or ArO

Scheme 49

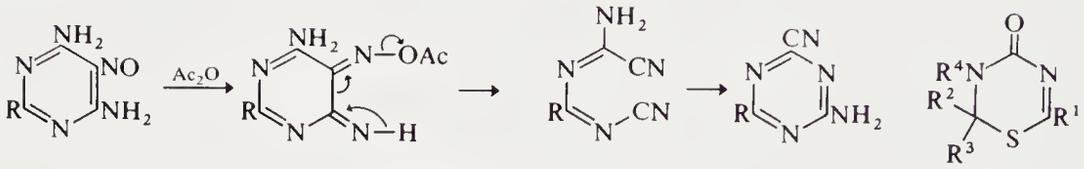
Benzoyl chloride condenses with benzonitrile or aryl cyanates in the presence of aluminum trichloride to give 1,3,5-oxadiazinium salts (Scheme 49) ⟨67CB3736⟩.

4.3.7.3 Synthesis from Heterocyclic Precursors

2-Substituted 4- or 5-halopyrimidines with sodamide in liquid ammonia give 4-methyl-1,3,5-triazines (Scheme 50); the reaction is general and yields are good; *cf.* the related conversion of 6-substituted 2-bromopyridines into pyrimidines (Section 4.3.3.3.3). 4-Amino-5-nitrosopyrimidines are converted into 1,3,5-triazines by acetic anhydride or phosphorus oxychloride (Scheme 51). 1,3,5-Triazines can be obtained from 1,3,5-oxadiazinium cations (Section 3.2.1.6.1.iii).



Scheme 50



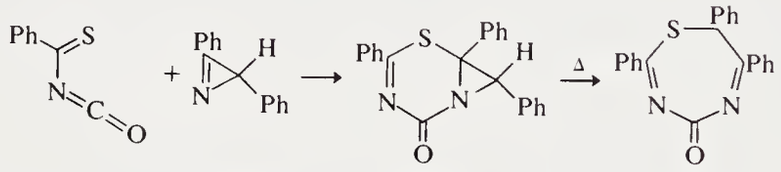
Scheme 51

(461)

1,3,5-Thiadiazines (**461**) are obtained by the cycloaddition of thioaryl isocyanates (R^1CSNCO) with imines $R^2R^3C{=}NR^4$.

4.3.7.4 Seven-membered Rings

The 1,3,5-thiadiazepine (**464**) has been prepared by the thermal rearrangement of the [4 + 2] cycloadduct (**463**) of the azirine (**462**) and thiobenzoyl isocyanate ⟨74JOC3763⟩.

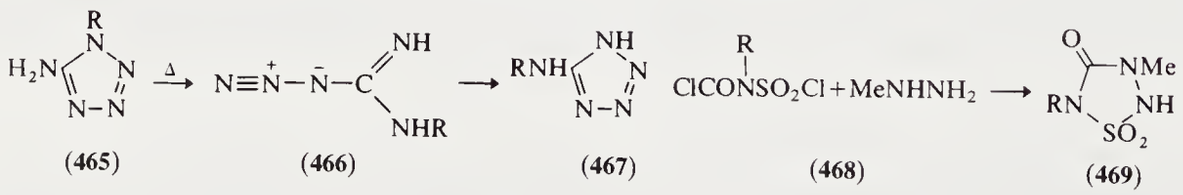


(462) (463) (464)

4.3.8 FOUR OR MORE HETEROATOMS

4.3.8.1 Five-membered Rings

The thermal conversion of 1-substituted 5-aminotetrazole (**465**) into a 5-substituted aminotetrazole (**467**) is rationalized by a 1,5-dipolar cyclization of (**466**).



(465) (466) (467) (468) (469)

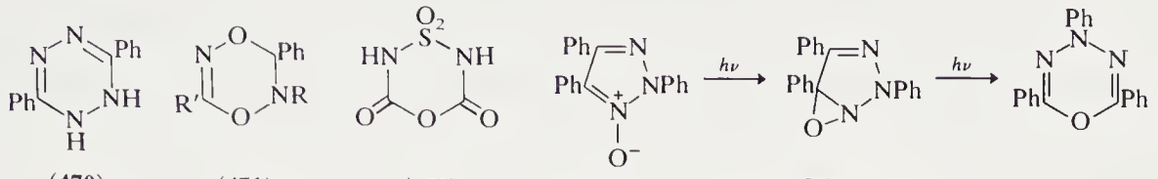
2-Alkyl-2-chlorosulfonylcarbamoyl chlorides (**468**) with methylhydrazine yield 1,2,3,5-thiatriazolidines (**469**) ⟨77JCR(S)238⟩ (CHEC 4.28).

4.3.8.2 Six-membered Rings

Dihydro-1,2,4,5-tetrazines (**470**) can be prepared from PhCN and N_2H_4.

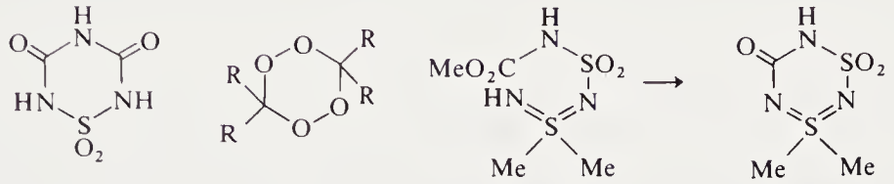
1,4,2,5-Dioxadiazines (**471**) are available by [3 + 3] cycloaddition of $PhCH{=}NR^+{-}O^-$ and $R'C{\equiv}N^+{-}O^-$. 1,4,3,5-Oxathiadiazines (**472**) result from hydration of $O_2S(NCO)_2$.

Photolysis of 2,4,5-triphenyl-1,2,3-triazole 1-oxide gives the triphenyl-1,3,4,5-oxatriazine shown in Scheme 52 ⟨80AJC2447⟩.



(**470**) (**471**) (**472**) **Scheme 52**

Sulfonyl diisocyanate gives the thiatriazine (**473**) on treatment with ammonia ⟨58CB1200⟩. Ketones and 86% hydrogen peroxide give 3,3,6,6-tetrasubstituted 1,2,4,5-tetroxanes (**474**) ⟨80JCR(S)35⟩.



(**473**) (**474**) (**475**) (**476**)

Symmetrical 1,2,4,5-dioxadiazines are formed by [3 + 3] dimerization of arene nitrile oxides in the presence of pyridine ⟨74JCS(P1)1951⟩. The sulfonylsulfur diimide (**475**) cyclizes to the 1,3,2,4,6-dithiatriazine (**476**) on heating in DMF ⟨71AG(E)264⟩.

4.4

Synthesis of Bicyclic Ring Systems without Ring Junction Heteroatoms

Material in this chapter is arranged firstly by the number of heteroatoms in the heterocyclic ring, secondly by the orientation of the heteroatoms to the fused ring (usually benzenoid), and finally by the size of the heterocyclic ring.

4.4.1 SYNTHESIS BY SUBSTITUENT INTRODUCTION AND MODIFICATION

Most benzo-fused heterocyclic systems are constructed from a substituted benzene by synthesis of the heterocyclic ring. Similarly most bicyclic heterocycles with heteroatoms in both rings commence with a monoheterocycle and build on the second heterocycle. However, substituent modification and, to a lesser extent, substituent introduction are also important, particularly in the later stages of a synthesis, and we now survey available methods for this.

4.4.1.1 In the Heterocyclic Ring

The reactivity of heterocyclic rings is modified but not radically changed by benzo- or hetero-ring fusion. We therefore refer readers to the appropriate sections dealing with the analogous monocyclic rings;

(i) pyrroles, furans and thiophenes (Section 4.2.3.2);
(ii) pyridines (Section 4.2.4.1);
(iii) azoles (Section 4.3.1.2);
(iv) azines (Section 4.3.1.3).

Benzo-ring fusion tends to facilitate reaction: it reduces the loss of resonance energy in non-aromatic transition states and intermediates.

4.4.1.2 In the Benzene Ring

Again, the reactivity of a benzene ring, although modified, is not radically changed by hetero-ring fusion. The reactivity sections of this book have dealt with the reactions of fused benzene rings and we refer now to those sections.

Since thiophene, pyrrole and furan are more readily attacked by electrophiles than is benzene, in the corresponding benzo-fused heterocycles attack generally, but not invariably, occurs in the heterocyclic ring (Section 3.3.3.2.1).

Conversely in benzopyridines and benzazines, electrophilic attack usually occurs in the benzene ring (Section 3.2.3.2).

Benzazoles occupy an intermediate position, but in most cases electrophilic attack occurs in the benzene ring (Section 3.3.3.2.1).

4.4.2 ONE HETEROATOM ADJACENT TO RING JUNCTION

4.4.2.1 Three- and Four-membered Rings

4.4.2.1.1 Three-membered rings

Fused-ring three-membered heterocycles fall into three classes:

(i) In the majority of cases the fused ring is saturated or partially saturated: the synthetic methods utilized for the corresponding non-fused systems apply.

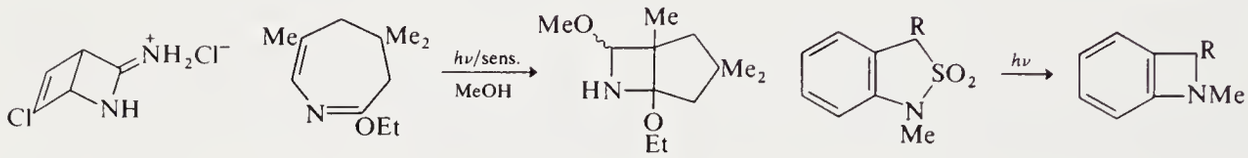
(ii) Compounds of the 'benzene oxide' and 'benzene imide' types are tautomeric with, and generally exist predominantly as, the seven-membered oxepin and azepine rings (see Section 3.5.2.2). For benzene polyepoxides and related derivatives see CHEC 5.07.6.

(iii) True fused-ring oxirenes and thiirenes are known only as intermediates (see CHEC 5.07.8).

4.4.2.1.2 Four-membered rings

(i) Azetidines, azetidinones. Synthetic routes to penicillins (CHEC 5.11), cephalosporins (CHEC 5.10) and other fused azetidines (CHEC 5.12) are described in the chapters quoted.

Photolytically induced valence bond isomerism of heterocycles is a useful method: 2-amino-5-chloropyridine gives (**1**) ⟨61JA2967⟩, and (**2**)→(**3**) illustrates the conversion of a seven-membered ring into a 4,5-fused derivative ⟨71JOC1934⟩. Benzazetidines are available by ring contraction (**4**→**5**) ⟨80CC471⟩.

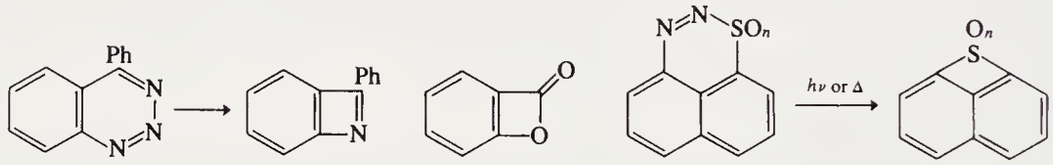


(**1**) (**2**) (**3**) (**4**) (**5**)

(ii) Benzazetes are obtained by thermolysis of 1,2,3-benzotriazines (**6**→**7**) ⟨75JCS(P1)45⟩.

(iii) Benzoxetan-2-one (**8**) has been prepared in an argon matrix by CO_2 loss from phthaloyl peroxide ⟨73JA4061⟩.

(iv) The preparation of fused thietane derivatives is discussed in CHEC 5.14.4.2; for example see (**9**)→(**10**).

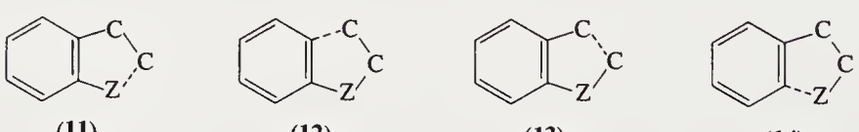


(**6**) (**7**) (**8**) (**9**) *n*=0, 1 or 2 (**10**)

(v) See Section 3.3.1.8.3 for the preparation of fused oxetanes by [2 + 2] cycloadditions.

4.4.2.2 Five-membered Rings

4.4.2.2.1 Survey of syntheses for indoles, benzofurans and benzothiophenes



(**11**) (**12**) (**13**) (**14**)

We deal successively with methods to construct the Z—C(2) (**11**), the ring—C (**12**), the C(2)—C(3) (**13**) and the ring—Z bonds (**14**), and methods from other heterocycles. Table 1 gives an overview of the most important methods for preparing these compounds.

Table 1 Important Ring Syntheses for Indoles, Benzo[*b*]furans, Benzo[*b*]thiophenes and their Derivatives

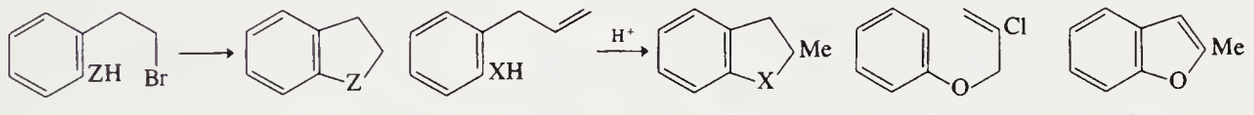
Ring	*Synthesis type*	*Synthesis name*	*Section*
Indoles	(11)	Nenitzescu	4.4.1.2.2.iii
	(11)	Reissert	4.4.1.2.2.iv
	(12)[a]	Fischer	4.4.1.2.3.i
	(12)	Bischler	4.4.1.2.3.iii
	(12)	Gassman	4.4.1.2.3.iv
	(13)	Madelung	4.4.1.2.4.i
Benzo[*b*]furans and benzo[*b*]thiophenes	(11)	—	4.4.1.2.2.iv, v, vi
	(12)	—	4.4.1.2.3.ii, iii, iv
	(13)	—	4.4.1.2.4.ii
Indolines and analogues	(11)	—	4.4.1.2.2.i
Indoxyls	(12)	—	4.4.1.2.3.v
Oxindoles	(11)	—	4.4.1.2.2.ii
	(12)	Brunner	4.4.1.2.3.vi
Indolenines	(12)[a]	Fischer	4.4.1.2.3.i
Isatins	(12)	—	4.4.1.2.3.vii

[a] Classified under (**12**) from the point of view of precursors although mechanistically should strictly be (**11**) for the indole ring-forming step.

4.4.2.2.2 Ring closure by formation of Z—C(2) bond

(i) Indolines (**16**; Z = NH) and their S- and O-analogues are prepared from *o*-substituted *β*-phenylethyl bromides (**15**) which cyclize spontaneously, on heating or on treatment with alkali.

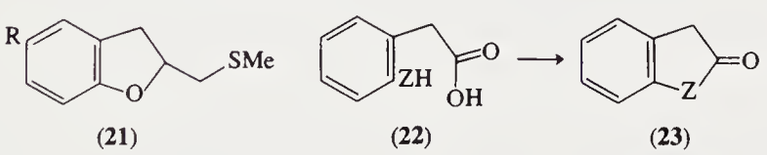
The intramolecular addition of the heteroatom to a suitably disposed double bond is the basis of a variety of ring syntheses. The cyclization of *o*-allylphenols to 2,3-dihydrobenzofurans (**17**→**18**; X = O) frequently accompanies the Claisen rearrangement of allyl aryl ethers, and is promoted by acid catalysis ⟨68JCS(C)1837⟩. 2,3-Dihydrobenzothiophenes ⟨66JOC413⟩ and 2,3-dihydrobenzoselenophenes ⟨67ZOR597⟩ have been obtained through analogous rearrangements (**17**→**18**; X = S, Se). *o*-Allylanilines can be converted into indolines (**17**→**18**; X = NH) ⟨61JA3319⟩. Cyclization of *o*-(2-chloroallyl)phenols leads directly to 2-methylbenzofurans (**19**→**20**) ⟨76JCS(P1)1⟩.



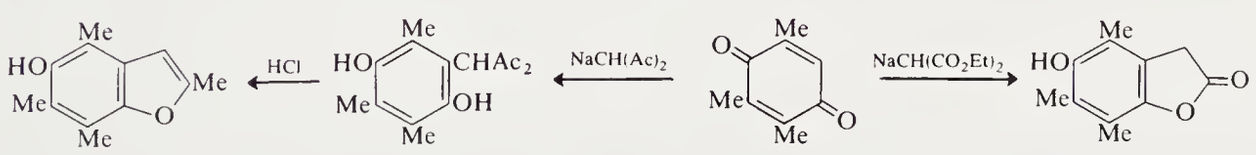
(**15**) (**16**) (**17**) (**18**) (**19**) (**20**)

The employment of non-protic electrophiles for the foregoing type of cyclization, as illustrated by (**17**; X = O) + $(MeS)_2SMe^+SbCl_6^-$ → (**21**), leaves a useful point of departure for further transformations ⟨81JCS(P1)3106⟩.

(ii) Oxindoles (**23**; Z = NH) and the corresponding S- and O-heterocycles are formed by spontaneous cyclization of acids of type (**22**).



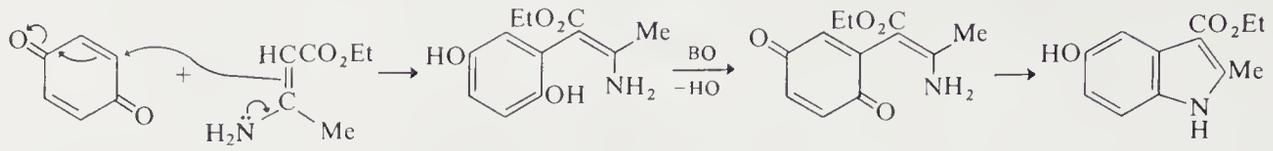
(**21**) (**22**) (**23**)



Scheme 1

(iii) The addition of α-keto carbanions to *p*-quinones having at least one unoccupied nuclear position provides syntheses of benzo[*b*]furans and α-benzo[*b*]furanones (Scheme 1) ⟨40JA133⟩. In

the Nenitzescu indole synthesis, a quinone is reacted with a β-aminocrotonate (Scheme 2) ⟨51JCS2029, 53JCS1262, 66CI(L)117, 70JA3740⟩.

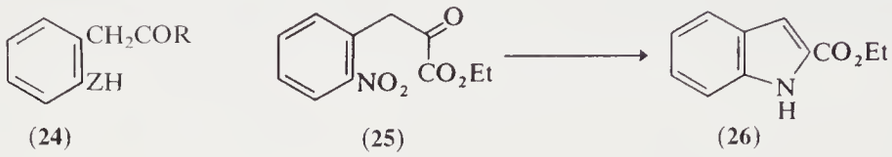


Scheme 2

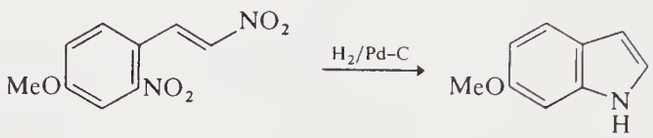
(iv) Fully aromatic derivatives result from the cyclizations of compounds of type (**24**) or of equivalents which can be constructed in a variety of ways, and are often not isolated.

Amino groups in compounds of type (**24**) are frequently derived from nitro groups. In the Reissert indole synthesis, *o*-nitrotoluene undergoes Claisen condensation with oxalic ester to yield the pyruvic ester (**25**). When this is reduced with Zn–AcOH the corresponding amino derivative spontaneously cyclizes to the 2-ethoxycarbonylindole (**26**) ⟨63OS(43)40⟩.

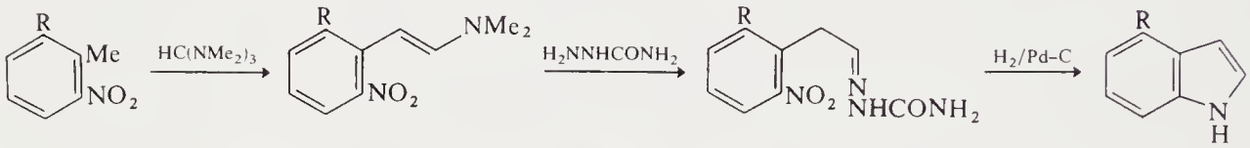
Reduction of the *o*-nitrophenylnitroethylene (**27**→**28**) ⟨70JOC1248⟩ and the transformation of Scheme 3 (R = Me, MeO, CO_2Me) ⟨81H(16)1119⟩ are related reactions.



(**24**) (**25**) (**26**)

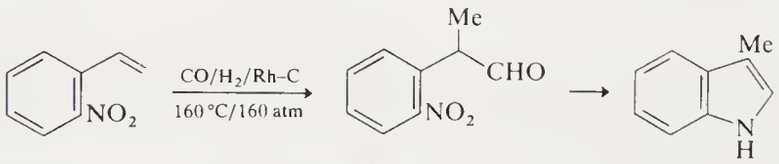


(**27**) (**28**)



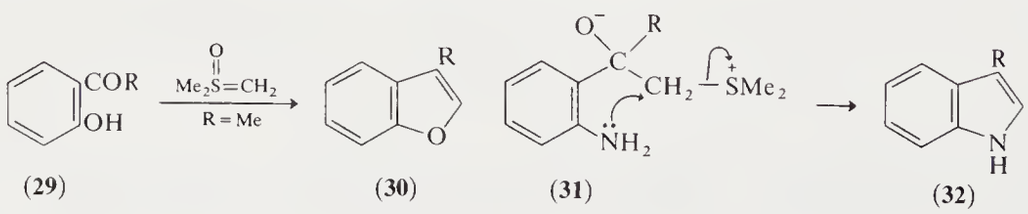
Scheme 3

The hydroformylation of *o*-nitrostyrene, subsequent reduction of the nitro group, and cyclization lead to the formation of skatole (Scheme 4) ⟨81CC82⟩.

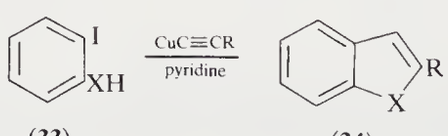


Scheme 4

(v) The addition of dimethylsulfoxonium methylide to carbonyl groups is the basis of a benzo[*b*]furan synthesis from *o*-acylphenols (**29**→**30**) ⟨66TL683⟩. In an analogous synthesis of indoles, *o*-acylanilines react with dimethylsulfonium methylide (**31**→**32**) ⟨70G652⟩.



(**29**) (**30**) (**31**) (**32**)



(**33**) (**34**)

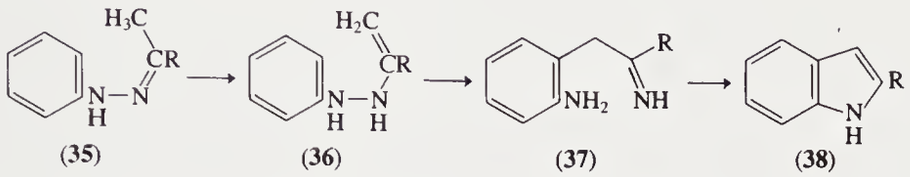
(vi) The reaction between copper(I) acetylides and *o*-halo-phenols or -anilines provides a general and convenient route to 2-substituted benzofurans or indoles (**33**→**34**; X = O, NH) ⟨66JOC4071⟩.

For ring closure of an *o*-substituted azide on to a double bond see Section 3.3.3.4.3.

4.4.2.2.3 Ring closure by formation of ring—C bond

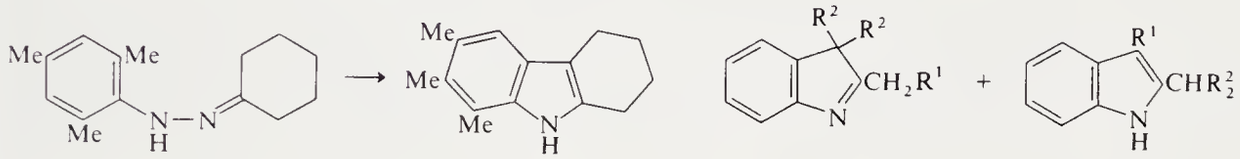
(i) The Fischer indole synthesis

The Fischer indole synthesis is the most important preparative method for indoles. The tautomeric form (**36**) of a phenylhydrazone (**35**) can undergo a Claisen-type rearrangement to give an intermediate (**37**) which spontaneously cyclizes by loss of ammonia to an indole (**38**).

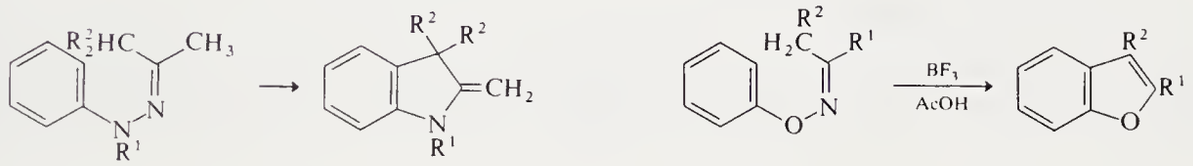


(**35**) (**36**) (**37**) (**38**)

Acidic conditions used range widely from warm acetic acid to fused zinc chloride. Phosphorus trichloride in benzene is mild and effective ⟨81CC563⟩. Electron-releasing *meta*-substituents in the aryl ring favor 6- over 4-substituted indoles, whereas the opposite is usually true for electron-withdrawing substituents ⟨57JCS3175⟩. Formal 1,4-methyl group migrations have been observed in the cyclization of mesitylhydrazones (**39**→**40**) ⟨80JA4772⟩. The preferred direction of cyclization of arylhydrazones of unsymmetrical ketones varies with the acid catalyst ⟨69JCS(B)446⟩: high acidity and temperature favor cyclization to the less substituted position ⟨78JOC3384⟩. However, the arylhydrazone of a ketone $R^1CH_2COCHR^2_2$ often yields the 3*H*-indole (**41**) in preference to the 1*H*-indole (**42**) ⟨55JCS2519⟩. If formation of an endocyclic double bond is precluded, then a methylene-indoline may result (**43**→**44**).



(**39**) (**40**) (**41**) (**42**)



(**43**) (**44**) (**45**) (**46**)

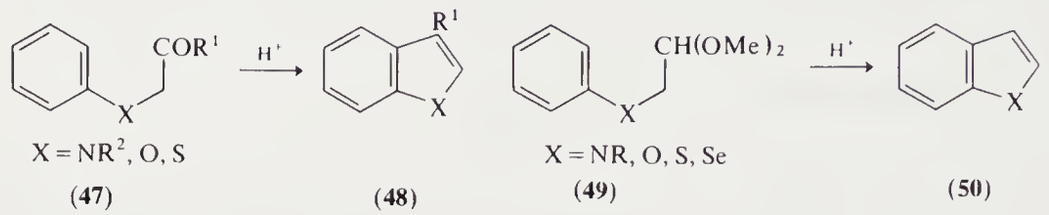
(ii) Benzofurans

An analogous synthesis of benzofurans from *o*-aryloximes is exemplified by (**45**→**46**) ⟨67TL2867, 73KGS31⟩.

(iii) Bischler indole synthesis and related methods for O- and S-analogues

The Bischler synthesis of indoles from α-arylamino ketones is acid catalyzed (**47**→**48**) ⟨1892CB2860, 1893CB1336⟩. α-Aryloxy and α-arylthio ketones can be cyclized similarly to benzo[*b*]furans ⟨1900LA(312)237⟩ and benzo[*b*]thiophenes ⟨49RTC509, 70JCS(C)2621⟩ respectively. Concurrent migrations of groups occur from position 3 to position 2, especially under vigorous conditions.

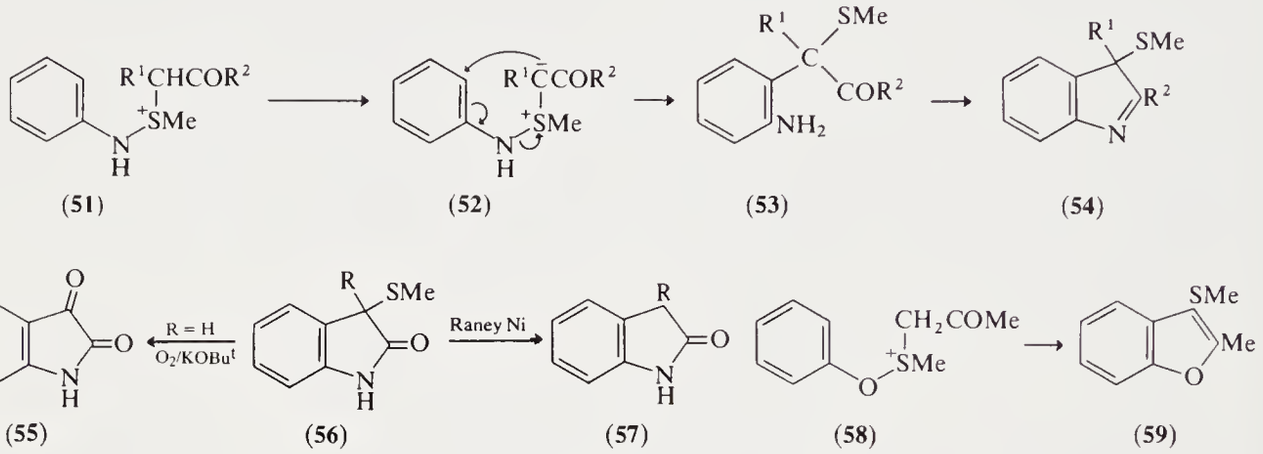
To obtain compounds unsubstituted at positions 2 and 3, cyclization of the acetals (**49**) using polyphosphoric acid catalysis gives indoles ⟨81JOC778⟩, benzo[*b*]furans, and benzo[*b*]thiophenes (**50**) ⟨71T1253⟩.



(47) (48) (49) (50)

(iv) Gassman synthesis of indoles and benzo[b]*furans*

The Gassman synthesis of indoles depends on a sigmatropic rearrangement to generate the ring–carbon bond. An *N*-chloroaniline with a *β*-keto sulfide forms a sulfonium salt (**51**); this is deprotonated to an ylide (**52**) which then rearranges and cyclizes (**52**→**53**→**54**); desulfurization then gives an indole ⟨79JA5512⟩. Likewise, an α-ethoxycarbonyl sulfide in place of the *β*-keto sulfide leads *via* (**56**) to an oxindole (**57**) or isatin (**55**) ⟨80JCR(S)347⟩. The synthetic approach has been extended to benzo[*b*]furans (**58**→**59**) ⟨75SC325⟩.

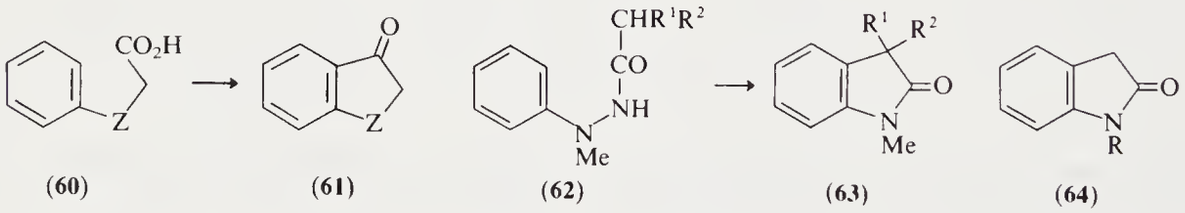


(51) (52) (53) (54)

(55) (56) (57) (58) (59)

(v) Indoxyls and their analogues

Indoxyls and their oxygen and sulfur analogues are prepared by the cyclization of anilino-, phenoxy- and phenylthio-acetic acids (**60**→**61**), with $NaNH_2$ (for Z = NH), P_2O_5 (for Z = O) and H_2SO_4 (for Z = S).



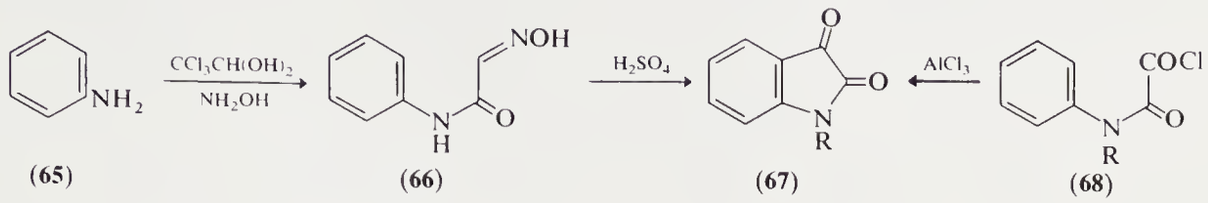
(60) (61) (62) (63) (64)

(vi) Oxindoles

Under conditions (CaO, 200 °C) different to those used to convert hydrazones in the Fischer indole synthesis, phenylhydrazides (**62**) give oxindoles (**63**) (Brunner synthesis). Treatment of *N*-chloroacetyl derivatives of primary or secondary arylamines with aluminum chloride also provides oxindoles ($PhNRCOCH_2Cl$→**64**) ⟨54JCS1697⟩.

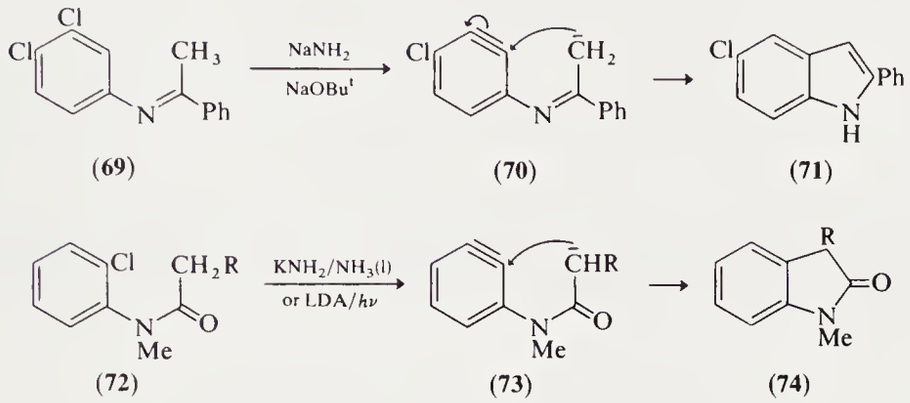
(vii) Isatins

Intramolecular acylation is involved in both isatin syntheses shown: **(65)**→**(66)**→**(67)** and **(68)**→**(67)** ⟨75AHC(18)1⟩.



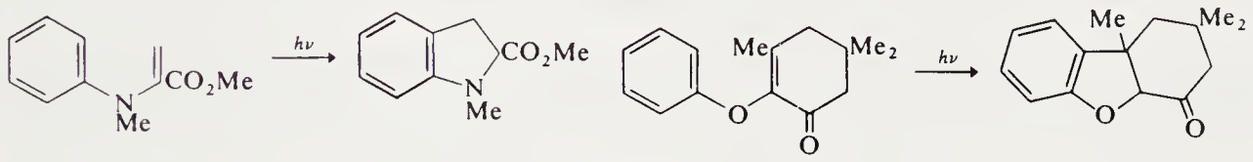
(viii) Reaction via *arynes*

The intramolecular addition of a carbanion to an aryne has been applied to the synthesis of indoles **(69**→**70**→**71)** ⟨75CC745⟩ and oxindoles **(72**→**73**→**74)** ⟨80JA3646⟩.



(ix) Photochemically mediated cyclizations

These have been used to produce indolines ⟨80T1757⟩ and 2,3-dihydrobenzofurans ⟨78JA2150⟩ (Scheme 5).

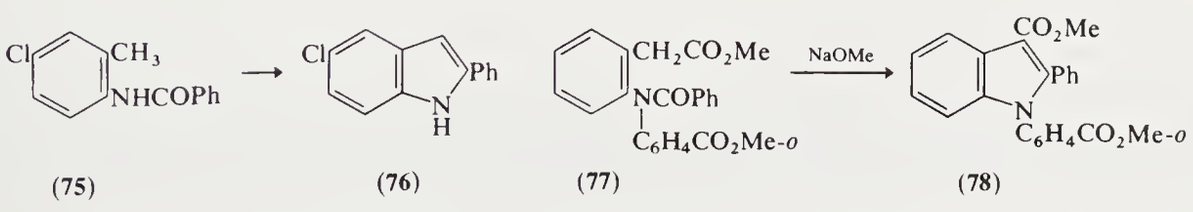


Scheme 5

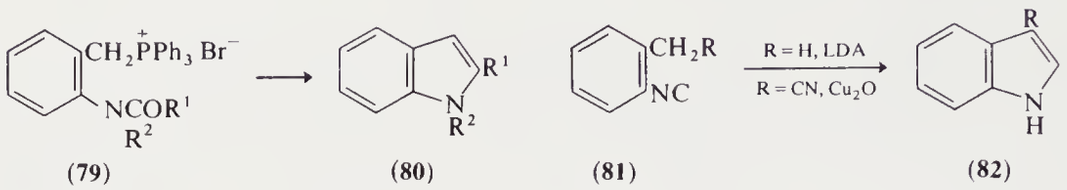
4.4.2.2.4 Ring closure by formation of C(2)—C(3) bond

(i) C(3) as nucleophile

The Madelung synthesis of indoles **(75**→**76)** from *N*-acyl-*o*-toluidines originally necessitated heating with sodamide at 250 °C; however the stronger bases *n*-butyllithium or LDA cause reaction at 20 °C ⟨81JOC4511⟩. Milder conditions can also be employed if the methyl group is activated as in **(77)**→**(78)** ⟨68JA7008⟩.



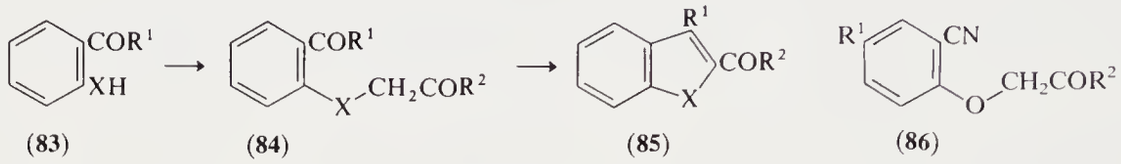
The ring closure (**79**)→(**80**) involves an intramolecular Wittig reaction ⟨81CC14⟩. Another variation on the Madelung indole synthesis is provided by the cyclization of *o*-isocyanobenzenes (**81**→**82**) ⟨77JA3532⟩.



(**79**) (**80**) (**81**) (**82**)

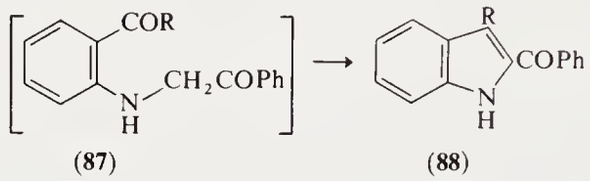
(ii) C(2) as nucleophile

These include useful ring syntheses for benzo[*b*]-fused compounds. The sequence (**83**)→(**84**)→(**85**) has been extensively applied to obtain benzo[*b*]furans ⟨48JCS2254⟩, benzo[*b*]thiophenes ⟨31LA(488)259⟩ and, less frequently, indoles ⟨27JCS1937⟩. Corresponding nitriles afford 3-amino derivatives, *e.g.* (**86**)→3-amino-2-aroylbenzofurans.



(**83**) (**84**) (**85**) (**86**)

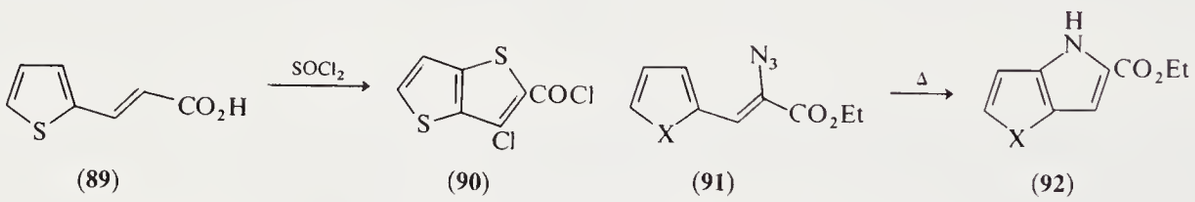
Halomethylcarbonyl compounds provide one-carbon components. For example, phenacyl bromide with *o*-acylanilines leads to indoles (**88**) ⟨72JOC3622⟩ by intramolecular aldol condensation of intermediate (**87**).



(**87**) (**88**)

4.4.2.2.5 Ring closure by formation of ring—Z bond

This is the least common of the four types of ring closure. It is illustrated by the transformations (**89**)→(**90**) ⟨72JHC879⟩ and (**91**)→(**92**) ⟨75CR(C)(281)793⟩. The latter illustrates the use of nitrene intermediates.

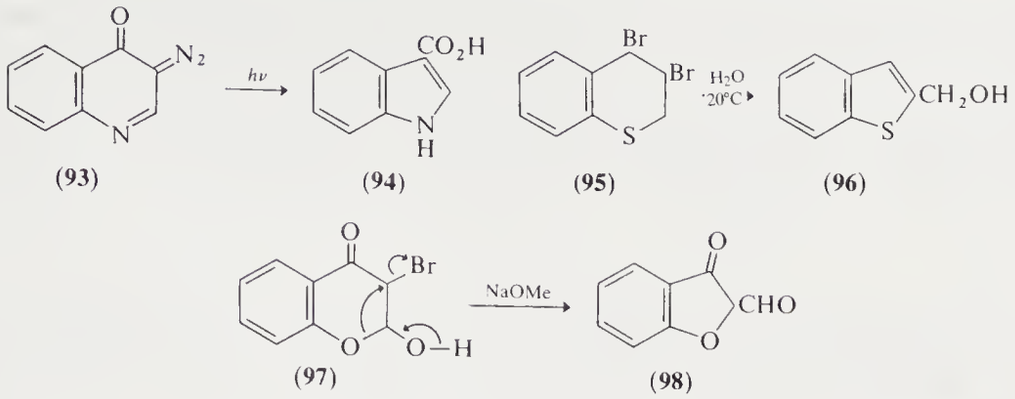


(**89**) (**90**) (**91**) (**92**)

Both these examples deal with annelations to heterocyclic rings, but analogous transformations can lead to benzothiophenes and indoles, respectively. Conversely, annelations to heterocyclic rings can also utilize the methods enumerated in the previous sections.

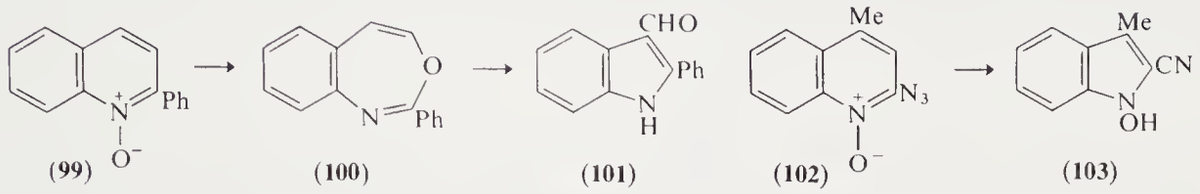
4.4.2.2.6 From other heterocycles

Preparations from six-membered rings by reactions analogous to those known for acyclic compounds are illustrated by the Wolff rearrangement (**93**→**94**) and analogues of the Meerwein rearrangement (**95**→**96** ⟨72JCS(P1)787⟩ and **97**→**98** ⟨75JHC981⟩).



(93) (94) (95) (96) (97) (98)

Quinoline 1-oxides can be rearranged photochemically into indoles (**99**→**100**→**101**) or *N*-hydroxyindoles (**102**→**103**). Cinnolines are reductively ring-contracted into indoles (Section 3.2.1.6.9.ii).



(99) (100) (101) (102) (103)

4.4.2.3 Six-membered Rings

4.4.2.3.1 Survey of synthetic methods for quinolines, benzo[b]*pyrans and their derivatives*

(104) (105)

The important methods involve ring closure of *o*-substituted anilines and phenols (type **104**) and cyclization of *o*-unsubstituted aniline, *etc.*, derivatives (type **105**). Additionally, cycloadditions and transformations from other heterocycles are considered. Table 2 gives an overview of the important methods for preparation of derivatives of these types.

Table 2 Important Ring Syntheses for Quinolines, Benzo[*b*]pyrans, Benzo[*b*]thiins and their Derivatives

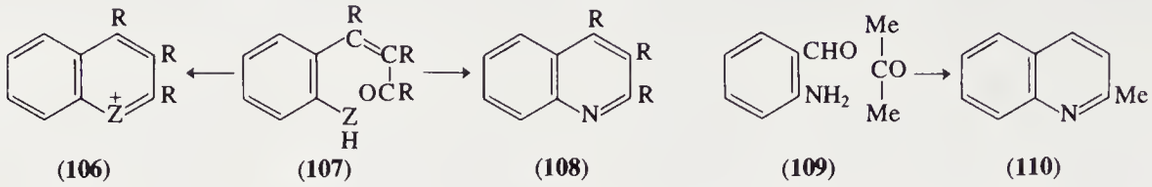
Ring	*Synthesis type*	*Synthesis name(s)*	*Section*
Quinolines	(**104**)	Friedländer, Pfitzinger	4.4.2.3.2.i (*a*, *b*)
	(**105**)	Skraup, Doebner–von Miller, Baeyer, Riehm	4.4.2.3.3.ii
Quinolones	(**104**)	Camps	4.4.2.3.2.ii
	(**105**)	β-Keto ester	4.4.2.3.3.i (*a*)
Tetrahydroquinolines	(**105**)	—	4.4.2.3.3.iii (*a*)
Benzo[*b*]pyryliums	(**104**)	—	4.4.2.3.2.i (*c*)
Coumarins and chromones	(**104**)	Kostanecki–Robinson	4.4.2.3.2.i (*d*)
Coumarins	(**105**)	von Pechmann	4.4.2.3.3.i (*b*)
Chromones	(**105**)	Simonis	4.4.2.3.3.i (*b*)
Chromans and tetrahydrobenzothiins	(**105**)	—	4.4.2.3.3.iii (*a*)

4.4.2.3.2 Ring closure of o*-substituted anilines or phenols*

(i) From or via o*-substituted cinnamoyl derivatives*

ortho-Substituted benzenes of type (**107**; Z = O, S, NH) can undergo ring closure (**107**→**106**, **108**). Amines of type (**107**; Z = NH), which usually cyclize spontaneously, are often prepared *in situ*

by reduction of nitro compounds, *e.g.* *o*-nitrocinnamic acid with $(NH_4)_2S$ gives 2-quinolone.



(106) (107) (108) (109) (110)

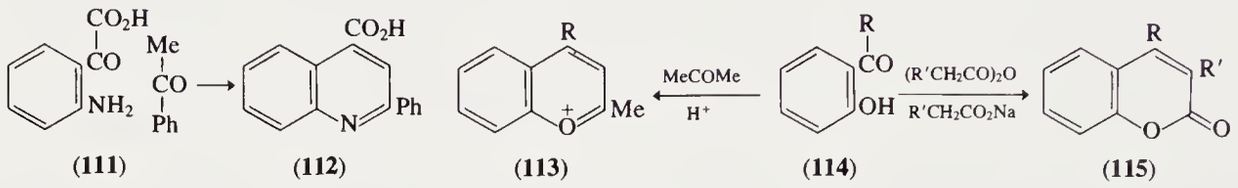
Important reactions that involve an aldol reaction to form the intermediate (**107**) *in situ* include:

(a) The Friedländer synthesis of quinolines from *o*-amino benzaldehydes and ketones (*e.g.* **109**→**110**).

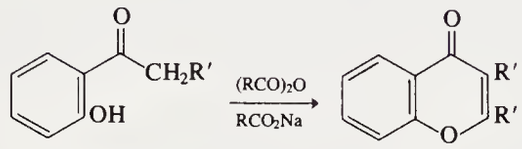
(b) The Pfitzinger synthesis of quinoline-4-carboxylic acids from a ketone and isatinic acid (obtained *in situ* from isatin), *e.g.* (**111**) yields (**112**).

(c) The preparation of benzopyrylium ions from ketones and *o*-acylphenols (**114**→**113**).

(d) The Kostanecki–Robinson synthesis which can lead to coumarins (**114**→**115**) or chromones (**116**→**117**).



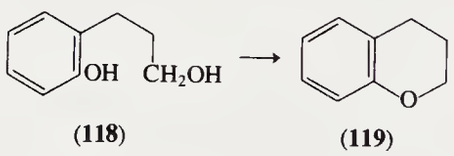
(111) (112) (113) (114) (115)



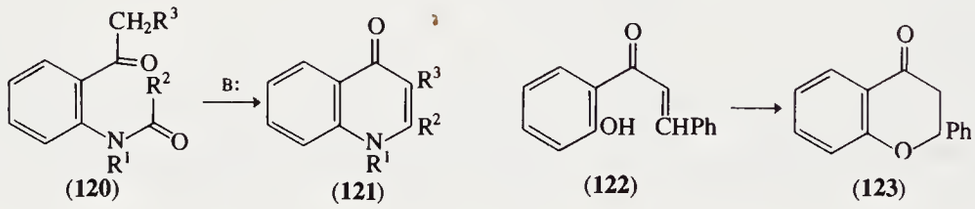
(116) (117)

(ii) From other o*-substituted benzenes*

Standard reactions of aliphatic chemistry can be applied; for example, chroman (**119**) can be prepared by ring closure of (**118**). 4-Quinolones result from the Camps reaction (**120**→**121**), and flavonone (**123**) by cyclization of (**122**).



(118) (119)



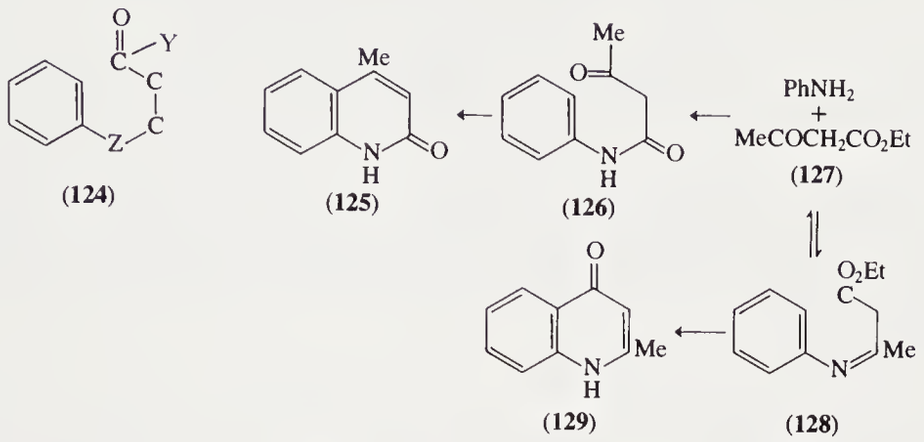
(120) (121) (122) (123)

4.4.2.3.3 Formation of a C—C bond by reaction of a multiple bond with a benzene ring

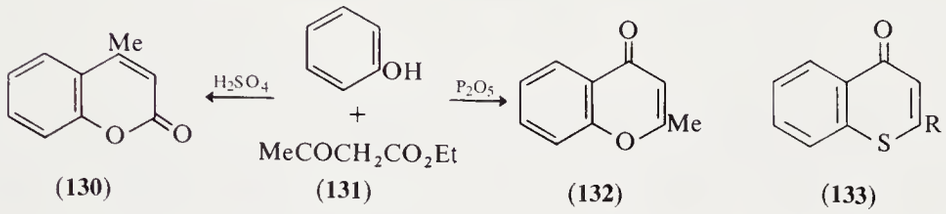
These reactions involve electrophilic attack on a benzene ring which is activated by the heteroatom (as in **124**).

(i) Quinolones, benzopyrones and benzothiinones

(a) Anilines and β-keto esters (**127**) give either Schiff's bases (**128**) at 20 °C, or at 100 °C the more slowly formed but more stable amides (**126**). Cyclization of the amide (**126**) with H_2SO_4 at 100 °C yields 2-quinolone (**125**), whereas the Schiff's base (**128**) is converted into 4-quinolone (**129**) at 280 °C.



(b) Phenols and β-keto esters (**131**) give either coumarins (**130**; von Pechmann reaction) or chromones (**132**; Simonis reaction) under the conditions indicated.



(c) Thiophenols and β-keto esters (with P_2O_5) give benzothiinones (**133**).

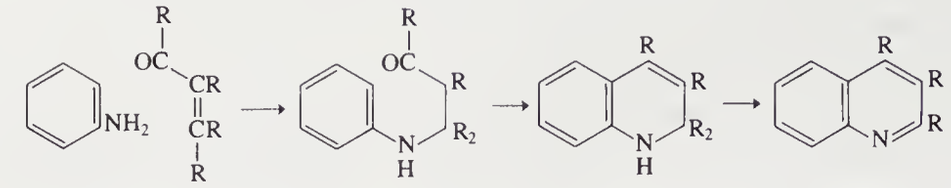
(ii) Quinolines

In the reactions of Table 3, Michael addition of a primary aromatic amine to an α,β-unsaturated aldehyde or ketone (prepared *in situ*) is followed by cyclization and oxidation of the intermediate dihydroquinoline to a quinoline (**134**→**137**).

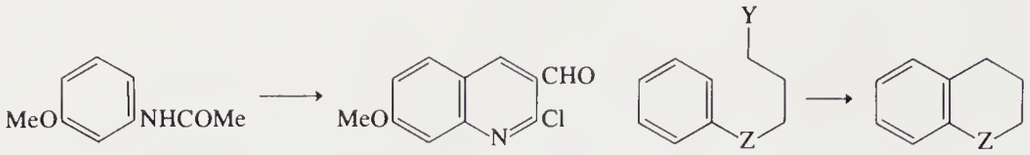
Table 3 Formation of Quinolines from Anilines

Name of reaction	*Starting materials*	*Catalyst*	*Intermediate carbonyl compound*	*Oxidizing agent*
Skraup	Glycerol	H_2SO_4	CH_2=CHCHO	As_2O_5, $ArNO_2$,[a] or *m*-$NO_2C_6H_4SO_3H$
Doebner–von Miller	RCHO and $R'CH_2$ CHO	$ZnCl_2$ – HCl	RCH=CR′CHO	ArN=CHR[b]
Baeyer	RCHO and $R'CH_2COR$	HCl, 20 °C	RCH=CR′COR	ArN=CHR[b]
Riehm	RCOR and $R'CH_2COR$	HCl, 200 °C	R_2C=CR′COR	None (RH lost from product)[c]

[a]Nitro compound corresponding to the amine. [b]Schiff's base from RCHO and amine. [c]Dihydroquinolines, *e.g.* (**136**; R = Me), can be isolated.



(134) (135) (136) (137)



(138) (139) (140) (141)

Acylanilines react with the Vilsmeier–Haack reagent ($POCl_3$–$HCONMe_2$) to give quinolines in good yield (*e.g.* **138**→**139**).

(iii) Partially saturated rings

Ring closure of compounds of types (**140**), (**142**), (**144**), (**146**) and (**148**) can give a wide variety of partially saturated rings.

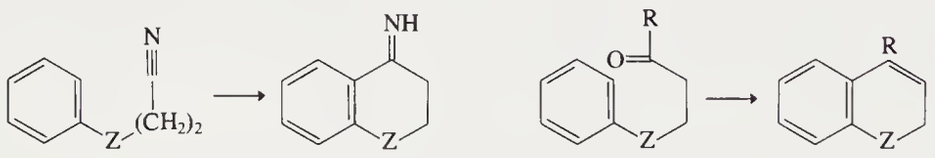
(a) Tetrahydroquinolines, chromans and tetrahydrobenzothiins (**141**) result from (**140**; Y = OH, OR, OTs or halogen) and from reactions of type (**142**)→(**143**).

Y = halogen, OH, OR, NR_2

(142) (143) (144) (145)

(b) Dihydro-4-quinolones, chromanones or dihydrobenzothiinones (**145**) are obtained from (**144**; Y = halogen, OH, OR or NR_2).

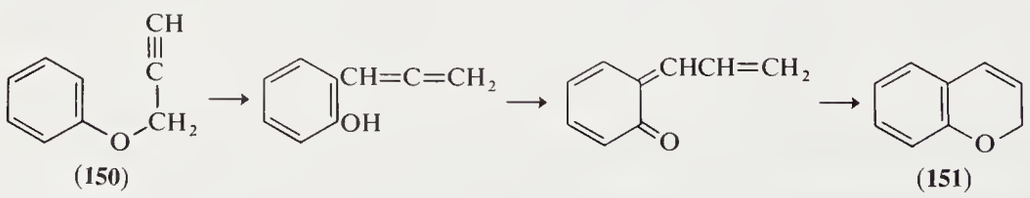
(c) Imino derivatives (**147**) are formed by the cyclization of nitriles (**146**).



(146) (147) (148) (149)

(d) 1,2-Dihydroquinolines and benzopyrans (**149**) are made from (**148**).

Sometimes the mechanism is complex. The propargyl ether (**150**) is converted on heating into 2*H*-chromene (**151**) *via* a Claisen rearrangement, a 1,5-hydrogen shift and electrocyclic ring closure (Scheme 6).

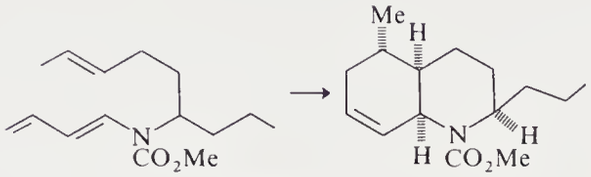


(150) (151)

Scheme 6

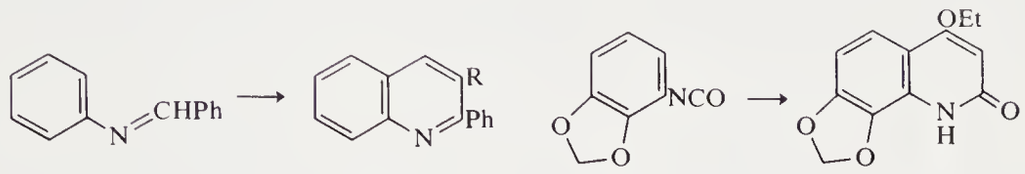
4.4.2.3.4 Synthesis via *cycloaddition reactions*

Intramolecular Diels–Alder reactions simultaneously form both rings. Precursors can be used which do *not* contain a heteroatom in either the 4π or the 2π component (*e.g.* Scheme 7).



Scheme 7

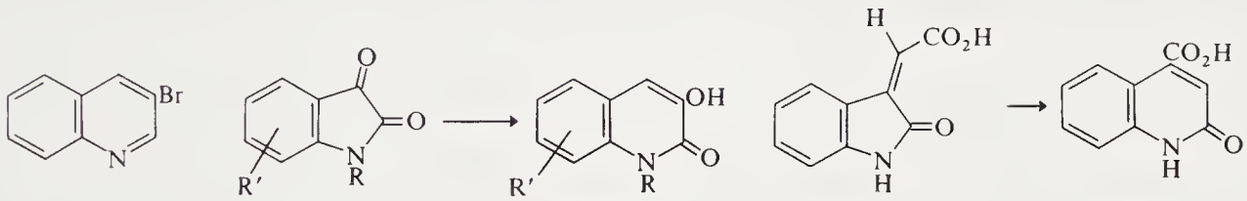
Intermolecular cycloaddition reactions include that of (**152**) and RCH=CHOEt to give quinoline (**153**). The 2-quinolone (**155**) is obtained from (**154**) and HC≡COEt.



(**152**) (**153**) (**154**) (**155**)

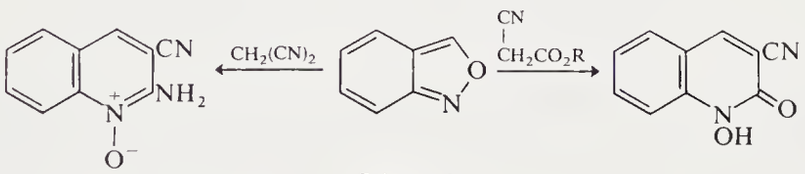
4.4.2.3.5 Synthesis from heterocycles

Indoles with dibromocarbene are ring-expanded to 3-bromoquinolines (**156**) and benzofurans behave analogously (Section 3.3.1.7.1). Isatins (**157**) with CH_2N_2 form 3-hydroxy-2-quinolones (**158**). With malonic acid they form 2-quinolone-4-carboxylic acids (**160**) by acid-catalyzed rearrangements of intermediates (**159**).



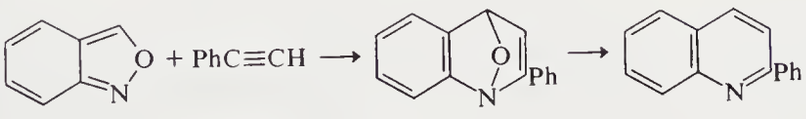
(**156**) (**157**) (**158**) (**159**) (**160**)

Anthranils undergo ring expansion to quinoline derivatives on treatment with various C-nucleophiles (see Scheme 8).



Scheme 8

Alkynes react with anthranils in a cycloaddition reaction to form quinolines (Scheme 9). For a similar reaction of benzazetidine see Section 3.5.8.1.

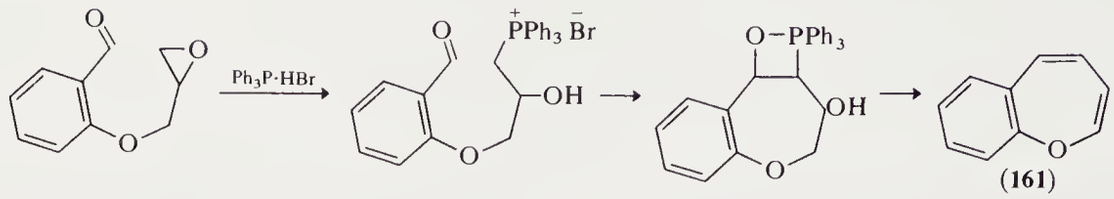


Scheme 9

4.4.2.4 Seven-membered and Larger Rings

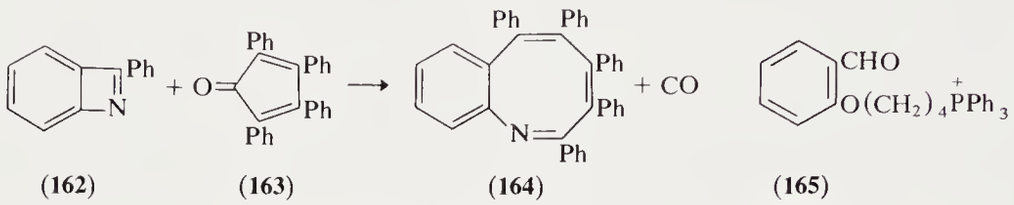
Tetrahydro-1-benzazepin-2-ones are formed from α-tetralone by Beckmann or related reactions (CHEC 5.16.4.1.1). Classical ring closures (of the Friedel–Crafts, Dieckmann, *etc.* types) can also be applied to benzazepine synthesis ⟨74AHC(17)45⟩.

The synthesis of the benzoxepin (**161**) involves an intramolecular Wittig reaction (Scheme 10) ⟨68JOC2591⟩.



Scheme 10

Diels–Alder addition of the benzazete (**162**) to tetraphenylcyclopentadienone (**163**) followed by CO loss yields the pentaphenylbenzazocine (**164**) ⟨75JCS(P1)45⟩. Intramolecular Wittig reaction of (**165**) gives some 3,4-dihydro-2*H*-benzoxocin ⟨74JOC3038⟩.

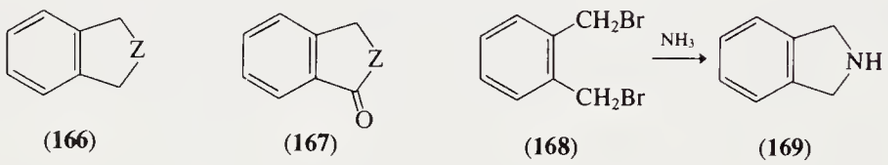


(**162**) (**163**) (**164**) (**165**)

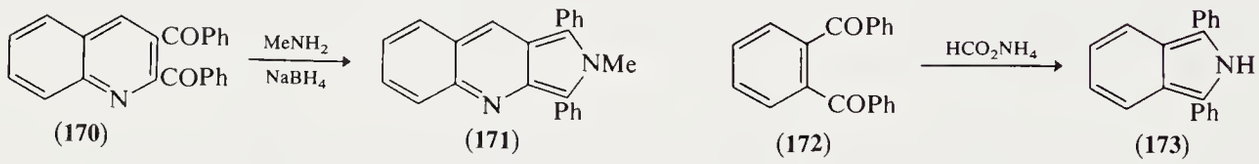
4.4.3 ONE HETEROATOM NOT ADJACENT TO RING JUNCTION

4.4.3.1 Five-membered Rings: Isoindoles and Related Compounds

(i) Compounds of types (**166**) and (**167**) can be prepared for *o*-disubstituted benzenes by standard reactions, *e.g.* (**168**)→(**169**). The application of this type of ring formation to ene-1,4-dione systems utilizes a reducing agent as in (**170**)→(**171**) ⟨73TL5185⟩ and (**172**)→(**173**) ⟨65CC272⟩.

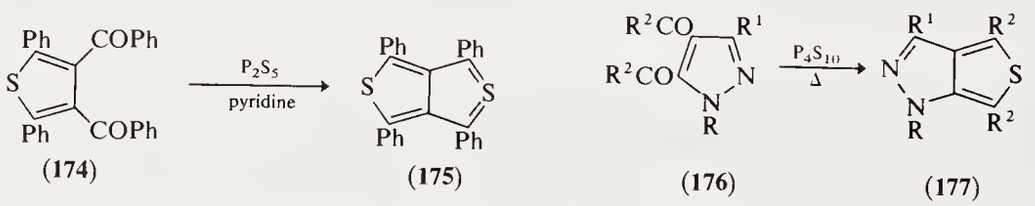


(**166**) (**167**) (**168**) (**169**)



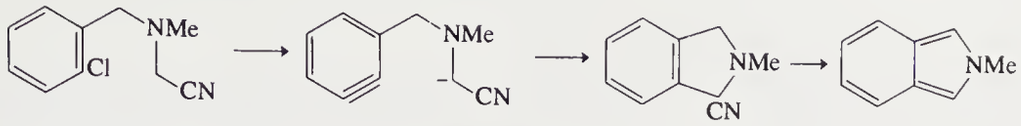
(**170**) (**171**) (**172**) (**173**)

Corresponding [*c*]-fused thiophenes are prepared with P_2S_5, *e.g.* (**174**)→(**175**) ⟨80JOC90⟩ and (**176**)→(**177**) ⟨73JOC1769⟩.



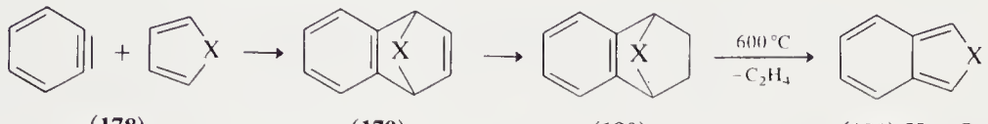
(**174**) (**175**) (**176**) (**177**)

(ii) A versatile isoindole synthesis (Scheme 11) proceeds through intramolecular carbanion addition to an aryne and subsequent aromatization by base-promoted elimination of hydrogen cyanide ⟨77T2255⟩.

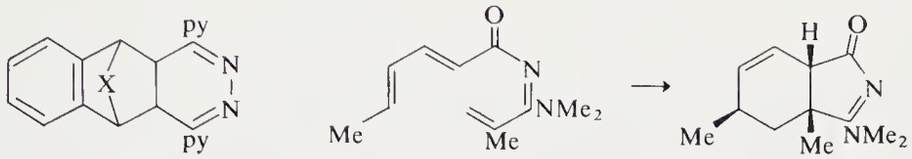


Scheme 11

Synthesis of benzo[*c*]furans and isoindoles (**181**) is also possible by the addition of benzyne to the respective monocycles (**178**), followed by reduction (**179**→**180**) and pyrolysis. In an alternative procedure, (**179**) is reacted with 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine, which affords (**181**) under far less vigorous conditions *via* a retro Diels–Alder reaction of the intermediate (**182**). 4-Phenyl-1,2,4-triazoles pyrolyze to form isoindoles (Section 3.4.3.12.2).



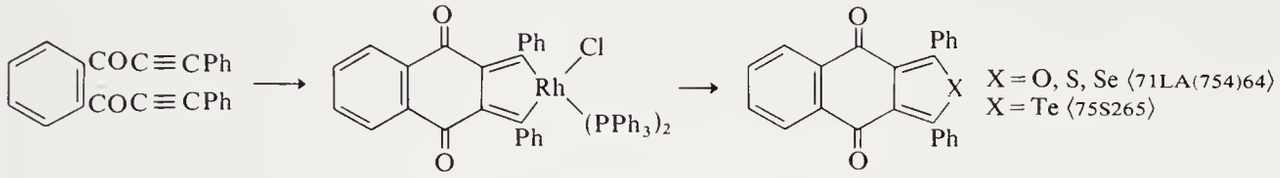
(**178**) (**179**) (**180**) (**181**) X = O



(**182**) (**183**) (**184**)

In the intramolecular cycloaddition reaction (**183**)→(**184**) ⟨81HCA1515⟩, the stereochemistry is rationalized by cycloaddition through an *exo* transition state followed by reversible enolization to yield the more stable *cis* ring junction.

(iii) The replacement of rhodium from rhodacycles forms condensed furans, thiophenes, selenophenes, tellurophenes and pyrroles (Scheme 12). Replacement of the rhodium by sulfur, selenium or tellurium is effected by direct treatment with the element, by oxygen with *m*-chloroperbenzoic acid, and by nitrogen with nitrosobenzene.

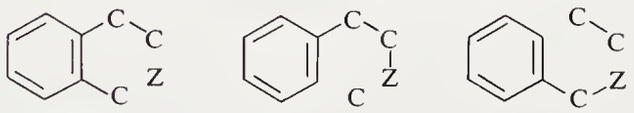


X = O, S, Se ⟨71LA(754)64⟩
X = Te ⟨75S265⟩

Scheme 12

4.4.3.2 Six-membered Rings

4.4.3.2.1 Overview of ring syntheses of isoquinolines, benzo[c]pyrans and their derivatives



(**185**) (**186**) (**187**)

We deal successively with methods of types (**185**), (**186**) and (**187**). Important methods are summarized in Table 4.

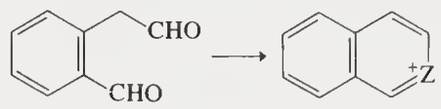
Table 4 Important Ring Syntheses for Isoquinolines, Benzo[*c*]pyrans and Derivatives

Ring	*Synthesis type*	*Synthesis name*	*Section*
Isoquinolines	(**185**)	—	4.4.2.2.2
	(**186**)	Pictet–Gams	4.4.2.2.3.ii
	(**187**)	Pomeranz–Fritsch	4.4.2.2.4
3,4-Dihydroisoquinolines	(**186**)	Bischler–Napieralski	4.4.2.2.3.i
Tetrahydroisoquinolines	(**186**)	Pictet–Spengler	4.4.2.2.3.ii
Benzo[*c*]pyrylium salts	(**185**)	—	4.4.2.2.2

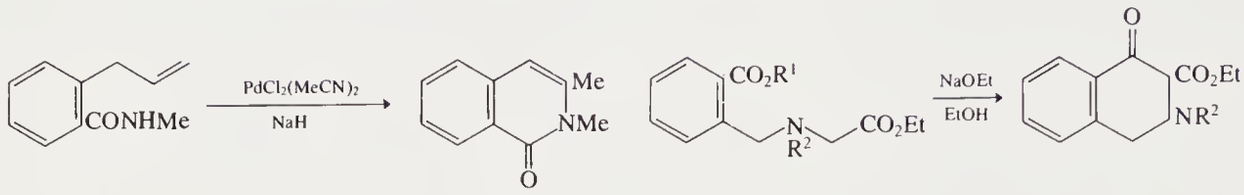
4.4.3.2.2 *Ring closure of an o-disubstituted benzene*

Homophthalaldehyde (**188**) gives isoquinoline, isoquinoline 2-oxide, 3,4-benzopyrylium salts, and 2-alkyl- and 2-aryl-isoquinolinium salts (**189**) by reaction with NH_3, NH_2OH, H^+ or RNH_2, respectively.

The transformation (**190**)→(**191**) exemplifies the use of transition metal reagents; the reaction probably involves aminopalladation of the C=C bond ⟨77JOC1329⟩. 2,3-Dihydro-4(1*H*)-isoquinolones are obtained by Dieckmann cyclization of *N*-(*o*-alkoxycarbonylbenzyl)glycine ester derivatives (**192**→**193**).



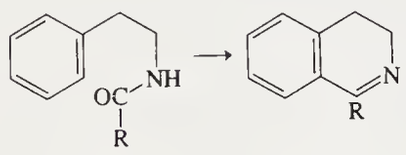
(**188**) (**189**)



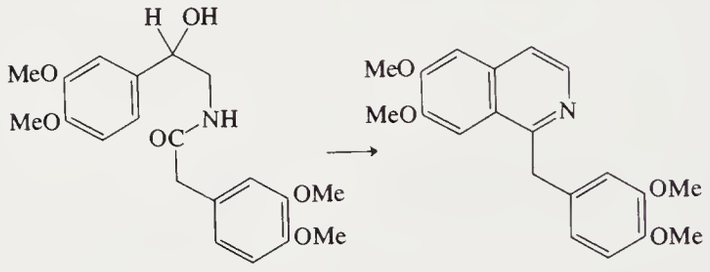
(**190**) (**191**) (**192**) (**193**)

4.4.3.2.3 *From a β-phenethylamine*

(i) In the Bischler–Napieralski synthesis of 3,4-dihydroisoquinolines (**195**) from acylated 2-phenethylamines (**194**), the amide carbonyl group is condensed with a benzene ring using acid catalysis (*e.g.* P_2O_5, $POCl_3$, $H_3PO_4-P_2O_5$). Electron-releasing substituents in the *meta* position generally facilitate reaction, but in the *para* position they can inhibit cyclization. *m*-Substituted phenethylamides form mainly 6-substituted dihydroisoquinolines.



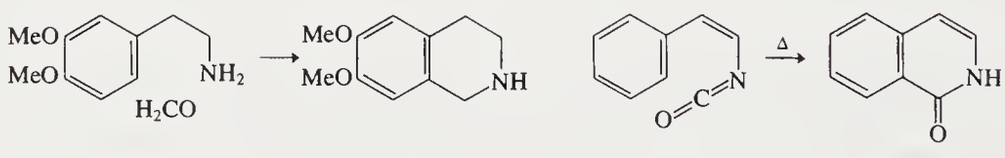
(**194**) (**195**)



(**196**) (**197**)

(ii) Pictet–Gams preparation of isoquinolines from *N*-acylated 2-hydroxyphenethylamines, *e.g.* (**196**)→papaverine (**197**), utilizes similar conditions.

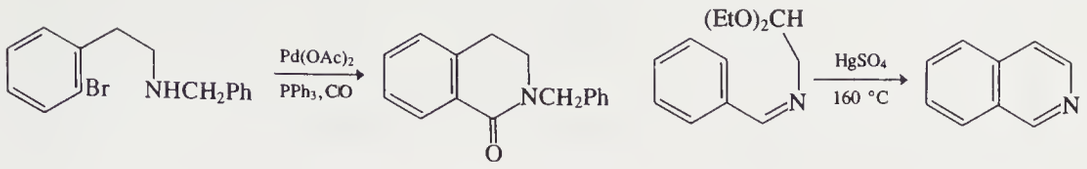
(iii) A Mannich-type reaction is used in the Pictet–Spengler synthesis of tetrahydroisoquinolines (**198**→**199**). Indoles similarly give β-carbolines (Section 3.3.1.5.7.iv).



(**198**) (**199**) (**200**) (**201**)

(iv) Styryl isocyanates, readily available by Curtius rearrangement of cinnamoyl azides, undergo thermal or Friedel–Crafts cyclization to 1-isoquinolones (**200**→**201**).

(v) 1-Isoquinolones (**203**) are obtained by a Pd-catalyzed CO insertion reaction of *o*-bromophenylethylamines (**202**).



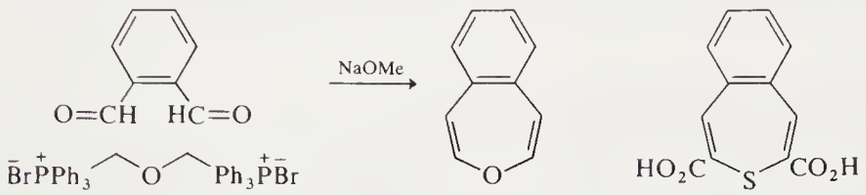
(202) (203) (204) (205)

4.4.3.2.4 From a benzylimine

The Pomeranz–Fritsch synthesis of isoquinolines is illustrated by the sequence $PhCHO + NH_2CH_2CH(OEt)_2$ at 160 °C→(**204**)→(**205**). See Section 3.3.1.5.6 for the synthesis of a thienotetrahydropyridine.

4.4.3.3 Seven-membered and Larger Rings

Two illustrative examples are presented. 3-Benzoxepin (**207**) is synthesized as shown in (**206**)→(**207**) ⟨66CB634⟩. The benzothiepin (**208**) is obtained by condensation of phthalaldehyde with $S(CH_2CO_2Et)_2$ and hydrolysis ⟨53JA6332⟩.

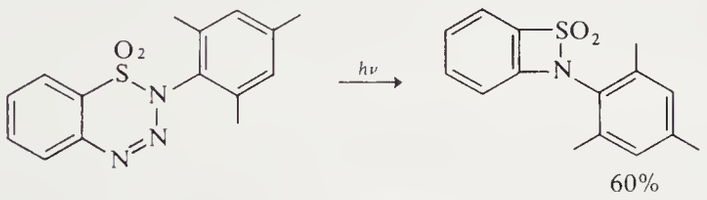


(206) (207) (208)

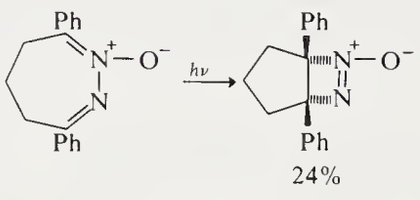
4.4.4 TWO HETEROATOMS 1,2 TO RING JUNCTION

4.4.4.1 Four-membered Rings

2-Mesityl-2*H*-benzo[*c*]-1,2-thiazetidine 1,1-dioxide is prepared from the corresponding benzothiatriazine by photochemically induced elimination of N_2 (Scheme 13) ⟨72LA(763)46⟩.



Scheme 13



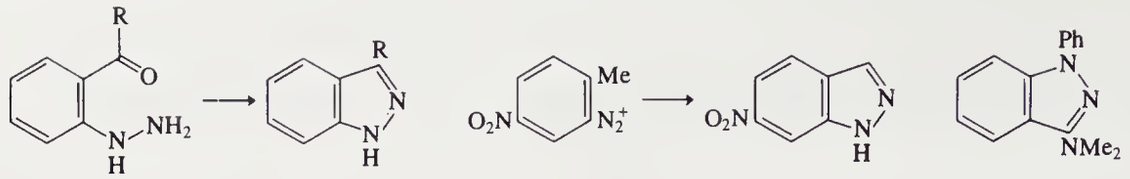
Scheme 14

Photoisomerization has been reported to give fused derivatives of 1,2-diazetidines (Scheme 14) ⟨68CC686, 69JA2818⟩.

4.4.4.2 Five-membered Rings

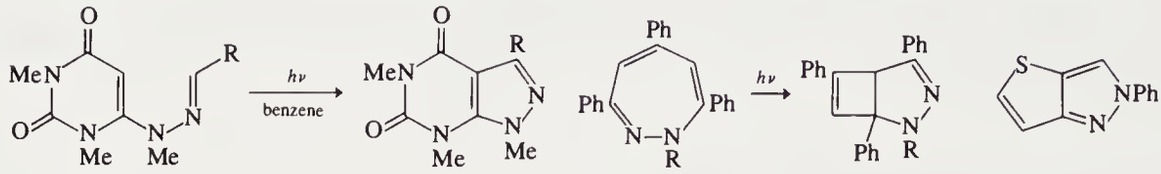
4.4.4.2.1 Indazoles

Indazoles (**210**) are formed by spontaneous cyclization of *o*-acylphenylhydrazines (**209**). Certain *o*-toluenediazonium salts cyclize spontaneously to indazoles (**211**→**212**); yields are good when the methyl group is activated by an *ortho* or *para* electron-withdrawing group. Pyrazoles are prepared similarly (Section 4.3.2.3.3).



(209) (210) (211) (212) (213)

Diphenylhydrazine (Ph_2NNH_2) is converted into indazole (**213**) by $Cl_2C{=}NMe_2^+$ Oxidative cyclizations are also known: thus fully methylated 6-(benzylidenehydrazino)uracils (**214**) give the pyrazolo[3,4-*d*]pyrimidines (**215**) ⟨75BCJ1484⟩.

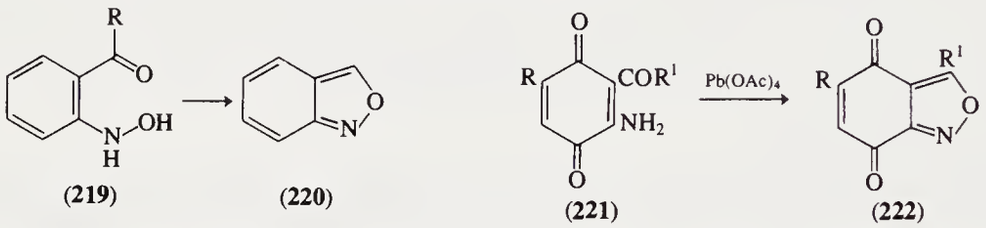


(214) (215) (216) (217) (218)

Ring contraction and intramolecular cyclization constitute a convenient route to some bicyclic systems. 1*H*-1,2-Diazepines (**216**) undergo electrocyclic ring closure to the fused pyrazole system (**217**) ⟨71CC1022⟩. Azepines undergo similar valence bond isomerizations. The anil of 3-nitrothiophene-2-aldehyde is deoxygenated by $P(OEt)_3$ to give (**218**) ⟨78CC453⟩.

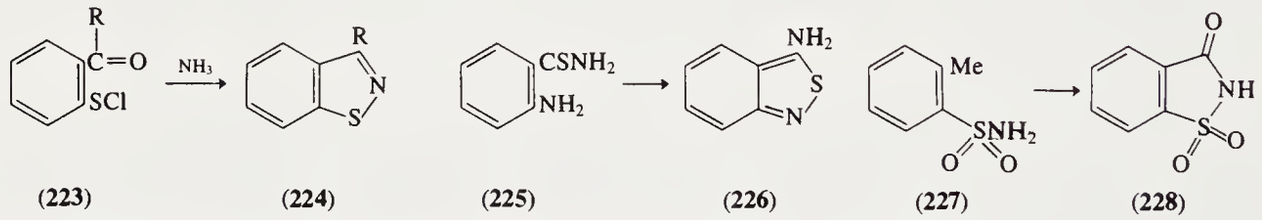
4.4.4.2.2 Anthranils, benzisothiazoles and saccharins

(i) Anthranils (**220**) are formed by spontaneous cyclization of *o*-acylphenylhydroxylamines (**219**) (themselves made by reduction of the corresponding nitro compounds). Treatment of the *β*-amino ketone (**221**) with lead tetraacetate gives the anthranil (**222**).



(219) (220) (221) (222)

(ii) Benz[*d*]isothiazoles (**224**) are prepared from sulfenyl chlorides (**223**), and their benz[*c*] isomers result from the H_2O_2 oxidation of *o*-aminothiobenzamides (**225**→**226**). Iminobenzodithioles equilibrate thermally with benzisothiazolethiones (Section 3.4.1.2.4).



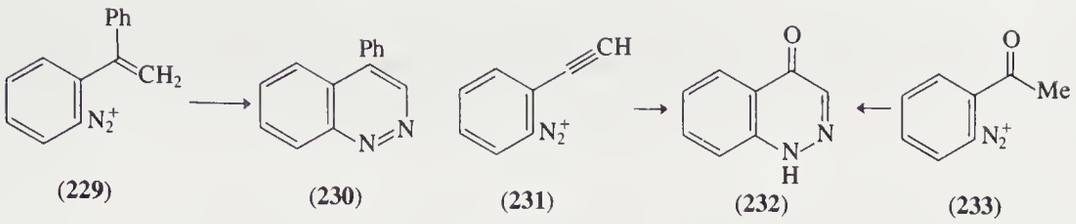
(223) (224) (225) (226) (227) (228)

(iii) Saccharins are obtained by $KMnO_4$ oxidation of *o*-methylbenzenesulfonamides (*e.g.* **227**→**228**).

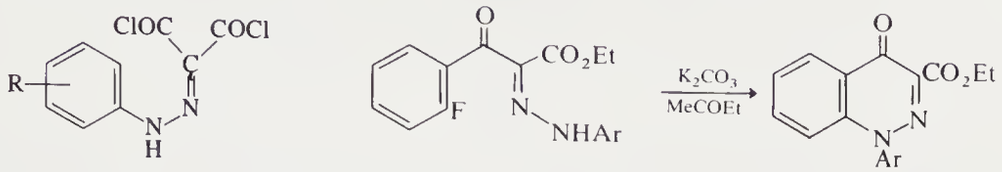
4.4.4.3 Six-membered Rings

4.4.4.3.1 Cinnolines

o-Alkenyl-, *o*-alkynyl- and *o*-acyl-diazonium ions cyclize spontaneously to give cinnolines or cinnolones (**229**→**230**; **231**, **233**→**232**). These are the usual preparative methods for these classes of compound. However, Friedel–Crafts cyclization of mesoxalyl chloride hydrazones (**234**) ⟨61JCS2828⟩ or benzene ring–N bond formation, as in (**235**→**236**) ⟨83S52⟩, can also be used.

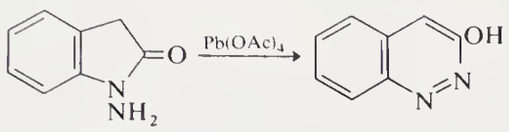


(229) (230) (231) (232) (233)

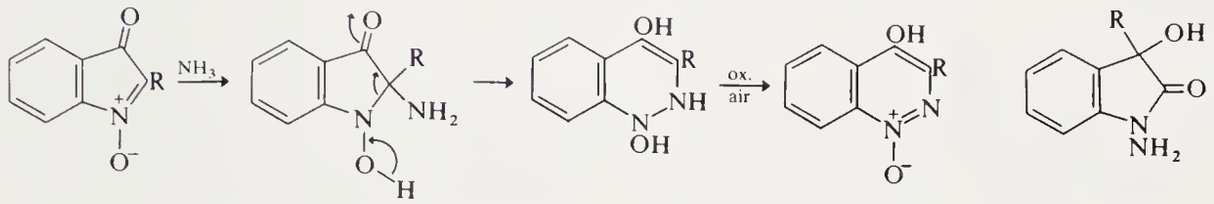


(234) (235) (236)

Preparations of cinnolines by expansion of five-membered heterocyclic rings include the oxidation of *N*-aminooxindoles (**237**→**238**), the treatment of isatogens with ammonia (Scheme 15) and the base-catalyzed conversion of 1-aminodioxindoles (**239**) into cinnolin-3-ones.

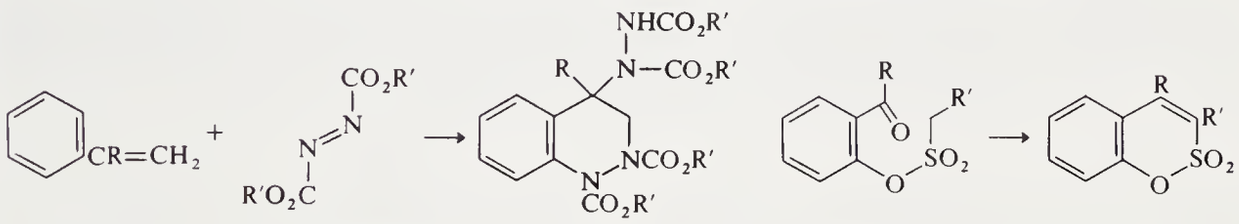


(237) (238)



Scheme 15 (239)

Tetrahydrocinnolines have been made by the cycloaddition method of Scheme 16.

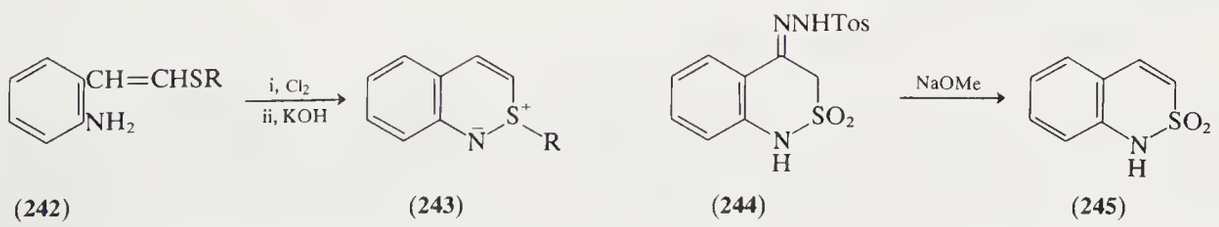


Scheme 16 (240) (241)

4.4.4.3.2 Rings containing O or S atoms

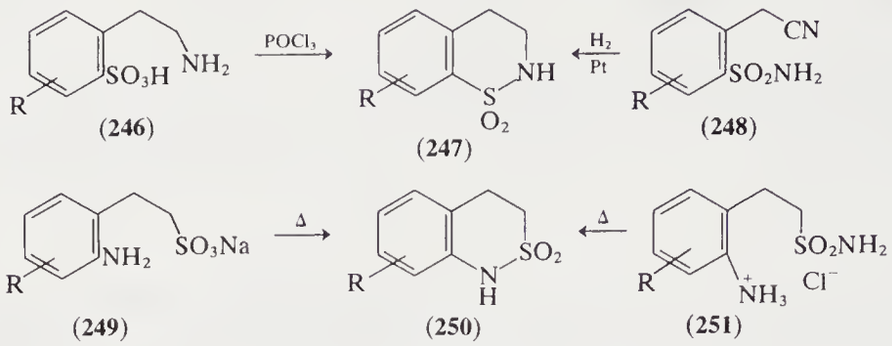
1,2-Benzoxathiin 2,2-dioxides (**241**) are prepared from 2-acylphenols by reaction with a sulfonyl chloride, followed by base-catalyzed cyclization of the sulfonate ester (**240**) ⟨66HC(21-2)792⟩.

The 2,1-benzothiazines (**243**) are the products from *N*-chlorosuccinimide and potassium hydroxide with 2-aminostyrenes (**242**) ⟨79TL3969⟩, and the sulfone (**245**) is obtained by the action of base on the tosylhydrazone (**244**) ⟨66JOC3531⟩.



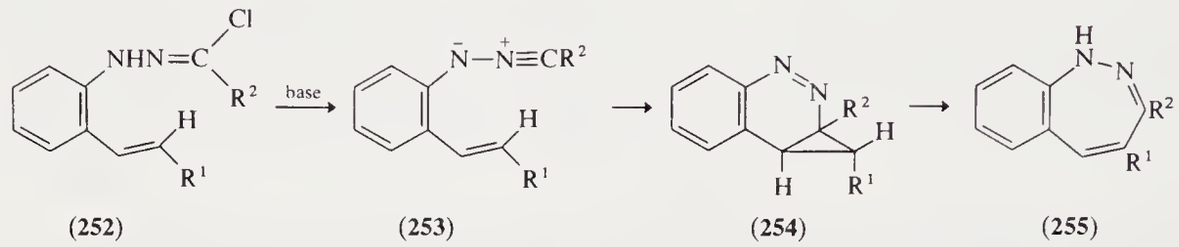
(242) (243) (244) (245)

Routes to 3,4-dihydro-2*H*-1,2-benzothiazine dioxides (**247**) include the cyclization of amino-sulfonic acids (**246**) or cyanosulfonamides (**248**). 2,4-Dihydro-1*H*-2,1-benzothiazine dioxides (**250**) are normally prepared by thermolysis of the sodium sulfonates (**249**) or amino sulfonamides (**251**) ⟨71CB1880⟩.

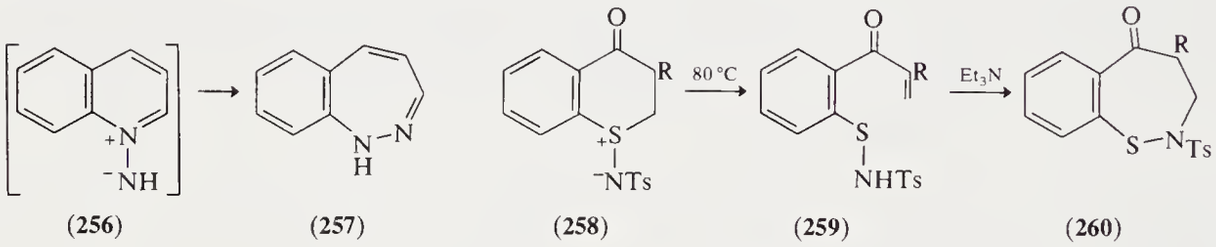


4.4.4.4 Seven-membered Rings

In an intramolecular 1,3-dipolar reaction, the nitrilimines (**253**), generated by the reaction of the hydrazoyl chlorides (**252**) with triethylamine at 80 °C, cyclize to give 1*H*-1,2-benzodiazepines (**255**) ⟨79S380⟩. At 20 °C using silver carbonate, the cyclopropa[*c*]cinnolines (**254**) are isolated; they rearrange *via* ring expansion and hydrogen migration to give the benzodiazepines (**255**) ⟨81JOC1402⟩.



The photolysis of quinoline *N*-imides (**256**) (which are in equilibrium with their dimers ⟨77JOC1856⟩) gives 1*H*-1,2-benzodiazepines (**257**). Reactions of this type have also provided routes to pyrido-, thieno- and furo-1,2-diazepines ⟨79CPB2183, 79H(12)471⟩.



N-Tosylsulfimines, *e.g.* (**258**), are converted into 1,2-benzothiazepines (**260**) by triethylamine. In the absence of base the intermediate (**259**) can be isolated ⟨81JCS(P1)1037⟩.

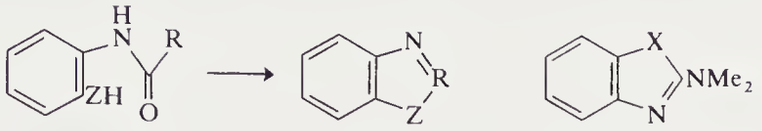
4.4.5 TWO HETEROATOMS 1,3 TO RING JUNCTION

4.4.5.1 Five-membered Rings

4.4.5.1.1 Ring closure of o*-disubstituted benzene*

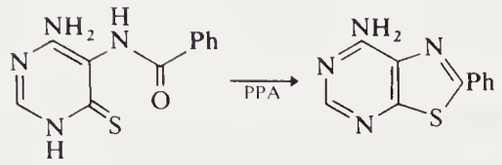
(i) *o*-Hydroxy-, *o*-mercapto- and *o*-amino-anilides (**261**; Z = O, S, NH) cyclize under mild conditions (*e.g.* heating at 150 °C or refluxing with H_2O–HCl) to benzoxazoles, benzothiazoles and benzimidazoles (**262**; Z = O, S, NH), respectively. The anilides are often prepared and cyclized *in situ* by heating the corresponding *o*-substituted anilines with a carboxylic acid, anhydride, acid

chloride, ester, nitrile, amidine, *etc.* *o*-Substituted anilines with the phosgeneiminium chloride $Cl_2C{=}NMe_2{}^+Cl^-$ give benzoxazoles, benzothiazoles and benzimidazoles (**263**) containing a 2-dimethylamino substituent ⟨73AG(E)806⟩. Similar *ortho*-substituted heterocycles react similarly, providing entry into a large number of ring-fused systems.

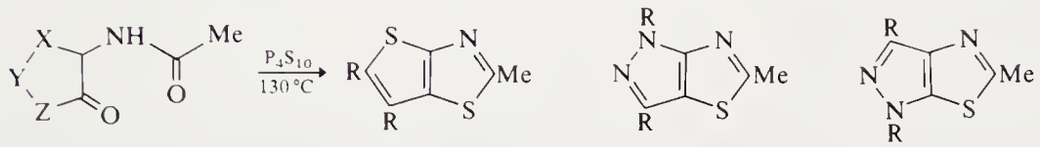


(**261**) (**262**) (**263**) X = O, S, NR

Similar methods lead to ring closure on a variety of other ring systems. The substituted pyrimidinethione (**264**) with polyphosphoric acid formed the thiazolo[5,4-*d*]pyrimidine (**265**) ⟨65JOC1916⟩. Using phosphorus pentasulfide as the thiation agent, reaction with the α-acylaminocarbonyl system contained in (**266**) led to thieno[2,3-*d*]thiazoles (**267**) ⟨70CHE1515⟩, pyrazolo[5,4-*d*]thiazoles (**268**) ⟨74CHE813⟩ and pyrazolo[4,5-*d*]thiazoles (**269**) ⟨64CHE165⟩.



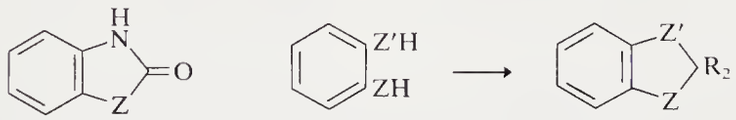
(**264**) (**265**)



(**266**) (**267**) (**268**) (**269**)

(ii) Benzoxazolones, benzothiazolones and benzimidazolones (**269a**) are prepared by the reaction of carbonic acid derivatives [$CO(OEt)_2$, $COCl_2$ or $ClCO_2Et$] with the corresponding *o*-substituted anilines.

(iii) If an aldehyde, ketone or *gem*-dihalo compound is used in place of the carbonic acid derivative, the corresponding non-aromatic compound is formed (**270**→**271**).

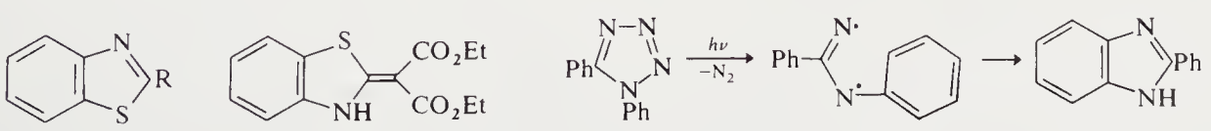


(**269a**) (**270**) (**271**)

4.4.5.1.2 Other methods

Oxidative C—S bond formation (I_2, Br_2 or $SOCl_2$) converts thioanilides PhNHCSR into benzothiazoles (**272**) (the Jacobson–Hugershoff synthesis). Thus, $ArNHCSCH(CO_2Et)_2$ with bromine yields the benzothiazole (**273**) ⟨73ZC176⟩.

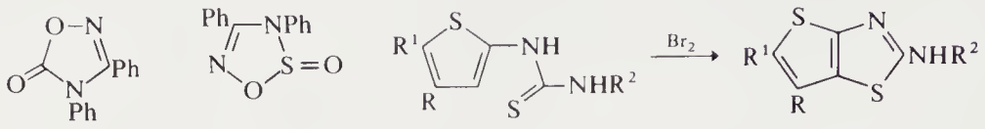
Nitrene-like intermediates can lead to C—N bond formation and thus to imidazole derivatives. 1,5-Diphenyltetrazole (**274**) fragments to (**275**), which is trapped intramolecularly to form (**276**) (Section 3.4.1.2.1).



(**272**) (**273**) (**274**) (**275**) (**276**)

Photolysis of (**277**) also gives the nitrene intermediate (**275**) and thus (**276**) (Section 3.4.3.12.2). Some (**276**) was obtained from photolysis of the oxathiadiazole 2-oxide (**278**) with loss of SO_2 ⟨68TL325⟩.

The 2-thienylthiourea (**279**) with bromine in acetic acid gives the thieno[3,2-*d*]thiazole (**280**) ⟨71AJC1229, 78JHC81⟩. Pyrazolo[3,4-*d*]thiazoles are formed similarly ⟨76GEP2429195⟩.



(**277**) (**278**) (**279**) (**280**)

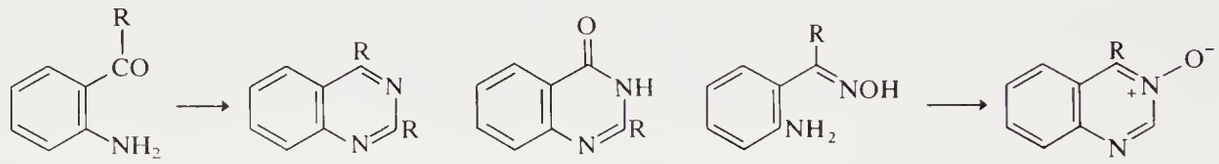
2-Acetamido-5-thiazolylthioglycolic acid (**281**) on heating with phosphorus oxychloride is cyclized to 2-acetamidothieno[3,2-*d*]thiazolin-4-one (**282**) ⟨56AC(R)275⟩.

(**281**) (**282**)

4.4.5.2 Six-membered Rings

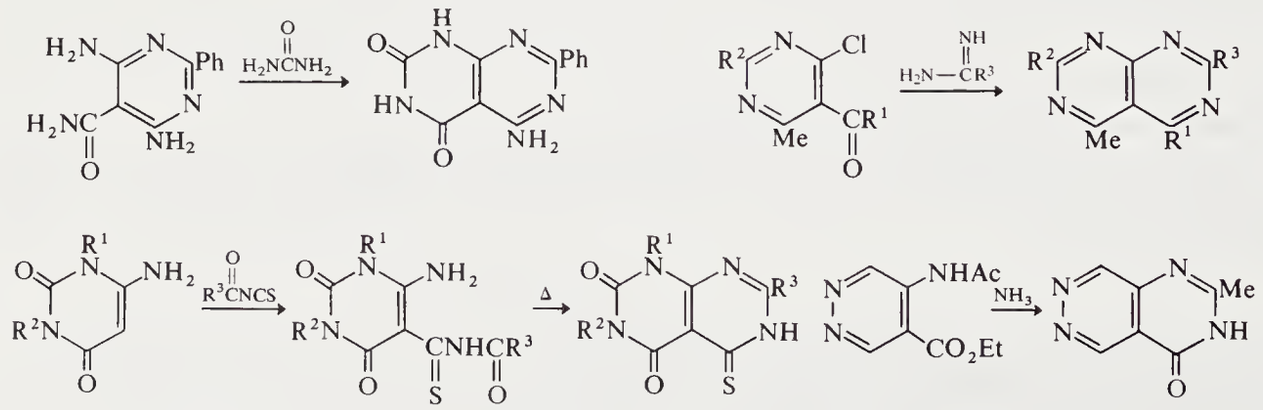
4.4.5.2.1 Quinazolines and azinopyrimidines by cyclization procedures

The usual precursor is an appropriately *ortho* disubstituted benzene. Thus, quinazolines (**284**) can be prepared by the reaction of *o*-acylanilines (**283**; R = alkyl) with amides $RCONH_2$. Heating anthranilic acid (**283**; R = OH) with amides or amidines yields 4-quinazolinones (**285**). The second nitrogen can be introduced into (**283**) before ring closure, as in (**286**) + $HC(OEt)_3$ → (**287**).

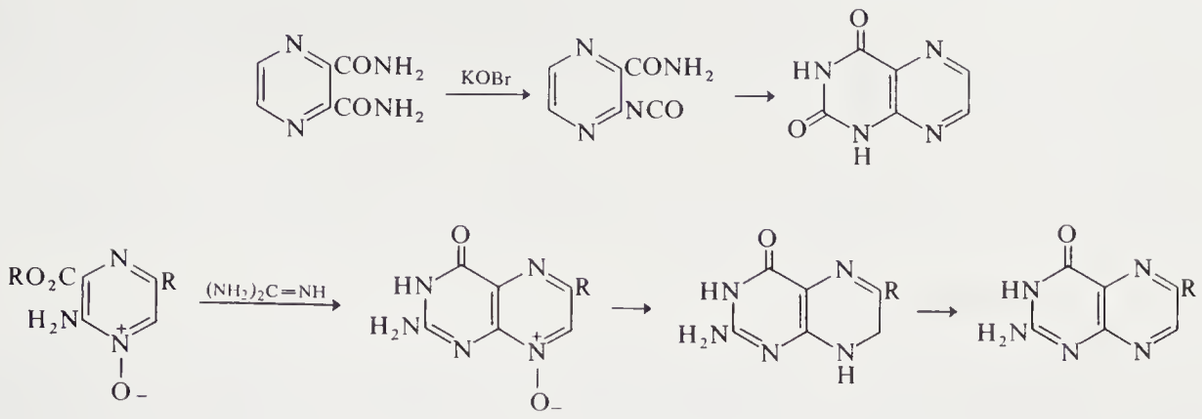


(**283**) (**284**) (**285**) (**286**) (**287**)

The synthesis of pyrimidopyrimidines, pyrimidopyridazines and pteridines is illustrated in Scheme 17. Full details are given in the appropriate chapters of CHEC. In addition to the syntheses that resemble those of quinazolines from anthranilic acid, the high reactivity to nucleophiles of the 4-chlorine in a pyrimidine and that of the 5-position in 6-aminouracil to electrophiles are exploited.



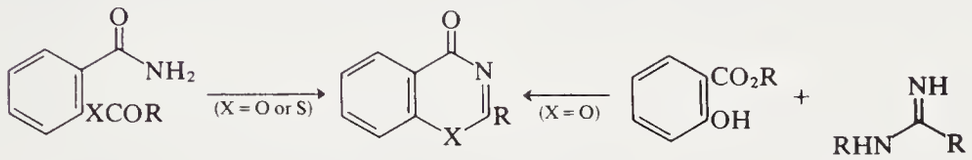
Scheme 17



Scheme 17 (*continued*)

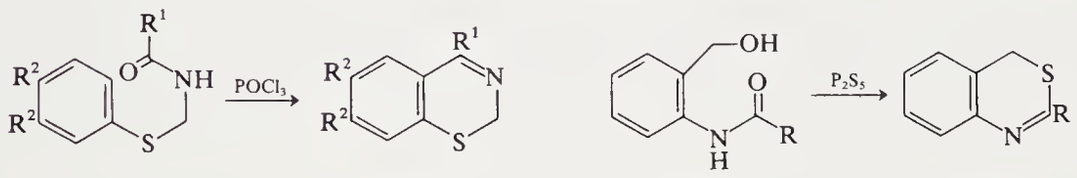
4.4.5.2.2 Rings containing O or S atoms

1,3-Benzoxazin-4-ones are made by the cyclization of *o*-benzoylsalicylamides or reactions between phenyl salicylates and benzamidines ⟨13LA(409)325⟩. The first method has wide applicability, and when 2-acylmercaptobenzamides are used 1,3-benzothiazin-4-ones are obtained (Scheme 18) ⟨67BSF(2)4441⟩.



Scheme 18

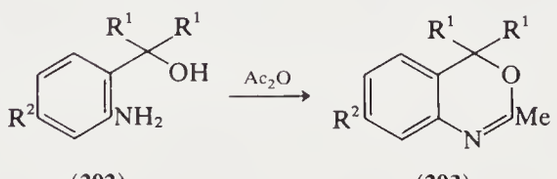
2*H*-1,3-Benzothiazines (**289**) are available through a Bischler–Napieralski-type cyclization of amides (**288**) ⟨77ACH(92)317⟩.



(**288**) (**289**) (**290**) (**291**)

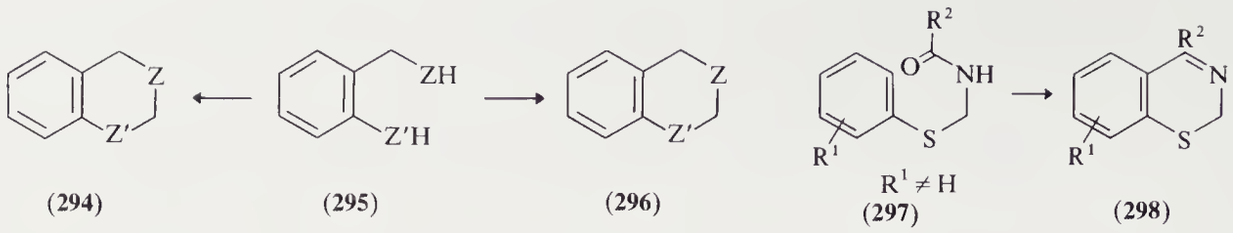
The amide (**290**) can be cyclized to benzothiazine (**291**) with phosphorus pentasulfide ⟨1894CB3509⟩.

2-Aminobenzyl alcohols (**292**) give 4,4-dialkyl-4*H*-3,1-benzoxazine derivatives (**293**) on treatment with acetic anhydride ⟨1883CB2576⟩.



(**292**) (**293**)

Saturated derivatives of types (**294**) and (**296**) can be made as shown from the *o*-tolyl compound (**295**) by reaction with H_2CO and $COCl_2$, respectively. An example of a less frequently used type of ring closure is (**297**)→(**298**).

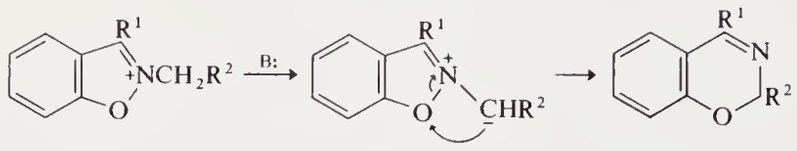


(294) (295) (296) (297) (298)

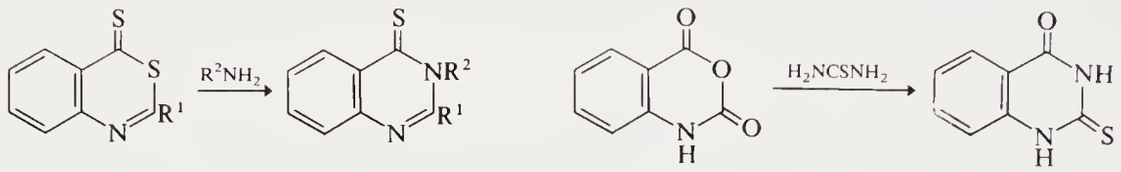
$R^1 \neq H$

4.4.5.2.3 *From other heterocycles*

N-Alkylbenz[*d*]isoxazolium cations undergo base-catalyzed ring expansion to 1,3-benzoxazines (**299**→**300**→**301**) (Section 3.4.3.12.3). Benzoxazinones are obtained by heating 3-acylanthranils (Section 3.4.3.4.4) or acylating anthranils (Section 3.4.1.7.5). 1,3-Benzoxazine and -thiazine derivatives can be converted into quinazolone compounds by sequences exemplified by (**302**)→(**303**) and (**304**)→(**305**).



(299) (300) (301)



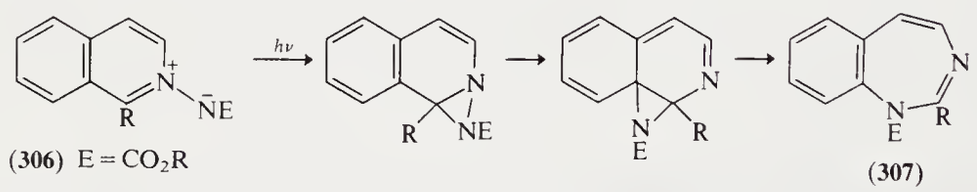
(302) (303) (304) (305)

4.4.5.3 Seven-membered Rings

Benzoxazepines are obtained photolytically from quinoline 1-oxides (Section 3.2.3.12.5.iv).

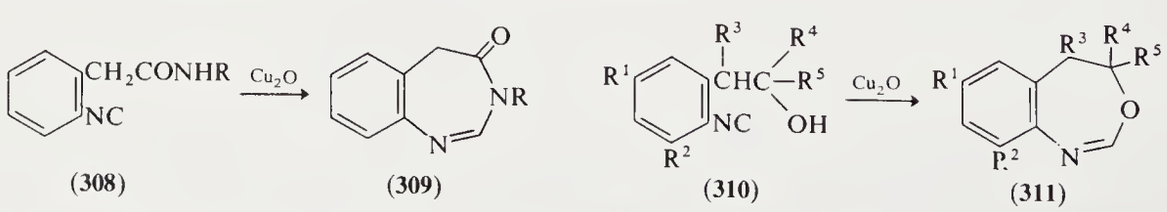
4.4.5.3.1 *Seven-membered rings with heteroatoms 1,3 to ring junction*

The fully unsaturated 1,3-benzodiazepine (**307**) is formed by a photoreaction of the 1-substituted isoquinoline *N*-imide (**306**) ⟨80CPB2602⟩. The same principle has been applied to prepare thieno-, furo- and pyrrolo-fused 1,3-diazepines ⟨80CC454, 81CPB1539⟩.



(306) $E = CO_2R$ (307)

1,3-Benzodiazepin-4-ones (**309**) have been synthesized by the Cu_2O-catalyzed cyclization of (**308**); the competing route to indoles is disfavored by bulky R groups ⟨79TL1039⟩.

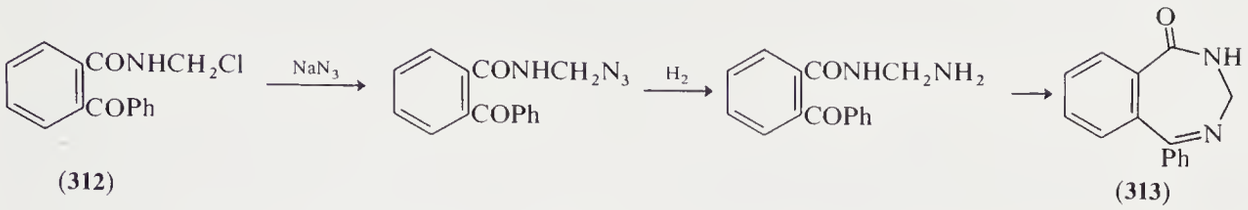


(308) (309) (310) (311)

The copper-catalyzed insertion of isocyanides (**310**) into the O—H bond of alcohols gives a high yielding route to 4,5-dihydro-3,1-benzoxazepines (**311**) ⟨78TL2087⟩.

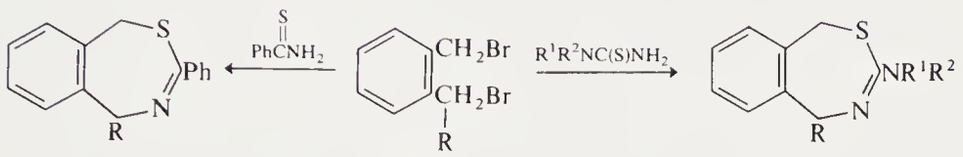
4.4.5.3.2 Seven-membered rings with heteroatoms 2,4 to ring junction

Treatment of (**312**) as shown gives 2,4-benzodiazepin-1-one (**313**) ⟨75JHC903⟩.



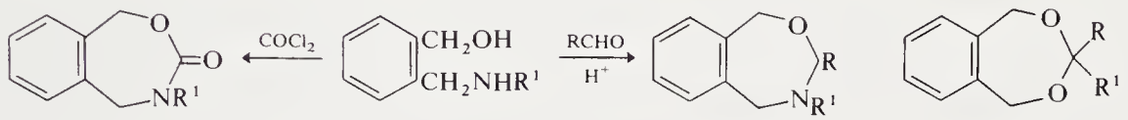
(**312**) (**313**)

1,4-Dihalo compounds react with thioureas or thioamides ⟨77HCA2872, 75CPB1764, 73RTC20⟩: syntheses of 2,4-benzothiazepines, *e.g.* (**314**) and (**316**), from *o*-xylyl dibromides (**315**) are shown. *o*-Chloromethylbenzoyl halides similarly give 2,4-benzothiazepin-5-ones and 4-bromobutyryl chloride gives the 1,3-benzothiazepin-4-one system.



(**314**) (**315**) (**316**)

One-pot reactions involving successive nucleophilic attack by oxygen and nitrogen on a 1,1-bis carbon electrophile are used in the synthesis of 2,4-benzoxazepine systems (**317**) and (**318**) ⟨72JHC1209, 75FES773⟩.



(**317**) (**318**) (**319**)

Reaction of 1,2-benzenedimethanol with aldehydes or related compounds gives 3*H*-2,4-benzodioxepins (**319**).

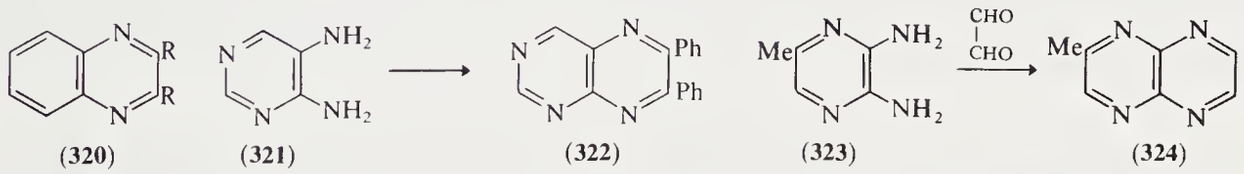
The analogous 1,5-dihydro-3*H*-2,4-benzodithiepin system can be prepared by the reaction of 1,2-benzenedimethanethiol with either methylene iodide in the presence of base or with aldehydes or ketones in the presence of acid.

4.4.6 TWO HETEROATOMS 1,4 TO RING JUNCTION

4.4.6.1 Quinoxalines and Azinopyrazines

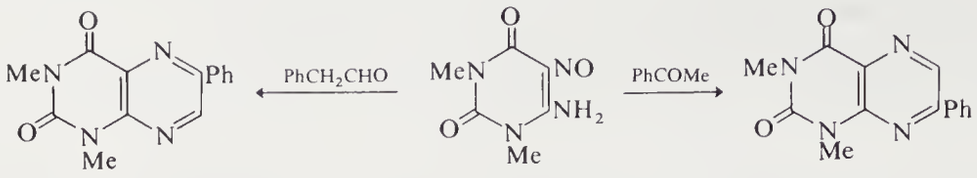
Quinoxalines (**320**) are prepared from *o*-phenylenediamines and α-diketones.

Heterocyclic *o*-diamines react analogously, as in the preparation of pteridines (**321**→**322**) and pyrazinopyrazines (**323**→**324**).



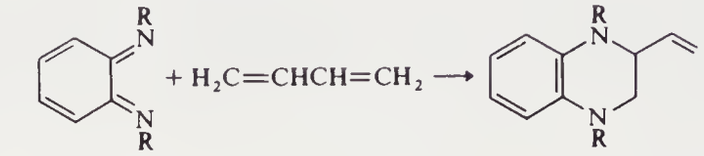
(**320**) (**321**) (**322**) (**323**) (**324**)

Ketomethylene structures react with 6-amino-5-nitrosopyrimidines ⟨49MI21600⟩, providing a general route to 6- and 7-substituted pteridines from ketones and aldehydes (Scheme 19) ⟨54JCS2881, 56JCS213⟩.



Scheme 19

The cycloaddition reaction (**325**) + (**326**) → (**327**) illustrates the preparation of tetrahydroquinoxalines from *o*-benzoquinone diimines.

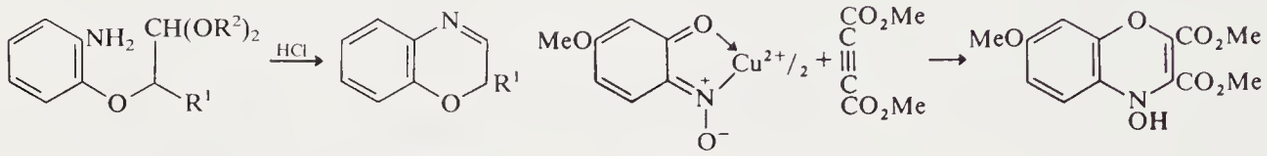


R = COAr, SO_2Ar

(**325**) (**326**) (**327**)

4.4.6.2 1,4-Benzoxazines and 1,4-Benzothiazines

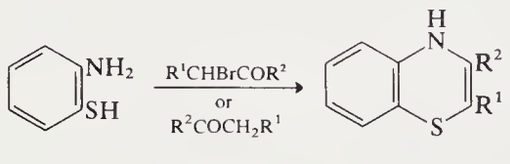
2*H*-1,4-Benzoxazines (**329**) result by the cyclization of acetals (**328**) in acid solution ⟨79M257⟩.



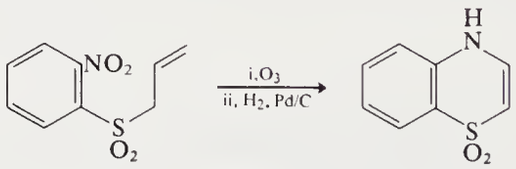
(**328**) (**329**) (**330**) (**331**)

4*H*-1,4-Benzoxazines are available by reaction of the copper complexes derived from *o*-nitrosophenols with alkynic dienophiles (**330** → **331**).

2*H*-1,4-Benzothiazines can be obtained from 2-aminothiophenols, by their reactions with either α-bromocarbonyl compounds ⟨70AC(R)383⟩ or active methylene compounds (Scheme 20) ⟨76JCS(P1)1146⟩.



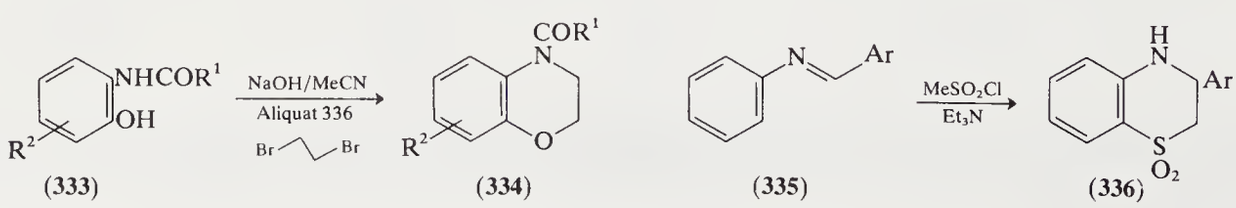
Scheme 20



(**332**) **Scheme 21**

4*H*-1,4-Benzothiazine 1,1-dioxide may be synthesized from the sulfone (**332**) by ozonolysis and hydrogenation of the ozonide over palladium on carbon (Scheme 21) ⟨68TL1041⟩.

Dihydro-1,4-benzoxazines (**334**) are prepared from 2-hydroxyacetanilides (**333**) with 1,2-dibromoethane and sodium hydroxide in acetonitrile containing a phase transfer catalyst ⟨79S541⟩. 1,1-Dioxides of dihydro-1,4-benzothiazines (**336**) are generated through the cyclization of imines (**335**) with methanesulfonyl chloride in the presence of triethylamine ⟨79CI(L)26⟩.



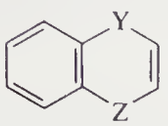
(**333**) (**334**) (**335**) (**336**)

4.4.6.3 Rings Containing Oxygen and/or Sulfur Atoms

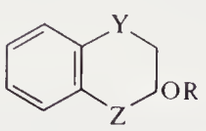
The monobenzo-fused derivatives of 1,4-dioxin, 1,4-oxathiin and 1,4-dithiin, (**337**), (**338**) and (**339**), can all be prepared by base-catalyzed reaction between the appropriate 1,2-disubstituted benzene and an α-haloketal *via* an intermediate 2-alkoxy-2,3-dihydro derivative (**340**). The pyrolysis of the acetoxy derivative (**341**) at 450 °C gives (**337**; 80%) ⟨67ZC152⟩. 2-Hydroxy-2-phenyl-1,4-benzodioxane, from catechol and phenacyl bromide, is dehydrated to (**337**) by thionyl chloride in pyridine.

In the 1,4-benzoxathiane series again the best yield (76%) is obtained by pyrolysis of the 2-acetoxy derivative (**342**) ⟨66HC(21-2)852⟩.

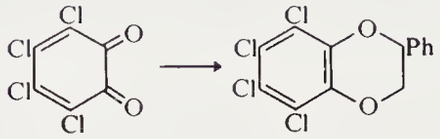
Elimination of EtOH from 2-ethoxy-1,4-benzodithiane (**343**) readily gives 1,4-benzodithiin (**339**; 75%) ⟨66HC(21-2)1143⟩.



(**337**) Y = Z = O
(**338**) Y = S, Z = O
(**339**) Y = Z = S



(**340**) Y, Z = O or S, R = alkyl
(**341**) Y = Z = O, R = COMe
(**342**) Y = S, Z = O, R = COMe
(**343**) Y = Z = S, R = Et

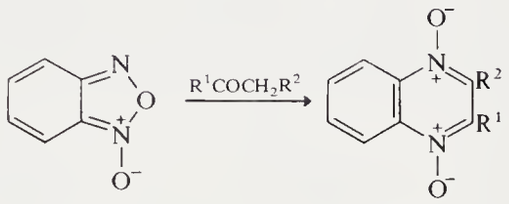


(**344**) (**345**)

Routes to benzo-fused derivatives of 1,4-dioxanes, -oxathianes and -dithianes make use of anions or dianions of the appropriate 1,2-disubstituted benzene. An alternative approach to the synthesis of 1,4-benzodioxanes involves Diels–Alder addition reactions of alkenes across the quinone function of 1,2-benzoquinones, *e.g.* (**344**)→(**345**).

4.4.6.4 Synthesis from Heterocyclic Precursors

Initial nucleophilic attack and ring opening are involved in the conversion of benzofuroxans into quinoxaline di-*N*-oxides by treatment with imines, enamines, carbonyl compounds and active methylene compounds (**346**→**347**) (Section 3.4.1.9.1).

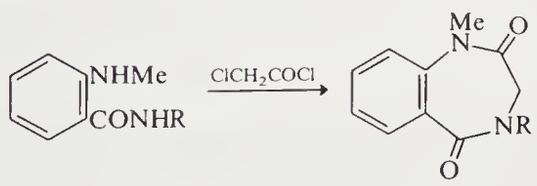


(**346**) (**347**)

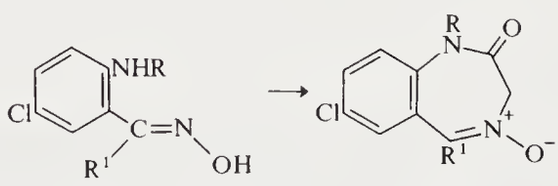
4.4.6.5 Seven-membered Rings with Two Heteroatoms 1,4 to the Ring Junction

4.4.6.5.1 1,4-Benzodiazepines

Reactions between 1,5-bis nitrogen nucleophiles and 1,2-bis electrophile equivalents have been used in the synthesis of 1,4-benzodiazepines ⟨67AHC(8)21⟩. Chloroacetyl chloride has been much used as the two-carbon fragment in the synthesis of 2-oxo-1,4-benzodiazepine systems, *e.g.* (**348**) and (**349**) ⟨68CRV747⟩.

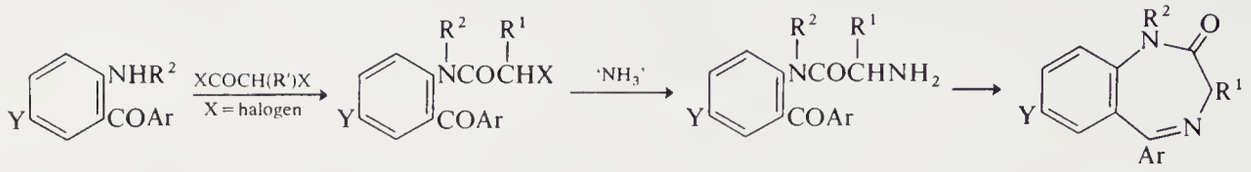


(**348**)



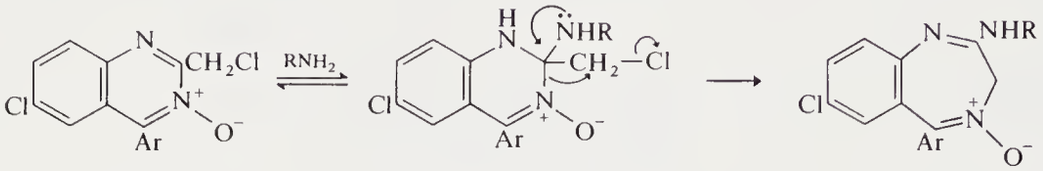
(**349**)

One of the commercially important routes to 1,4-benzodiazepin-2-ones (**353**) from 2-aminobenzophenones (**350**) involves the reaction of (**351**) with ammonia. Intermediate (**352**) can be isolated.



(**350**) (**351**) (**352**) (**353**)

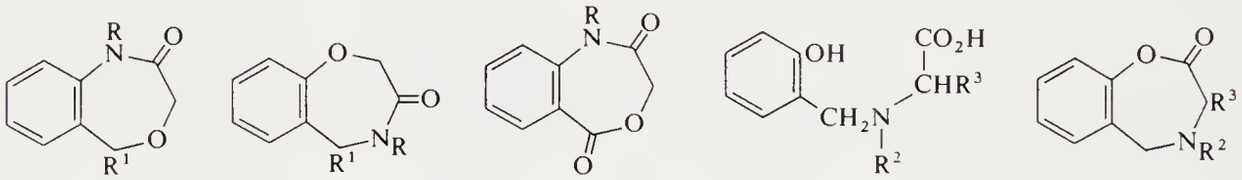
Quinazoline 3-oxides, *e.g.* (**354**), react with ammonia and primary amines to give 2-amino-1,4-benzodiazepine 4-oxides (**355**) ⟨79JMC1⟩.



(**354**) (**355**)

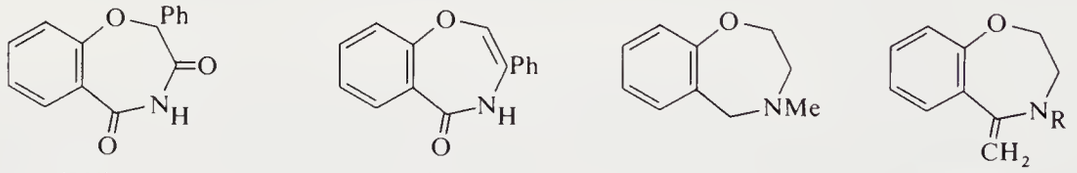
4.4.6.5.2 1,4- and 4,1-Benzoxazepines, 1,4- and 1,5-benzothiazepines and 1,4-benzodioxepins

o-Aminobenzyl alcohols give 4,1-benzoxazepin-2-ones (**356**) ⟨65FES323⟩, *o*-hydroxybenzylamines give 1,4-benzoxazepin-3-ones (**357**) ⟨66JHC237⟩, and anthranilic acids give 4,1-benzoxazepine-2,5-diones (**358**). Compounds of type (**356**) are also obtained by the reaction of *o*-aminobenzyl alcohols with chloroacetic esters ⟨71JOC305⟩. Compound (**359**) can be cyclized by thionyl chloride to give the 1,4-benzoxazepin-2-one system (**360**).



(**356**) (**357**) (**358**) (**359**) (**360**)

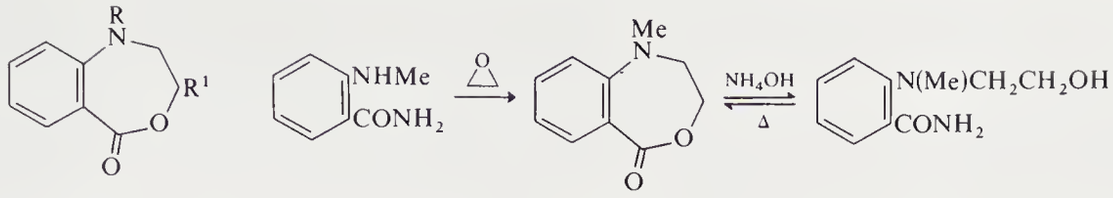
Salicylamide with 2-chlorophenylacetic acid followed by acetyl chloride gives the 3,5-dione (**361**). Similarly phenacyl bromide gives (**362**).



(**361**) (**362**) (**363**) (**364**)

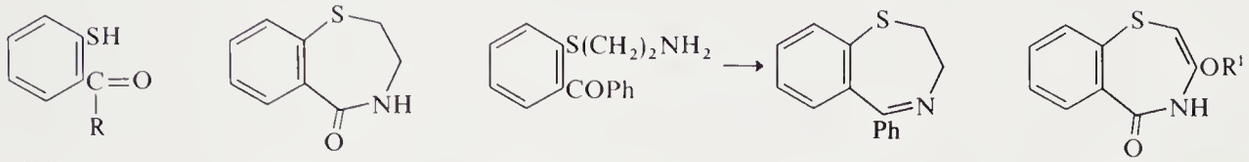
The reaction of methylamine with *o*-chloromethylphenyl 2-chloroethyl ether gives (**363**). *o*-(2-Chloroethoxy)acetophenone reacts with amines to give (**364**) ⟨63HCA1696⟩ and the analogous benzophenones react with formamide to give analogues of (**363**) with a 5-phenyl substituent ⟨69JPS1460⟩.

Anthranilic acids and esters ⟨75BSF(2)283⟩ with halohydrins give the 4,1-benzoxazepin-5-one system (**365**). *o*-Methylaminobenzamide with ethylene oxide gives (**366**) which is cleaved to (**367**) by ammonia ⟨66JOC4268⟩.



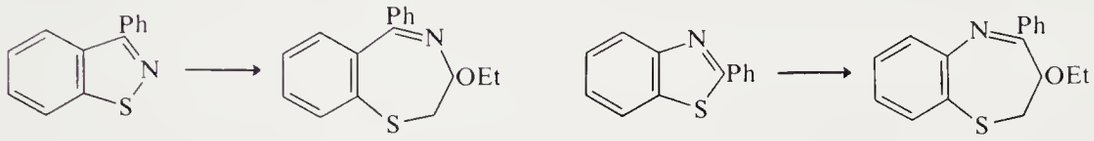
(365) (366) (367)

1,4-Benzothiazepines can be constructed from substrates of type (**368**) and an appropriate C—C—N fragment; thus 2,3-dihydro-1,4-benzothiazepin-5-one (**369**) can be prepared by reaction of (**368**; R = OH) with aziridine. The reaction of 2-mercaptoaryl ketone (**368**; R = Ph) with 2-bromoethylamine is a two-stage process; intermediate (**370**) cyclizes in the presence of pyridine to give (**371**). The reaction of (**368**; R = OMe) with chloroacetonitrile in the presence of alcohols (R^1OH) gives (**372**) ⟨74OPP287⟩.



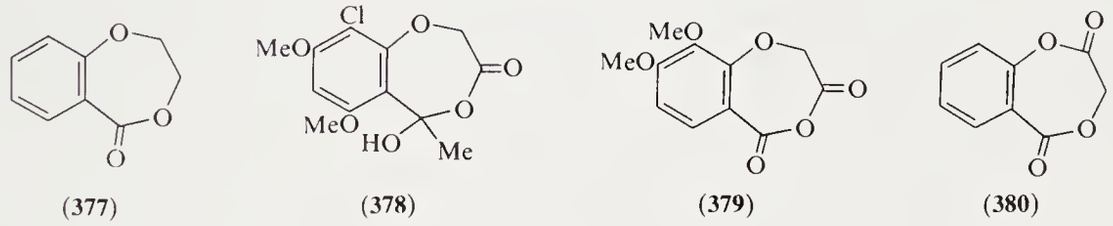
(368) (369) (370) (371) (372)

The 1,4- and 1,5-benzothiazepines (**374**) and (**376**) have been prepared by the photochemical reactions of the benzisothiazole (**373**) and the benzothiazole (**375**), respectively, with ethyl vinyl ether ⟨81TL529, 81TL2081⟩.



(373) (374) (375) (376)

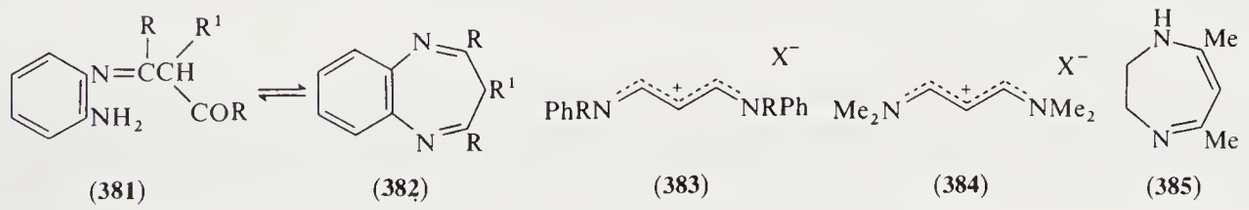
5*H*-1,4-Benzodioxepin-ones and -diones have been prepared ⟨72HC(26)319, p. 339⟩: sodium salicylate and 2-chloroethanol give (**377**) ⟨75BSF(2)277⟩ and the methyl ester of 2-acetyl-6-chloro-3,5-dimethoxyphenoxyacetic acid with hydrochloric acid gives (**378**). The dicarbonyl compound (**379**) is prepared by heating 2-carboxy-5,6-dimethoxyphenoxyacetic acid in acetic anhydride. Dicarbonyl compound (**380**) is prepared from chloroacetylsalicylic acid.



(377) (378) (379) (380)

4.4.6.6 Seven-membered Rings with Two Heteroatoms 1,5 to the Ring Junction

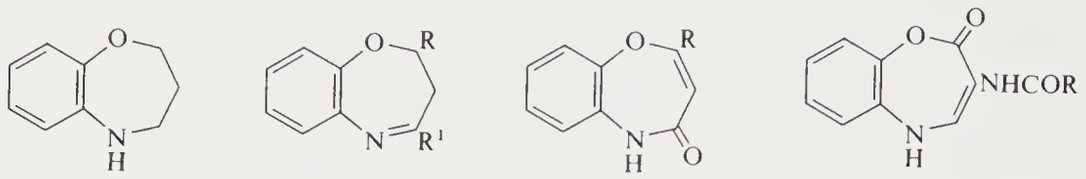
The method generally used is from the appropriately *o*-disubstituted benzene with a 1,3-bis carbon electrophile, *e.g.* for 1,5-benzodiazepines, *o*-phenylenediamine + RCOCHR′COR → (**381**) → (**382**).



(381) (382) (383) (384) (385)

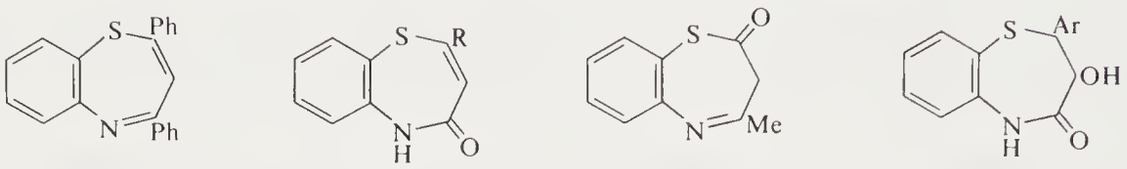
The use of derivatives of dicarbonyl compounds such as diazapentadienium or vinamidinium salts, *e.g.* (**383**) and (**384**), is a recent development which offers advantages in providing access to dihydrodiazepines (**385**) not easily prepared in other ways ⟨78H(11)550, 78JCS(P1)1453⟩.

o-Aminophenols react with a variety of functionalized three-carbon chains: 3-bromo-1-chloropropane gives (**386**) and 3-chloropropionyl chloride gives the analogous 4-oxo derivative. Similarly α,β-unsaturated ketones give (**387**), β-keto esters give (**388**) and 1,3-oxazolid-5-ones give (**389**).



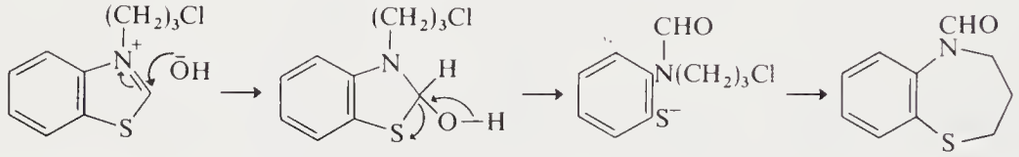
(**386**) (**387**) (**388**) (**389**)

In a similar fashion, 2-aminothiophenol can be reacted with 1,3-bis carbon electrophiles to give various types of 1,5-benzothiazepine. Thus 1,3-diphenylpropynone gives (**390**), reaction with β-keto esters gives products of type (**391**), reaction with diketene gives (**392**), and the reaction with methyl 3-arylglycidates gives (**393**).



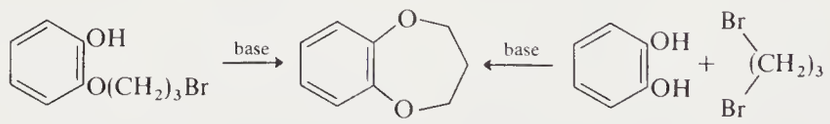
(**390**) (**391**) (**392**) (**393**)

The thiazolium salt (**394**) undergoes base-induced ring expansion to give (**395**) ⟨80TL2429⟩, a direct parallel of the conversion of analogous oxazolium salts into 1,5-benzoxazepines.



(**394**) (**395**)

The major routes to 3,4-dihydro-2*H*-1,5-benzodioxepins (**397**) from (**396**) and (**398**) are applicable to a wide range of substituted derivatives. The 3-oxo derivative can be prepared *via* the reaction of 1,2-dihydroxybenzene with chloroacetonitrile ⟨75CJC2279⟩ or *via* a Dieckmann cyclization ⟨74USP3799892⟩.

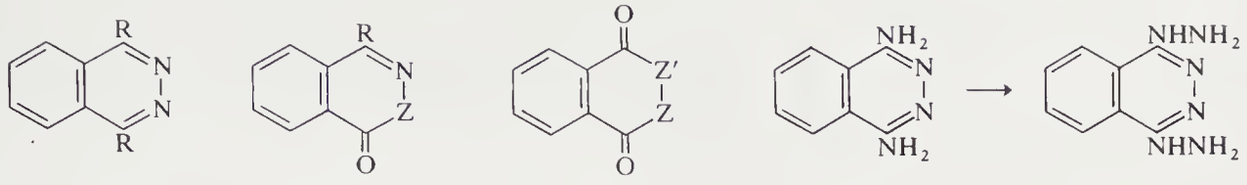


(**396**) (**397**) (**398**)

4.4.7 TWO HETEROATOMS 2,3 TO RING JUNCTION

4.4.7.1 Six-membered Rings

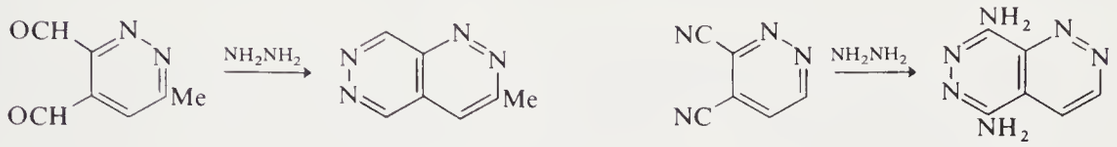
o-Diacylbenzenes with hydrazine form phthalazines (**399**). Monoxo compounds of type (**400**) result from *o*-acylbenzoic acids and hydrazine or hydroxylamine, and dioxo derivatives (**401**) from phthalic acid derivatives with N_2H_4, NH_2OH or H_2O_2.



(399) (400) (401) (402) (403)

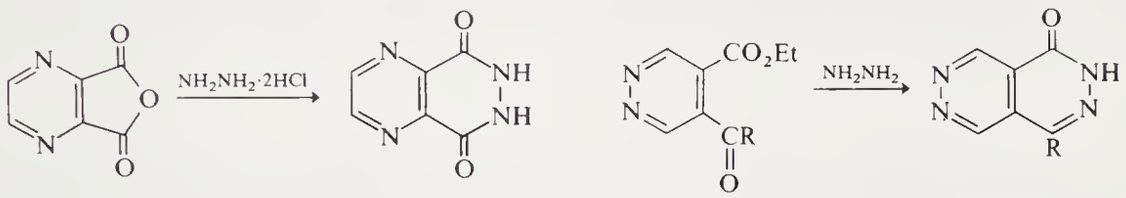
Phthalodinitrile is converted by methanolic hydrazine into 1,4-diaminophthalazine (**402**) ⟨68JHC111⟩, and with excess of hydrazine 1,4-dihydrazinophthalazine (**403**) is obtained, *via* the 1,4-diamino compound ⟨59JOC1205⟩.

Many other [*c*]-fused pyridazines have been prepared similarly. 6-Methylpyridazine-3,4-dicarbaldehyde (**404**) with hydrazine gives 3-methylpyridazino[4,5-*c*]pyridazine (**405**) ⟨73JHC1081⟩. 5-Oxo- and 5,8-dioxo-substituted pyridazino[4,5-*c*]pyridazines are prepared from ethyl 3-formylpyridazine-4-carboxylates and diethyl pyridazine-3,4-dicarboxylates, respectively, with hydrazine. Pyridazine-3,4-dicarbonitrile (**406**) with hydrazine gives the diamino heterocycle (**407**) ⟨67JHC393⟩.



(404) (405) (406) (407)

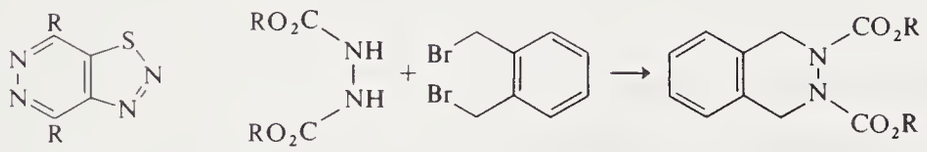
Pyrazino[2,3-*d*]pyridazine-5,8-dione (**409**) can be prepared from pyrazine-2,3-dicarboxylic acid anhydride (**408**). Condensation of hydrazine with ethyl 5-acylpyridazine-4-carboxylates (**410**) gives pyridazino[4,5-*d*]pyridazin-1(2*H*)-ones (**411**) ⟨79M365⟩.



(408) (409) (410) (411)

The 1,2,3-thiadiazolo[4,5-*d*]pyridazines (**412**) are prepared similarly from the appropriate thiadiazoles ⟨76JHC301⟩.

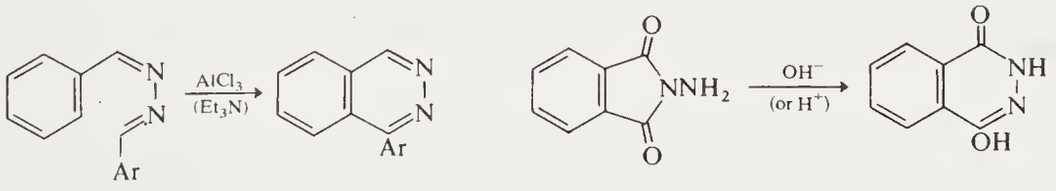
Tetrahydropyridazines and analogues can be made as indicated in Scheme 22.



(412)

Scheme 22

Aromatic aldazines undergo oxidative cyclization to 1-arylphthalazines (**413**→**414**) on treatment with aluminum chloride/triethylamine at 180 °C.



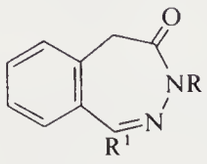
(413) (414)

Scheme 23

2-Aminophthalimide when heated with dilute alkali or acid is rearranged into 4-hydroxyphthalazin-1(2*H*)-one (Scheme 23) ⟨55JCS852⟩.

4.4.7.2 Seven-membered Rings

Reactions of appropriate carbonyl precursors with hydrazine have been used to obtain compounds such as 3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones (**415**) ⟨76H(4)509⟩ and 2,5-dihydro-1*H*-2,3-benzodiazepin-1-ones (**416**) ⟨67AHC(8)21⟩.



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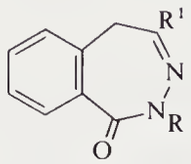

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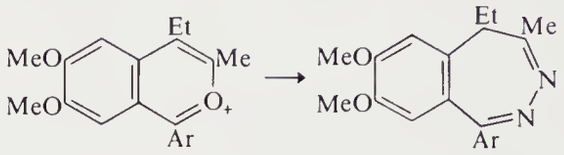
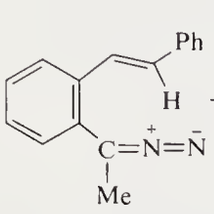


(417)

Reaction of the isobenzopyrylium cation shown with N_2H_4 gives (**417**). 1*H*-2,3-Benzodiazepines (**419**) ⟨73JCS(P1)2543⟩ and analogous thienodiazepines ⟨80JCS(P1)1718⟩ are obtained from electrocyclic reaction of diazo derivatives (**418**).



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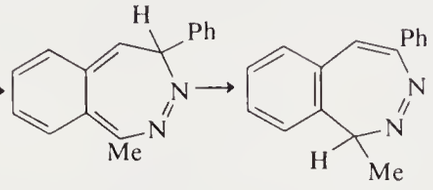

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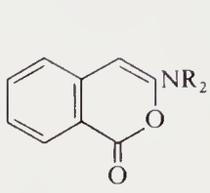

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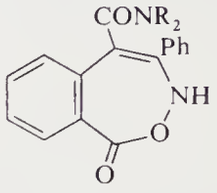
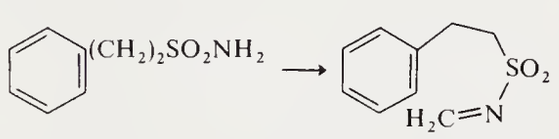


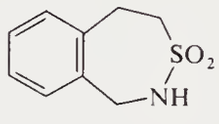
(421)

The 2,3-benzoxazepin-1-one system (**421**) is prepared by the reaction of benzonitrile oxide with the benzopyranone (**420**) ⟨80JCS(P1)846⟩.

The tetrahydro-3,2-benzothiazepine 3,3-dioxide (**423**) was prepared from (**422**) by intramolecular sulfonyl-amidomethylation ⟨76CC470⟩.



(422)



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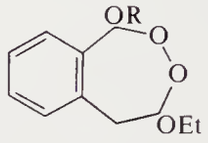


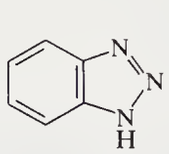
(424)

The 1*H*-tetrahydro-2,3-benzodioxepin (**424**; R = H) can be prepared from indene with ozone in the presence of EtOH. It reacts further with ethanol in the presence of acid to give (**424**; R = Et).

4.4.8 THREE OR MORE HETEROATOMS

4.4.8.1 Five-membered Heterocyclic Rings

o-Phenylenediamine is readily converted by HNO_2 into 1,2,3-benzotriazole (**425**) and by $SOCl_2$ into 2,1,3-benzothiadiazole (**426**). The 4,5-diaminopyrazole (**428**) gives the dihydropyrazolo[3,4-*c*]-[1,2,5]thiadiazole *S*-oxide (**429**) with thionyl chloride ⟨68JMC1164⟩ and the aromatic system (**427**) with sulfur monochloride ⟨81JOC4065⟩. Lead tetraacetate in glacial acetic acid effects closure between the primary amino group and the azo group of (**430**) giving the triazolo[4,5-*d*]pyrimidine (**431**) ⟨72CPB605⟩.



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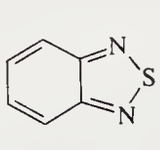

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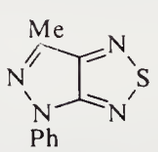

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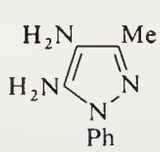

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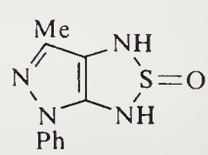

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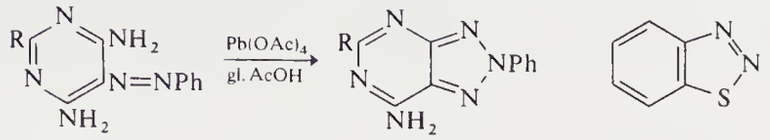


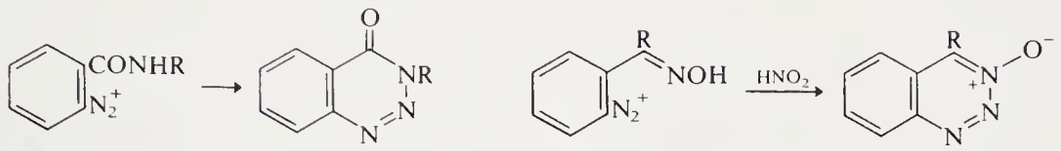
(430) (431) (432)

o-Mercaptoaniline and nitrous acid form 1,2,3-benzothiadiazole (**432**). Benzofurazans can be obtained by the benzazole rearrangement (Section 3.4.3.2.4).

4.4.8.2 Six-membered Heterocyclic Rings

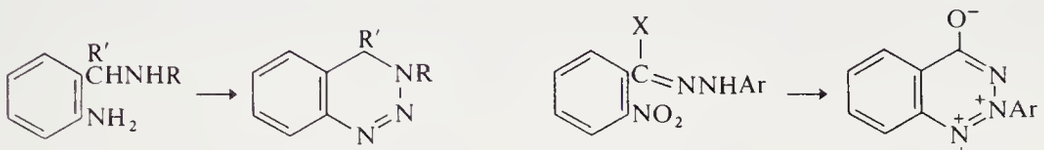
4.4.8.2.1 Three heteroatoms in the 1,2,3-positions

(i) 1,2,3-Benzotriazines are prepared by methods of the type illustrated for (**434**) and (**436**), which resemble those used for the synthesis of cinnolines (*cf.* Section 4.4.4.3.1).



(433) (434) (435) (436)

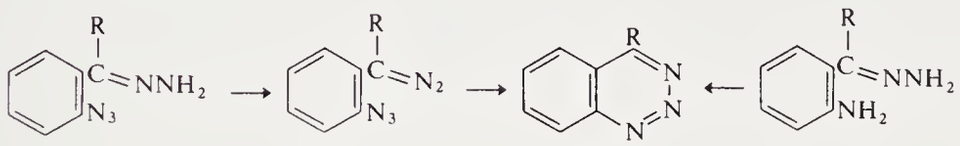
Dihydro-1,2,3-benzotriazines (**438**) result from 2-aminobenzylamines (**437**) with nitrous acid ⟨78HC(33)91⟩.



(437) (438) (439) (440)

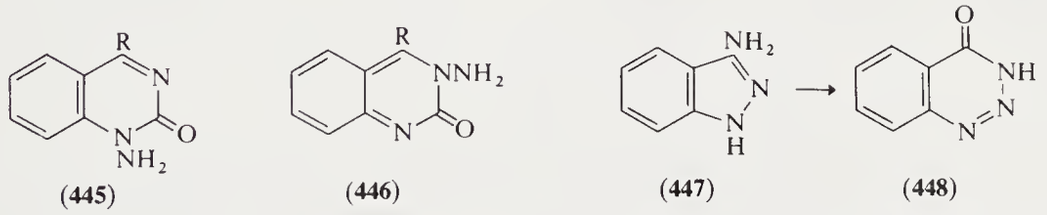
2-Nitrobenzaldehyde arylhydrazones with a halogen give compounds (**439**), which on treatment with base form 2-aryl-4-oxido-1,2,3-benzotriazinium betaine 1-oxides (**440**; R = Ar) ⟨74JOC2710⟩.

Oxidation of 2-azidophenyl ketone hydrazones (**441**) affords the 2-azidophenyldiazoalkanes (**442**) which can be cyclized thermally to 1,2,3-benzotriazines (**443**) ⟨75JCS(P1)31⟩. Similarly, 2-aminophenyl ketone hydrazones (**444**) give 1,2,3-benzotriazines (**443**) on oxidation with lead tetraacetate ⟨75JCS(P1)31⟩.



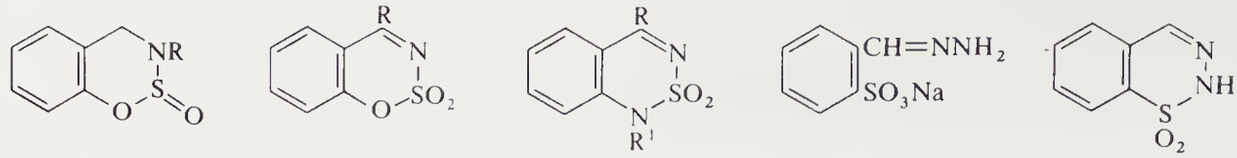
(441) (442) (443) (444)

1-Amino- (**445**) and 3-amino-quinazolin-2-ones (**446**) can be oxidized to 1,2,3-benzotriazines ⟨75JCS(P1)31⟩. *C*-Amino compounds can also give triazines; oxidation of 3-aminoindazole (**447**) with hydrogen peroxide forms 1,2,3-benzotriazin-4-one (**448**) ⟨1899LA(305)289⟩.



(445) (446) (447) (448)

(ii) 1,2,3-Benzoxathiazine and 2,1,3-benzothiadiazine derivatives are prepared by insertion of the S atom; thus (**449**) results from *o*-$C_6H_4(OH)CH_2NHR$ with $SOCl_2$, and (**450**) and (**451**) result from reaction of sulfamide, $SO_2(NH_2)_2$, with *o*-acylphenols and *o*-acylanilines, respectively.



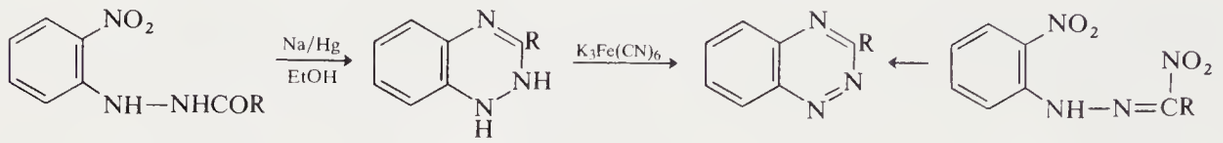
(449) (450) (451) (452) (453)

1,2,3-Benzothiadiazine 1,1-dioxides, which are cyclic sulfonylhydrazides, are prepared by treating appropriate hydrazones with phosphorus pentachloride, *e.g.* (**452**)→(**453**).

4.4.8.2.2 Three heteroatoms in the 1,2,4- or 1,3,4-positions

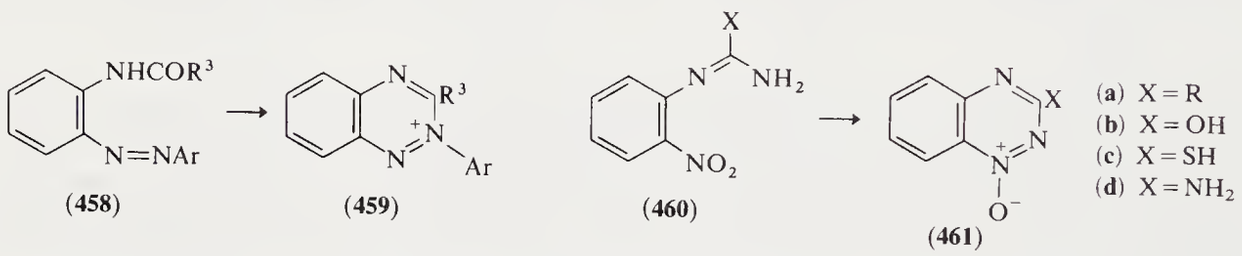
(i) 1,2,4-Benzotriazines

2-(2-Nitrophenyl)hydrazides (**454**) give 1,2-dihydro-1,2,4-benzotriazines (**455**) with sodium amalgam in ethanol. In most cases the initial dihydro compounds (**455**) are oxidized by potassium ferricyanide to the aromatic 1,2,4-benzotriazines (**456**) ⟨78HC(33)189⟩. Similarly, reduction of the nitrohydrazones (**457**) affords 1,2,4-benzotriazines (**456**) ⟨78HC(33)189, p. 666⟩.



(454) (455) (456) (457)

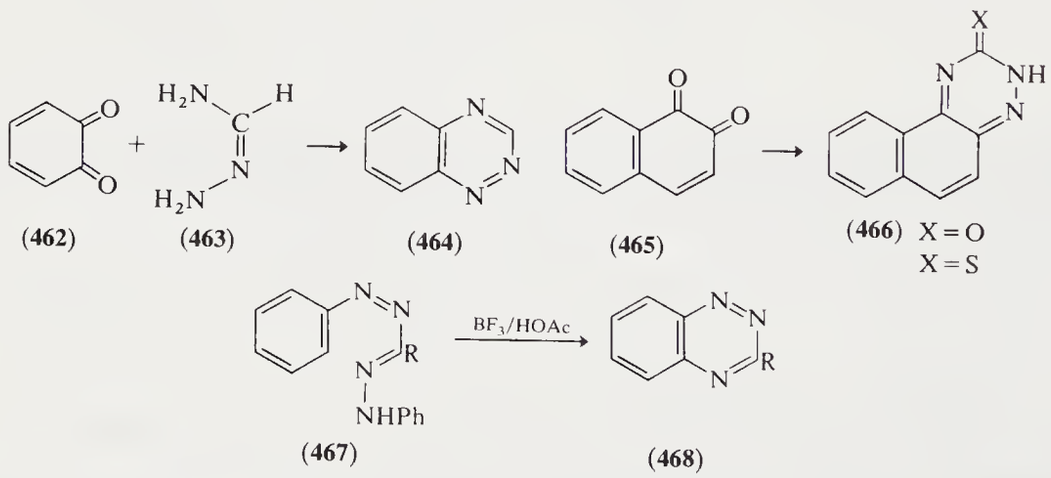
Cyclization of the 2-acylaminoazobenzenes (**458**) leads to 2-aryl-1,2,4-benzotriazinium salts (**459**) ⟨74GEP2241259⟩. 2-Nitrophenylamidines (**460a**) with base afford 1,2,4-benzotriazine 1-oxides (**461a**) ⟨78HC(33)189⟩. Similar treatment of the 2-nitrophenyl-ureas (**460b**), -thioureas (**460c**) and -guanidines (**460d**) yields the 3-hydroxy- (**461b**), 3-mercapto- (**461c**) and 3-amino-1,2,4-benzotriazine 1-oxides (**461d**) or their tautomers ⟨78HC(33)189⟩.



(458) (459) (460) (461)

(a) X = R
(b) X = OH
(c) X = SH
(d) X = NH_2

o-Benzoquinone (**462**) with formamidrazone (**463**) gives 1,2,4-benzotriazine (**464**) in low yield ⟨68CB3952⟩. Better yields, of (**466**), were obtained from 1,2-naphthoquinone (**465**) using semicarbazide or thiosemicarbazide; compounds (**466**) are apparently formed regiospecifically ⟨78HC(33)189, p. 725⟩.

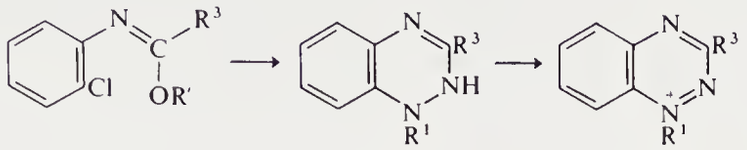


(462) (463) (464) (465) (466) X = O, X = S

(467) (468)

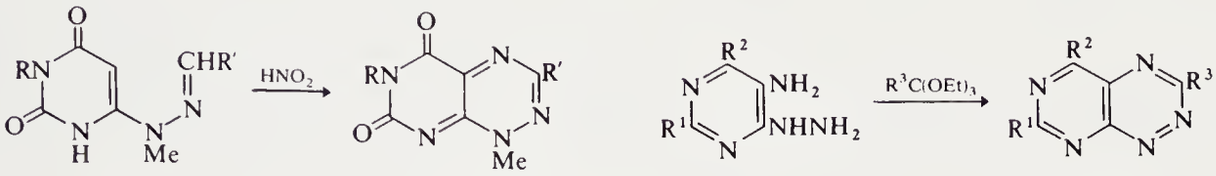
3-Substituted 1,2,4-benzotriazines can be prepared by cyclization of arylfurazans (**467**→**468**) ⟨82T1793⟩.

1,2-Dihydro-1,2,4-benzotriazines (**470**) are obtained from the reaction of *N*-(2-chlorophenyl)-imidates (**469**) with hydrazines. They can be oxidized to 1-alkyl-1,2,4-benzotriazinium salts (**471**) ⟨67MI21900⟩.



(**469**) (**470**) (**471**)

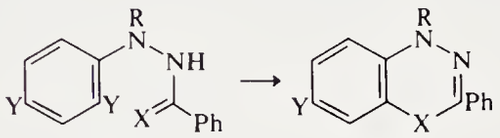
Nitrosation of the hydrazinouracil (**472**) leads to the pyrimidotriazine (**473**). Pyrimidotriazines can also be made by the sequence (**474**)→(**475**).



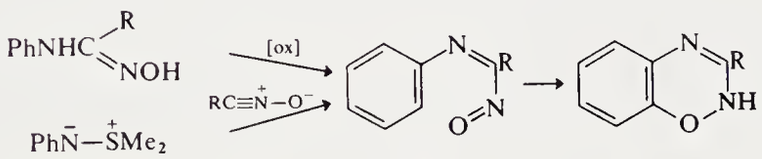
(**472**) (**473**) (**474**) (**475**)

(ii) Six-membered rings containing O or S atoms

1,3,4-Benzoxadiazines (**477**; X = O) result from ring closure of the phenylhydrazide (**476**; X = O, Y = Br or NO_2) with displacement of Y ⟨80JOC3677⟩. Routes to 1,2,4-benzoxadiazines include reaction of *N*-aryl-*S,S*-dimethylsulfimides with nitrile oxides, and oxidation of *N*-arylamidoximes to give the benzoxadiazines (**478**). Both reactions involve nitrosoimine intermediates (Scheme 24).

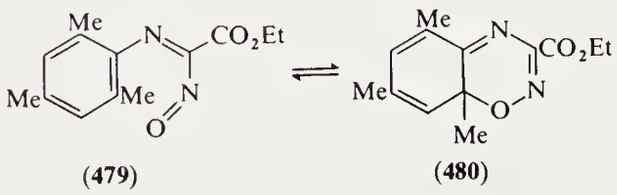


(**476**) (**477**)

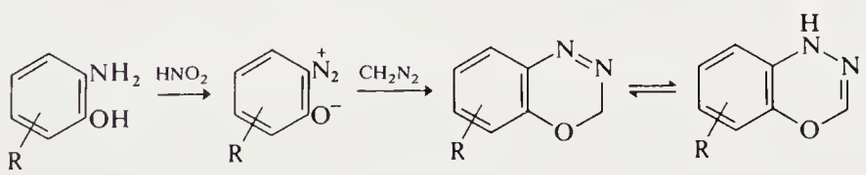


Scheme 24 (**478**)

An electrocyclic reaction is involved in the reversible formation of the oxadiazine ring in (**479**)⇌(**480**).



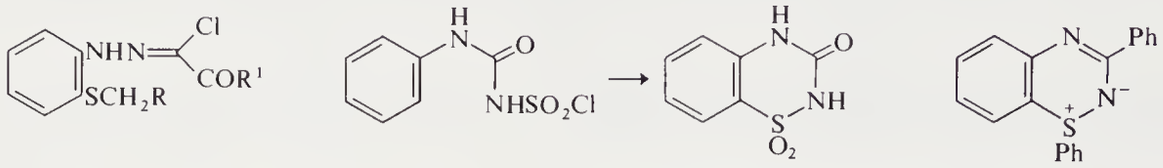
(**479**) (**480**)



Scheme 25

Diazotization of 2-aminophenols followed by reaction with diazomethane gives 1,3,4-benzoxadiazines (Scheme 25); the initially formed 2*H*-isomers readily tautomerize to the more stable 4*H*-isomers ⟨70CB331⟩.

1,3,4-Benzothiadiazines (**477**; X = S) are prepared by cyclization of (**476**; X = S, Y = Br or NO_2) ⟨80JOC3677⟩ and analogous compounds result from cyclization of the chlorohydrazones (**481**) with triethylamine ⟨81JCS(P1)2245⟩. Intramolecular aromatic sulfonation gives 1,2,4-benzothiadiazine 1,1-dioxides (**483**) from (**482**) and aluminum trichloride ⟨79JCS(P1)1043⟩.



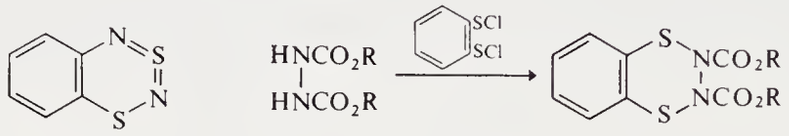
(**481**) (**482**) (**483**) (**484**)

Treatment of *N*-(2-phenylthio)phenylbenzamidine with *N*-chlorosuccinimide (NCS) leads to the cyclic sulfimide (**484**) ⟨78CC1049⟩.

4.4.8.2.3 Four heteroatoms

The benzodithiadiazine (**485**) is formed by the ring closure of PhN=S=NSCl ⟨83CC74⟩.

1,2-Hydrazinedicarboxylates with 1,2-disulfenyl chlorides give 1,4,2,3-benzodithiadiazines (Scheme 26) ⟨71AG(E)408, 74CB771⟩.



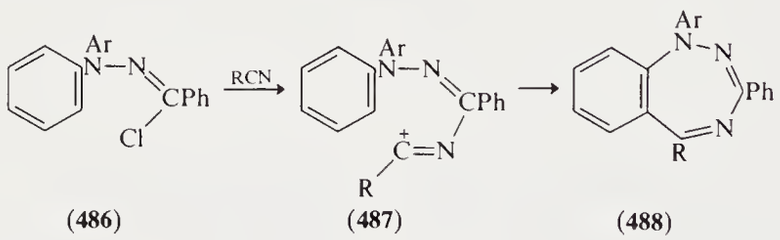
(**485**)

Scheme 26

4.4.8.3 Seven-membered and Larger Rings

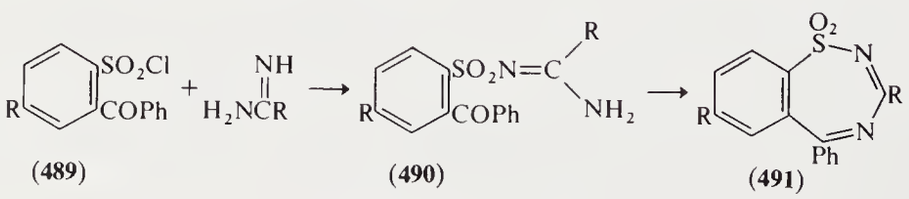
4.4.8.3.1 Heteroatoms 1,2,4 to ring junction

1*H*-1,2,4-Benzotriazepines (**488**) can be prepared by reaction of hydrazidoyl chlorides (**486**) with cyano compounds *via* the nitrilium salt (**487**) ⟨74T195⟩.



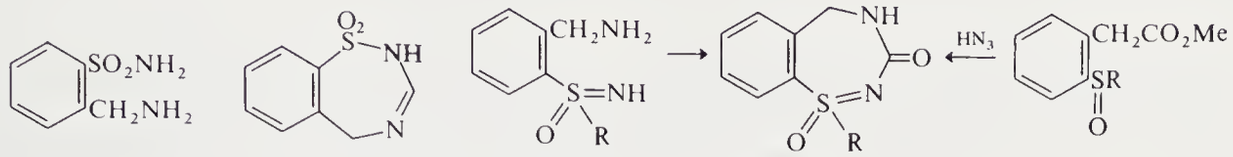
(**486**) (**487**) (**488**)

2-Benzoylarenesulfonyl chlorides (**489**) with amidines, guanidine or *S*-alkylthioureas give arenesulfonyl derivatives (**490**; R = Ph, NH_2 or SMe) which cyclize on heating to 1,2,4-benzothiadiazepine 1,1-dioxides (**491**) ⟨68JHC719⟩.



(**489**) (**490**) (**491**)

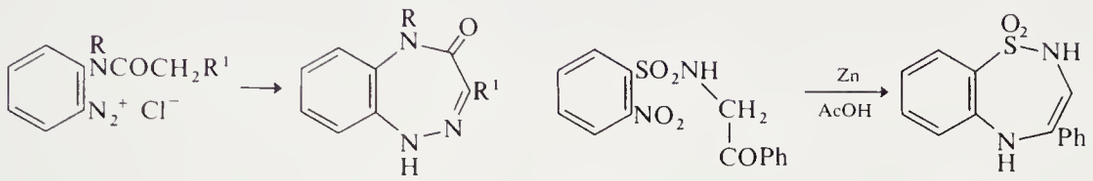
2-Aminomethylsulfonamide (**492**) with ethyl orthoformate gives the 1,2,4-benzothiadiazepine (**493**) ⟨60JA1594⟩, and (**495**) is prepared from the sulfoximide (**494**) with *N,N'*-carbonyldiimidazole ⟨72CB2575⟩. The cyclic sulfoximides (**495**) are also prepared from (**496**) with hydrazoic acid ⟨72CB2575⟩.



(**492**) (**493**) (**494**) (**495**) (**496**)

4.4.8.3.2 Heteroatoms 1,2,5 to ring junction

1*H*-4,5-Dihydro-1,2,5-benzotriazepin-4-ones (**498**; $R^1 = CO_2Et$ or CN) can be prepared by cyclization of the diazonium salts (**497**).

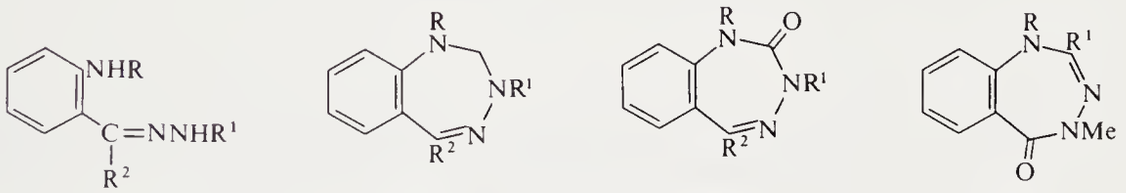


(**497**) (**498**) (**499**) (**500**)

The 1,2,5-benzothiadiazepine 1,1-dioxide (**500**) and its 3,4-dihydro analogue have been prepared by the reaction of 2-nitrobenzenesulfonyl chloride with ω-aminoacetophenone to give (**499**) followed by reductive cyclization ⟨79JHC835⟩.

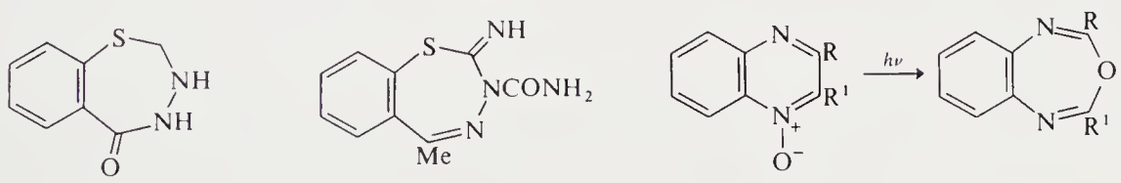
4.4.8.3.3 Heteroatoms 1,3,4 to ring junction

The hydrazones or semicarbazones of 2-aminoaryl ketones (**501**) react with paraformaldehyde to give the 2,3-dihydro-1*H*-1,3,4-benzotriazepine (**502**) ⟨70BCJ135⟩, and with ethyl chloroformate to give the 2-oxo analogue (**503**) ⟨74JPS838⟩. Compounds of type (**503**) can also be prepared by the reaction of 2-aminoaryl ketones with ethoxycarbonylhydrazine. 2-Aminobenzoyl hydrazides have similarly been used in the preparation of 1,3,4-benzotriazepin-5-ones (**504**) by reaction with ortho esters ⟨76JOC2732, 76JOC2736, 67JHC967⟩.



(**501**) (**502**) (**503**) (**504**)

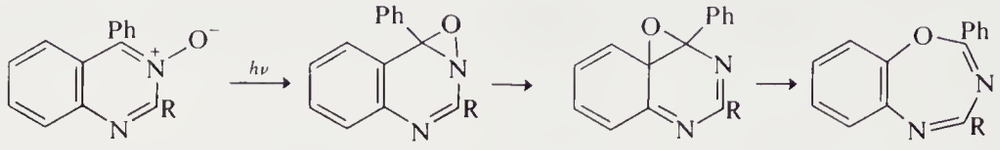
2-Mercaptobenzoylhydrazide with formaldehyde gives (**505**) ⟨53JOC1380⟩ and *o*-thiocyanatoacetophenone with semicarbazide gives (**506**) ⟨79JCR(S)395⟩.



(**505**) (**506**) (**507**) (**508**)

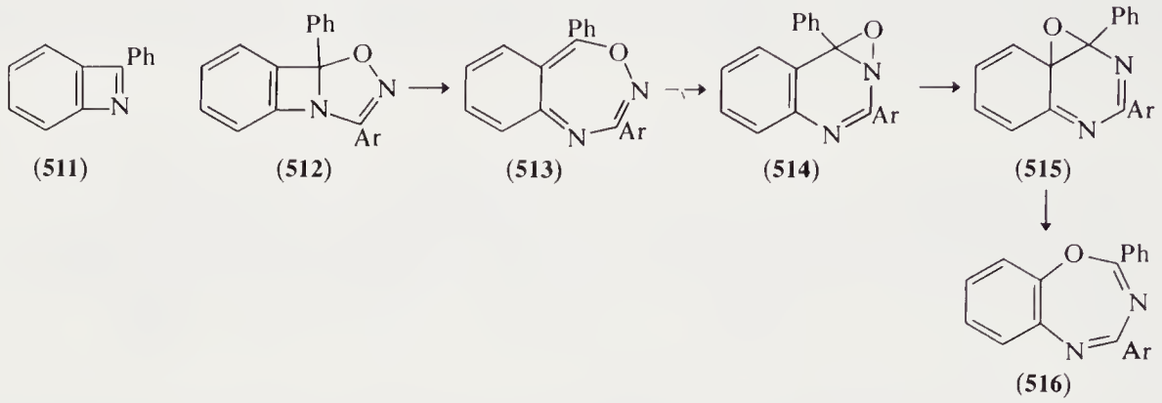
4.4.8.3.4 Heteroatoms 1,3,5 to ring junction

The photoisomerizations of quinoxaline 1-oxides (**507**) give the 3,1,5-benzoxadiazepines (**508**) ⟨67TL1873, 68ACS877⟩. The photoisomerization of quinazoline 3-oxides (**509**; R = H or Me) leads, by the rearrangement shown, to the isolable 1,3,5-benzoxadiazepines (**510**).



(**509**) (**510**)

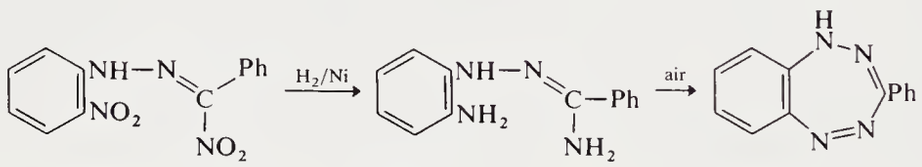
2-Phenylbenzazete (**511**) with nitrile oxides $ArC{\equiv}\overset{+}{N}{-}\bar{O}$ gives labile adducts (**512**) which rearrange to the 1,3,5-benzoxadiazepines (**516**) ⟨75CC740⟩, probably *via* (**513**), (**514**) and (**515**).



(**511**) (**512**) (**513**) (**514**) (**515**) (**516**)

4.4.8.3.5 Four heteroatoms

The 1,2,4,5-benzotetrazepine (**519**) is produced in good yield by the oxidative ring closure of (**518**) or by the action of zinc and aqueous sodium hydroxide on (**517**) ⟨55CB1284⟩.

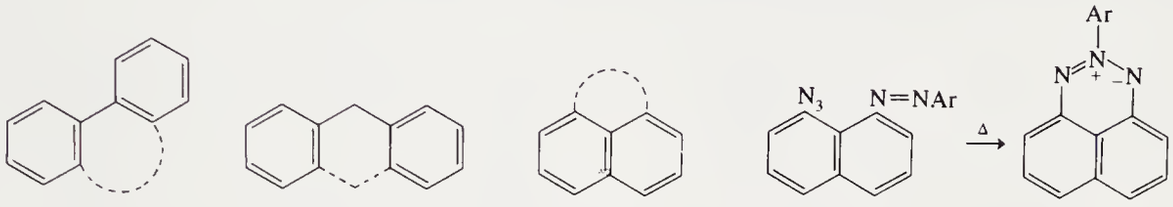


(**517**) (**518**) (**519**)

4.5

Synthesis of Tri- and Poly-cyclic Ring Systems without Ring Junction Heteroatoms

The arrangement of the material in this chapter follows closely that for the bicyclic analogues: it is ordered first by the mutual relationship of the fused rings, second by the number of heteroatoms and finally by the size of the heterocyclic ring. We define 'adjacent' as in (**1**) and 'non-adjacent' fused rings as in (**2**). Rings of type (**3**) are of lesser importance: the conversion (**4**)→(**5**) shows an example of their formation.

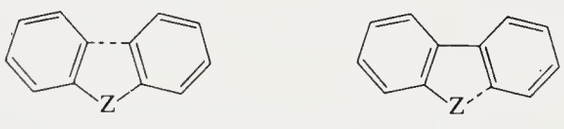


(**1**) (**2**) (**3**) (**4**) (**5**)

4.5.1 TWO ADJACENT FUSED RINGS, ONE HETEROATOM

4.5.1.1 Five-membered Heterocyclic Ring

4.5.1.1.1 Overview of synthetic methods for carbazoles, dibenzofurans and dibenzothiophenes

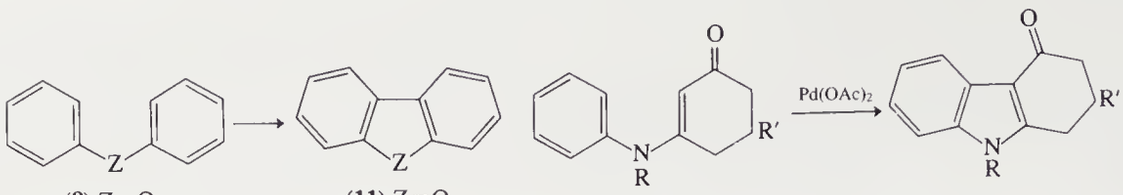


(**6**) (**7**)

Most of the important methods involve C—C (**6**) or C—Z (**7**) bond formation and these are considered in turn. There are a variety of miscellaneous methods.

4.5.1.1.2 Formation of C—C bond

(i) The photochemically initiated cyclizations of diphenyl ethers to dibenzofurans (**8**→**11**) ⟨75S532, 75AJC1559⟩, diphenyl sulfides to dibenzothiophenes (**9**→**12**) ⟨75S532⟩ and diarylamines to carbazoles (**10**→**13**) ⟨66CC272, 66TL661⟩ normally require the presence of an oxidizing agent such as iodine or oxygen. The oxidative ring closure of diphenyl ethers to dibenzofurans (**8**→**11**) is also effected by palladium(II) acetate ⟨75JOC1365, 76JCS(P1)1236⟩, as is that of diphenylamines to carbazoles ⟨75JOC1365⟩. This approach has been extended to the conversion of *N*-arylenaminones to tetrahydrocarbazoles (**14**→**15**) ⟨80JOC2938⟩.



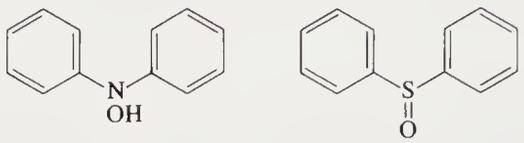
(8) Z=O
(9) Z=S
(10) Z=NH

(11) Z=O
(12) Z=S
(13) Z=NH

(14)

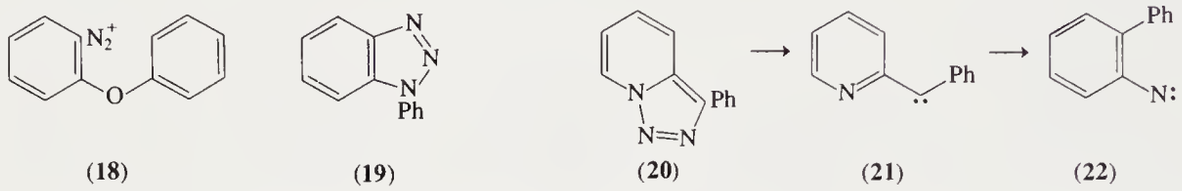
(15)

Sulfuric acid promotes cyclization of *N,N*-diphenylhydroxylamine (**16**) to carbazole (**13**) ⟨13CB3306⟩. The parallel conversions of diphenyl sulfoxide (**17**) and diphenyl selenoxide to dibenzothiophene (**12**) ⟨23CB2275⟩ and dibenzoselenophene ⟨39CR(199)531⟩ are effected by sodamide.



(16) (17)

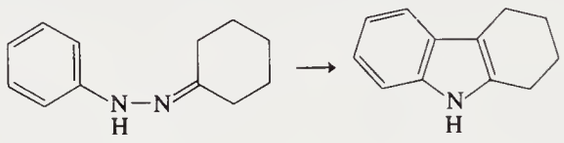
(ii) Dibenzofurans (**11**) ⟨81BCJ2374⟩, dibenzothiophenes (**12**) ⟨36JCS1435⟩ and *N*-substituted carbazoles ⟨52JCS2276⟩ are formed by spontaneous Pschorr-type cyclization of appropriate diazonium salts, thus (**18**) gives dibenzofuran (**11**).



(18) (19) (20) (21) (22)

(iii) Carbazoles are prepared by the Graebe–Ullmann synthesis: benzotriazoles (**19**) on pyrolysis yield carbazoles (**13**) ⟨57JCS110⟩, *cf.* Section 3.4.3.12.2. Pyrolysis of 3-phenyltriazolopyridine (**20**) is more complex, ultimately providing carbazole (**13**) *via* (**21**) and (**22**) ⟨75JA7467⟩.

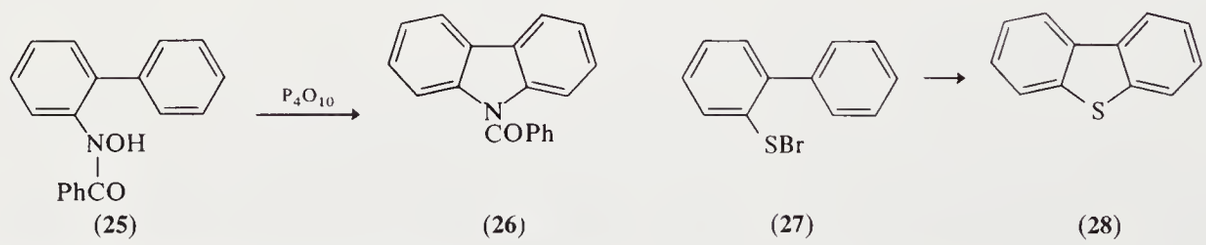
(iv) The Borsche synthesis of tetrahydrocarbazoles, *e.g.* (**23**)→(**24**), is a special case of the Fischer indole synthesis in which cyclohexanone phenylhydrazones are used as the starting materials.



(23) (24)

4.5.1.1.3 Formation of C—Z bond

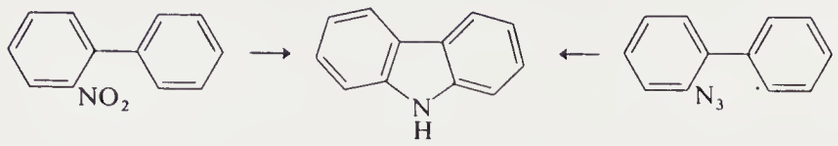
Electrophilic attack by the *ortho* heteroatom of biphenyl derivatives is involved in the conversions (**25**)→(**26**) ⟨82JOC3585⟩ and (**27**)→(**28**) ⟨62JOC4111⟩.



(25) (26) (27) (28)

A variety of pyrrole ring closure reactions are conveniently formulated as proceeding *via* nitrene intermediates, although it is doubtful whether a free nitrene is involved. Pyrolysis of *o*-

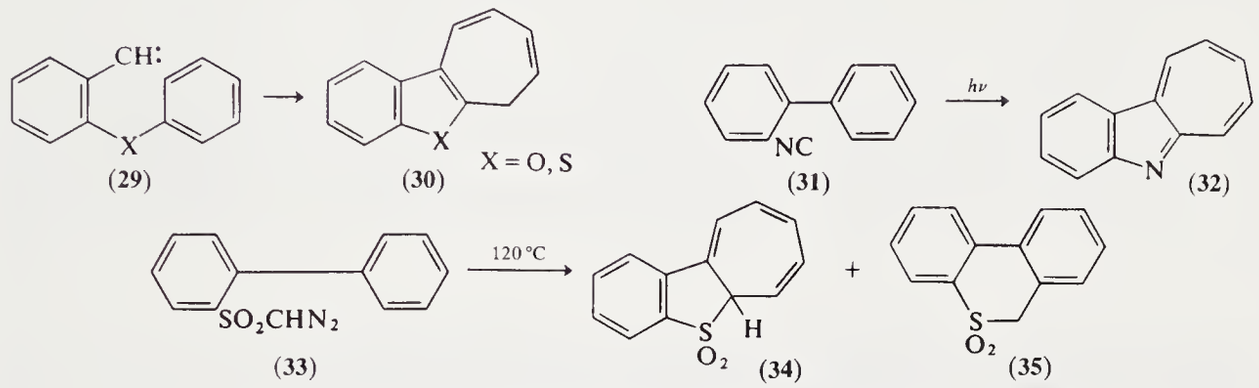
nitrobiphenyls with iron(II) oxalate ⟨61T(16)80⟩, or reduction under milder conditions with triethyl phosphite ⟨65JCS4831⟩ or tris(trimethylsilyl) phosphite ⟨79TL375⟩, leads to the carbazole, as does the pyrolysis or photolysis of 2-azidobiphenyls (Scheme 1) ⟨75 JA6193⟩.



Scheme 1

4.5.1.1.4 Miscellaneous methods

Intramolecular attack of the carbenes (**29**) provides benzo[*b*]cyclohepta[*d*]-furans and -thiophenes (**30**; X = O, S). Photolysis of 2-biphenyl isocyanide (**31**→**32**) ⟨72JOC3571⟩ and thermolysis of 2-biphenylsulfonyl diazomethane (**33**→**34**→**35**) ⟨72CC893⟩ also result in ring expansion.



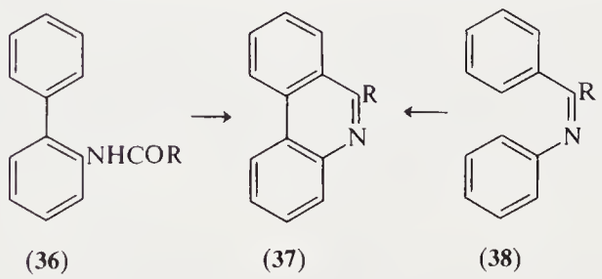
The extrusion of sulfur from phenothiazine and thianthrene, leading to carbazole ⟨75CJC2293⟩ and dibenzothiophene ⟨37RTC627⟩, respectively, is effected by thermolysis in the presence of copper bronze.

4.5.1.2 Six-membered Rings

Phenanthridines are obtained:

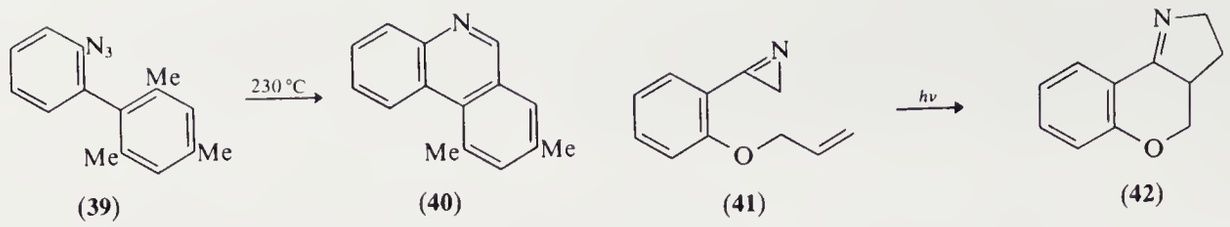
(i) By cyclodehydration of acylated 2-aminobiphenyls (**36**→**37**).

(ii) By photochemical dehydrogenation of azomethines (**38**→**37**); dihydro compounds are initially formed and aromatization is effected with either oxygen or iodine.



(iii) By thermolysis of the azide (**39**) in hexadecane at 230 °C; insertion of the nitrene into the methyl group gives (**40**).

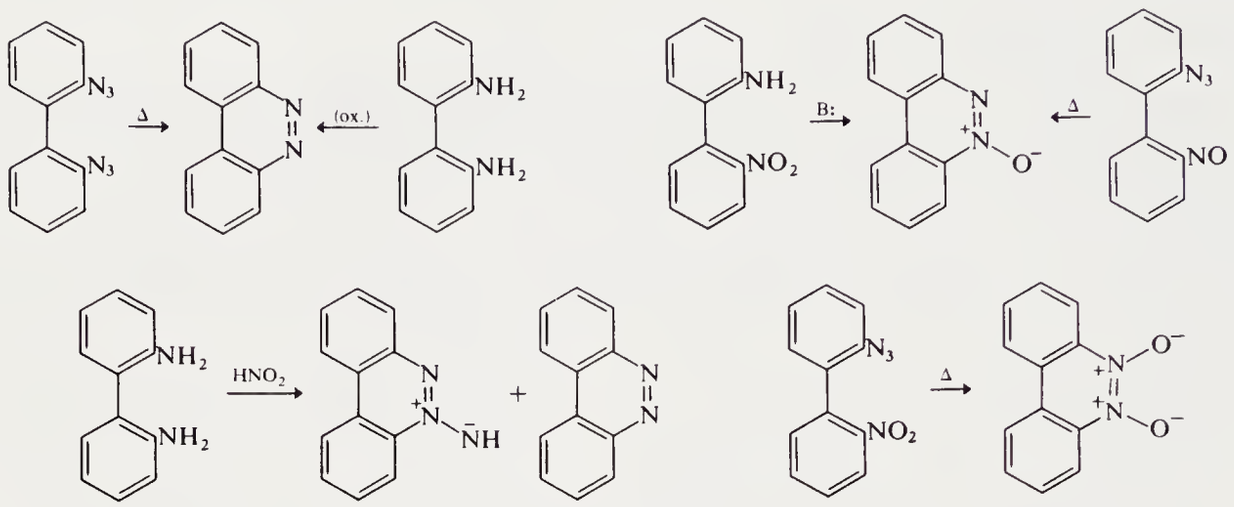
Intramolecular 1,3-dipolar cycloaddition of (**41**) affords the tricycle (**42**) ⟨78JA3494⟩.



(39) (40) (41) (42)

4.5.2 TWO ADJACENT FUSED RINGS, TWO HETEROATOMS

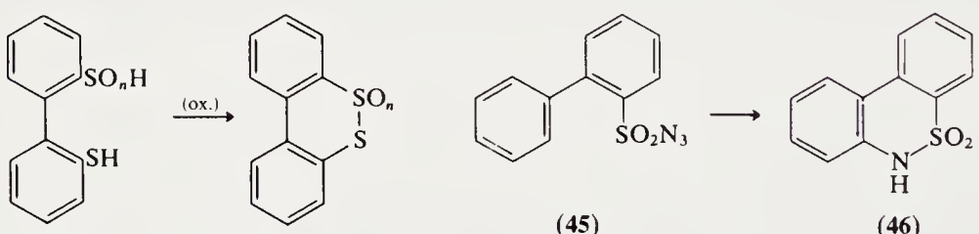
Benzo[*c*]cinnoline derivatives of different oxidation levels are prepared by N—N bond formations from suitable 1,1′-disubstituted biphenyls as outlined in Scheme 2.



Scheme 2

Benzo[*c*]cinnoline is also available by irradiation of azobenzene.

Dibenzo[1,2]dithiins are prepared by oxidation of appropriate dithiols and related starting materials, *e.g.* (**43**)→(**44**).

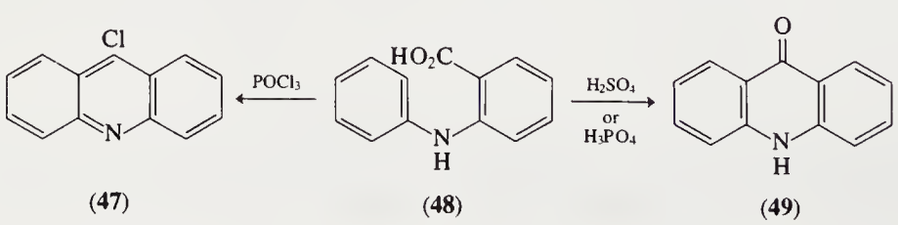


(43) (44) (45) (46)

Sultone (**46**) is obtained by thermolysis of the azide (**45**) ⟨69JA1219⟩.

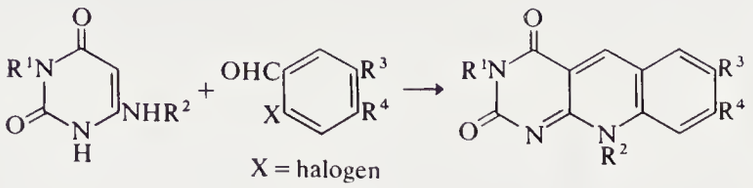
4.5.3 TWO NON-ADJACENT FUSED RINGS, ONE HETEROATOM

(i) *o*-Anilinobenzoic acids give 9-chloroacridines (**48**→**47**) and acridones (**48**→**49**) under the conditions indicated.



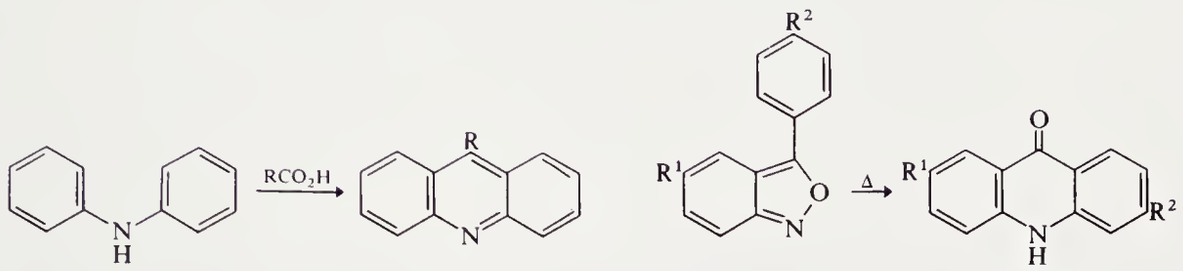
(47) (48) (49)

In Scheme 3, an aminouracil reacts with an *o*-halobenzaldehyde as 1,3-bis electrophile to provide a simple preparation of 5-deazaflavins ⟨82CC1085⟩.



Scheme 3

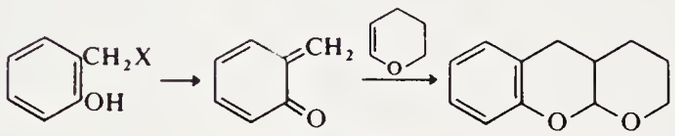
(ii) In the Bernthsen synthesis, diphenylamines and carboxylic acids form 9-substituted acridines (**50**→**51**).



(**50**) (**51**) (**52**) (**53**)

(iii) 3-Arylanthranils give acridones on thermolysis (**52**→**53**) or on nitrous acid treatment (Section 3.4.3.4.2).

(iv) The generation and trapping of *o*-quinone methides with a dienophile are illustrated in Scheme 4.

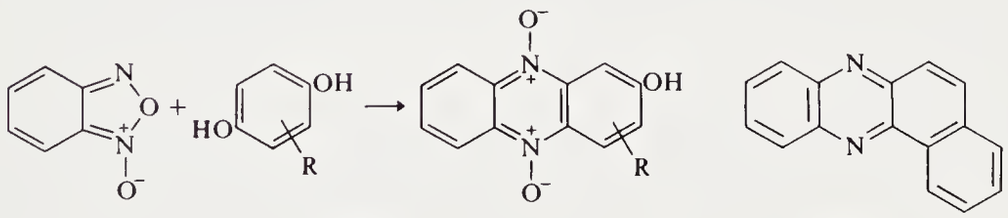


Scheme 4

4.5.4 TWO NON-ADJACENT FUSED RINGS, TWO HETEROATOMS

4.5.4.1 Phenazines

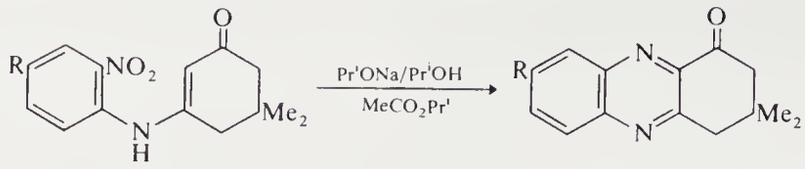
Phenazines can be obtained from *o*-nitrodiphenylamines by reduction or from *o*-aminodiphenylamines by oxidative techniques. The preferred method is that of phenazine 9,10-dioxides from benzofuroxans, thus benzofuroxan itself with hydroquinone gives the 2-hydroxy derivative (Scheme 5).



Scheme 5 (**54**)

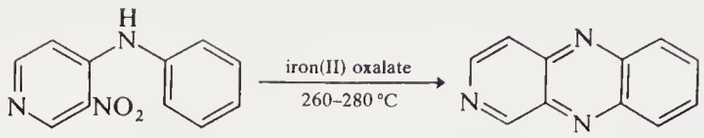
o-Phenylenediamine with *o*-quinone gives phenazines, thus α-naphthoquinone yields (**54**).

The C=C bond of an enamide functions as a nucleophile in the synthesis of the 3,4-dihydrophenazin-1(2*H*)-ones (**56**) ⟨82S852⟩.



(55) (56)

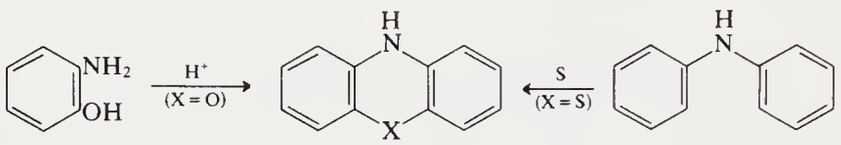
o-Nitroanilinopyridines, *e.g.* (**57**), are cyclized to pyrido[2,3-*b*]- or -[3,4-*b*]-quinoxalines (**58**) by reduction with iron(II) oxalate ⟨74JCS(P1)1965⟩.



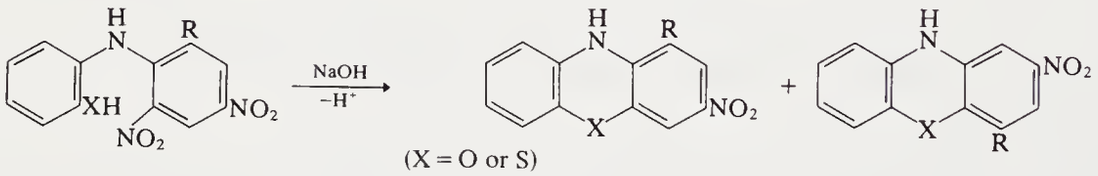
(57) (58)

4.5.4.2 Phenoxazines and Phenothiazines

Traditional routes to phenoxazines include the thermolysis of 2-aminophenol and catechol, the latter acting as an acid catalyst, or catechol and ammonia. Phenothiazines are prepared similarly by heating diphenylamines with sulfur (Scheme 6) ⟨B-78MI22701⟩. 2-Hydroxy- (or mercapto-) 2′,4′-dinitrodiphenylamines cyclize to phenoxazines (or phenothiazines) in base by elimination of nitrous acid. This reaction is complicated by Smiles-type rearrangement so that mixtures of isomeric products are obtained (Scheme 7)

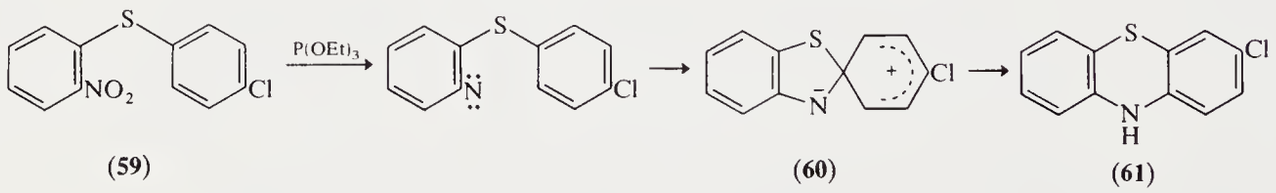


Scheme 6



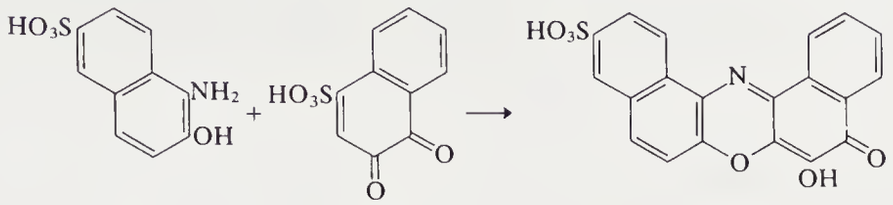
Scheme 7

Deoxygenation of the diaryl sulfide (**59**) with triethyl phosphite gives the phenothiazine (**61**) in good yield *via* formation and rearrangement of the spiro intermediate (**60**).

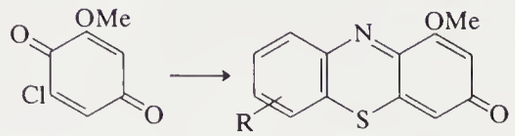


(59) (60) (61)

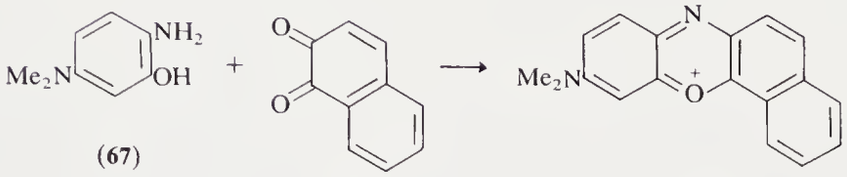
Phenoxazin-3-ones and phenothiazin-3-ones can be prepared by condensation of 2-aminophenols or -thiols with quinones. Alizarin Green G (**64**), for example, is obtained from (**62**) and (**63**). Similarly, 2-aminothiophenols and 6-chloro-2-methoxy-1,4-benzoquinone (**65**) afford phenothiazin-3-ones (**66**).



(62) (63) (64)



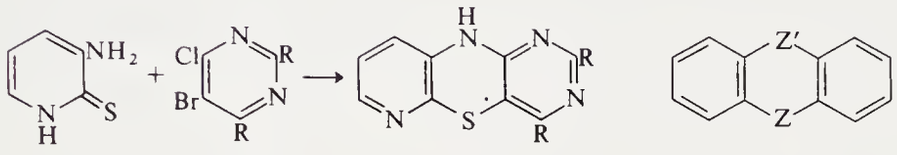
(65) (66)



(67) (68) (69)

o-Aminophenols react with quinones to give phenoxazonium salts, *e.g.* (**67**) + (**68**)→(**69**).

The triazaphenothiazine (**72**) is prepared from the aminopyridine (**70**) with the halopyrimidine (**71**).



(70) (71) (72) (73)

4.5.4.3 Dibenzo[1,4]dioxin, Phenoxathiin and Thianthrene

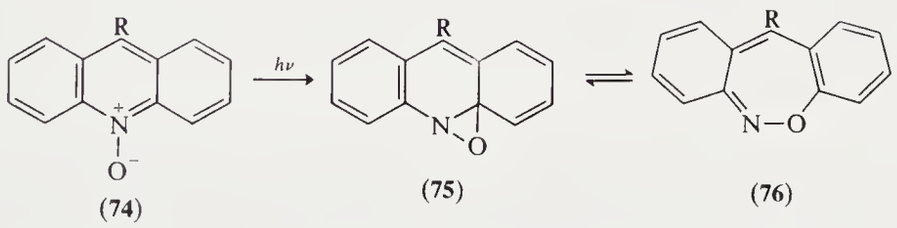
Dibenzo[*b*,*e*][1,4]dioxin (**73**; Z, Z′ = O) is prepared by heating 2-chlorophenol, potassium carbonate and copper ⟨57JA1439⟩.

A general route to phenoxathiins (**73**; Z = O, Z′ = S) utilizes the reaction of diphenyl ethers with sulfur.

One route to thianthrene (**73**; Z, Z′ = S) involves reaction of sulfur monochloride with benzene over aluminum chloride ⟨66HC(21-2)1155⟩.

4.5.4.4 Dibenzoxepins and Dibenzothiepins

Unstable dibenz[*c*,*f*][1,2]oxazepines (**76**; R = CN, Cl) are major products of the UV irradiation of 9-cyano- and 9-chloro-acridine 10-oxides (**74**) in benzene. No oxaziridine tautomer (**75**) was detectable by UV spectroscopy.



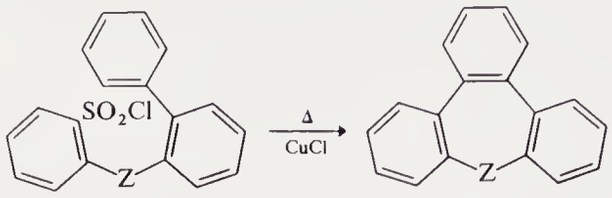
(74) (75) (76)

Dibenzo[*b*,*e*][1,4]thiazepines have been prepared by the thermolysis of 2-azido-2′,6′-dimethyldiphenyl sulfide ⟨70CC233⟩.

Thioxanthen-9-one 10,10-dioxides with sodamide undergo ring expansion to dibenzo[*b*,*f*]-[1,4]thiazepin-11-one 5,5-dioxides ⟨75JHC1211⟩.

4.5.5 THREE FUSED RINGS

The tribenz[*b*,*d*,*f*]oxepin (**78**; Z = O) is made from the biphenyl-2-yl ether (**77**; Z = O), and the thio analogue (**78**; Z = S) is prepared similarly ⟨65TL299⟩.



(**77**) (**78**)

4.6

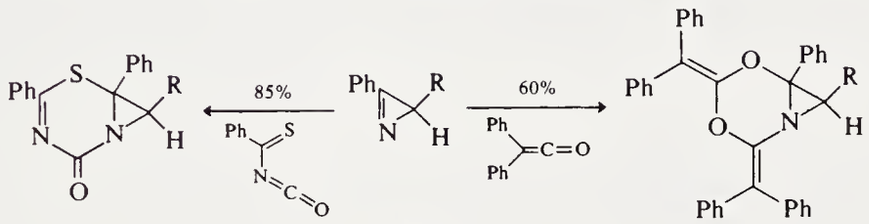
Synthesis of Fused Ring Systems with Ring Junction Heteroatoms

This chapter considers the formation of rings containing one or more N or S atoms at a ring junction. For nitrogen, this is possible with the retention of a three-coordinate neutral, or four-coordinate positively charged, nitrogen atom. We consider successively the formation of small (three- or four-membered) rings with such a feature, five-membered and then six-membered rings with one ring junction N, and finally rings containing two ring junction N atoms.

Systems with ring junction sulfur atoms are generally best considered as containing tetravalent sulfur.

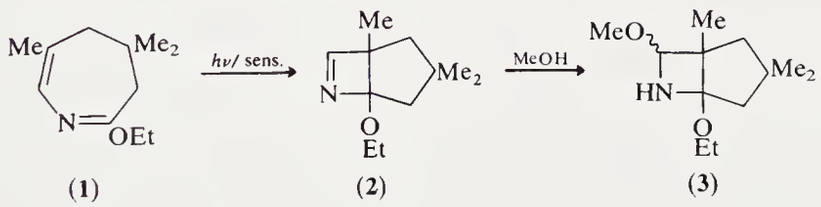
4.6.1 FORMATION OF THREE- OR FOUR-MEMBERED FUSED RINGS WITH ONE OR TWO RING JUNCTION N ATOMS

Cycloaddition of azirines can give fused systems as shown in Scheme 1 ⟨72TL1353, 74TL1487⟩.



Scheme 1

Photochemical, electrocyclic disrotatory ring closure converts the dihydroazepine (**1**) into (**2**), which is trapped as the MeOH addition product (**3**).

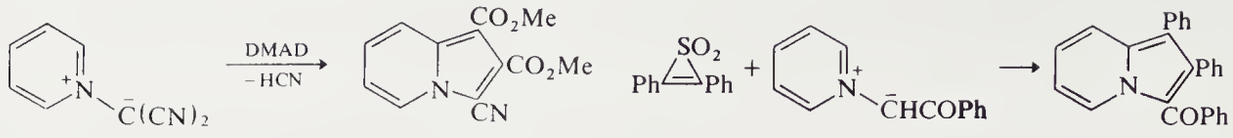


(**1**) (**2**) (**3**)

4.6.2 FORMATION OF A FIVE-MEMBERED RING WITH ONE N ATOM AT A RING JUNCTION

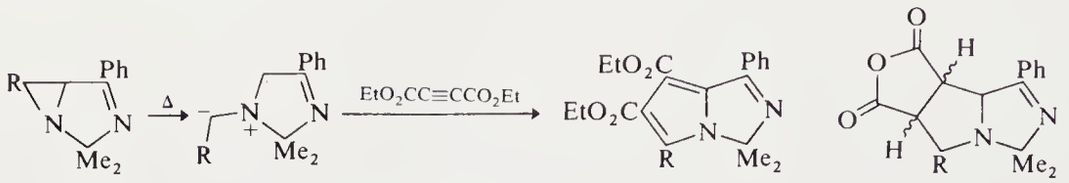
4.6.2.1 No Other Heteroatoms

Pyridinium ylides undergo cycloadditions with suitable alkynes, generating indolizines, *e.g.* (**4**)→(**5**) ⟨65JA3651⟩. Diphenylthiirene dioxide (**6**) in its reactions with pyridinium, quinolinium and isoquinolinium phenacylides behaves as an acetylene equivalent. The pyridinium phenacylide (**7**) gave the indolizine (**8**) with elimination of SO_2 and loss of hydrogen ⟨73BCJ667⟩.



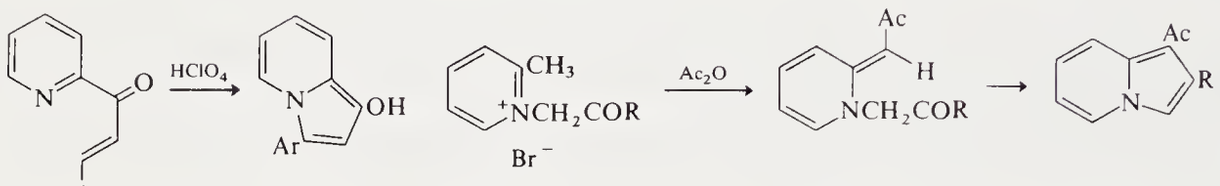
(4) (5) (6) (7) (8)

Thermal or photochemical ring openings of aziridines when applied to ring-fused aziridines generate ylides which may be trapped. The ring-fused aziridine (**9**) in refluxing xylene gives the azomethine ylide (**10**), converted by diethyl acetylenedicarboxylate into the 3*H*-pyrrolo[1,2-*c*]imidazole (**11**). With maleic anhydride the ylide gives the 1:1 cycloadduct (**12**) ⟨68JOC1097⟩. Similar adducts are formed with diethyl fumarate, *cis*- or *trans*-dibenzoylethylene, diethyl azodicarboxylate and *N*-phenylmaleimide. Indolizines can also be produced from pyridine and acetylenedicarboxylic ester (Section 3.2.1.3.7).



(9) (10) R = *p*-$NO_2C_6H_4$ (11) (12)

Indolizines can also be made by intramolecular Michael additions, *e.g.* 2-acetylpyridine + ArCHO→(**13**)→(**14**), or by cyclic aldol reactions, *e.g.* (**15**)→(**16**)→(**17**) ⟨72AJC1003⟩.

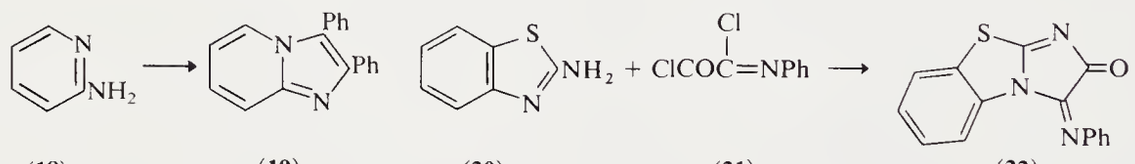


(13) (14) (15) (16) (17)

4.6.2.2 One Additional Heteroatom

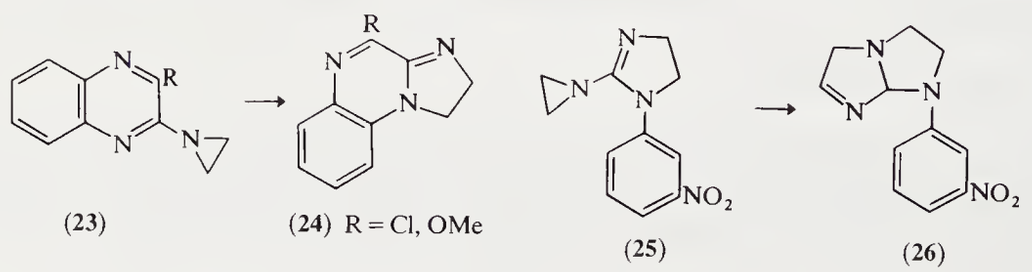
4.6.2.2.1 Imidazo[a]*-fused systems*

Such bicyclic systems are readily formed from a heterocycle containing a cyclic amidine. Thus 2-aminopyridine (**18**) with PhCOCHBrPh gives (**19**) and 2-aminobenzothiazole (**20**) with iminochloride (**21**) gives (**22**).

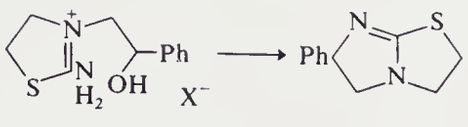


(18) (19) (20) (21) (22)

Corresponding reduced rings (*cf.* **24**, **26**) can be obtained from α-aziridinyl heterocycles (**23**, **25**). Related ring systems are obtained by formation of an alternative C—N bond, *e.g.* the alcohol (**27**) on heating with sulfuric acid afforded racemic tetramisole (**28**) ⟨68JOC1350⟩.



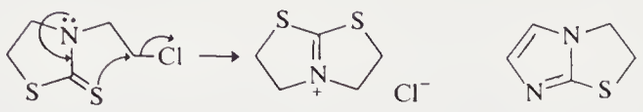
(23) (24) R = Cl, OMe (25) (26)



(27) (28)

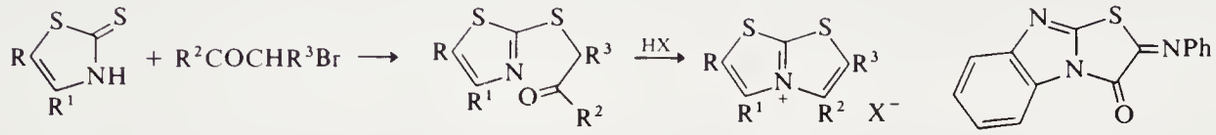
4.6.2.2.2 Thiazolo[b]-fused systems

The usual precursor is a cyclic thioamide. On formation, the *N*-β-chloroethylthiazolidine-2-thione (**29**) spontaneously ring-closed to the tetrahydrothiazolo[2,3-*b*]thiazolium chloride (**30**) ⟨71CHE1534⟩. Similar reactions of imidazole analogues of (**29**) give compounds of type (**31**).



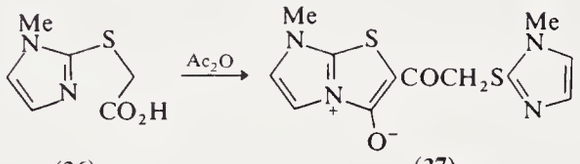
(29) (30) (31)

The thiazole-2-thione (**32**) with an α-halo ketone gives the intermediate (**33**) which is cyclized by strong acid into the thiazolo[2,3-*b*]thiazolium salt (**34**) ⟨77HC(30-1)1⟩. A wide variety of [5,5]-fused systems are prepared in this way: another example is (**35**) ⟨71KGS471⟩.

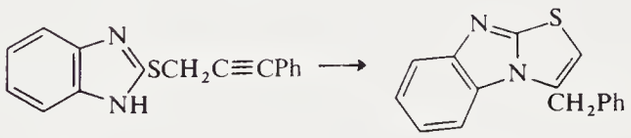


(32) (33) (34) (35)

Conversion of (1-methylimidazol-2-yl)thioglycolic acid (**36**) into the ring-fused mesoionic system (**37**) requires acetic anhydride ⟨79JOC3803⟩ and is accompanied by an acylation characteristic of reactive mesoionic systems. The thioether (**38**) with ethanolic sodium ethoxide gives the 3-benzylthiazolo[3,2-*a*]benzimidazole (**39**).

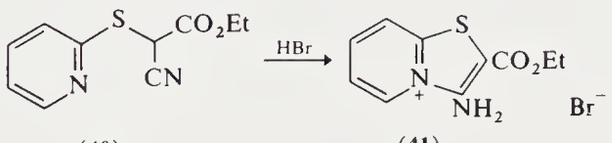


(36) (37)



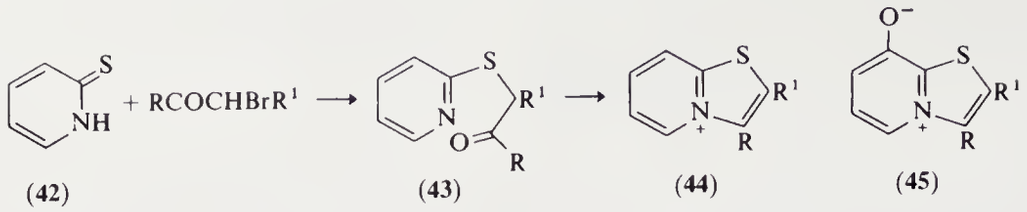
(38) (39)

The cyano group is also a precursor for intramolecular cyclization. The thioacetonitrile derivative (**40**) with HBr formed 3-amino-2-ethoxycarbonylthiazolo[3,2-*a*]pyridinium bromide (**41**) ⟨78JCR(S)407⟩. This is a general reaction for such annelation to a variety of five- and six-membered heterocycles.



(40) (41)

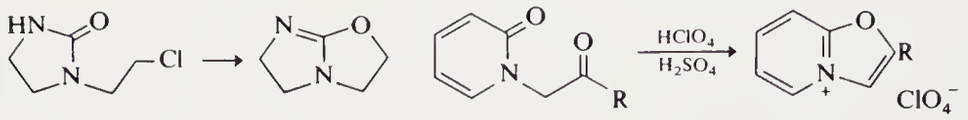
2(1*H*)-Pyridinethione (**42**) with an α-halo ketone gives the 2-β-oxoalkylthiopyridine (**43**) which is ring-closed with strong acid to the thiazolo[3,2-*a*]pyridinium system (**44**). The 3-hydroxypyridine analogue of (**42**) cyclizes to (**45**). Further variations are described in CHEC 4.10 and 4.29.



(42) (43) (44) (45)

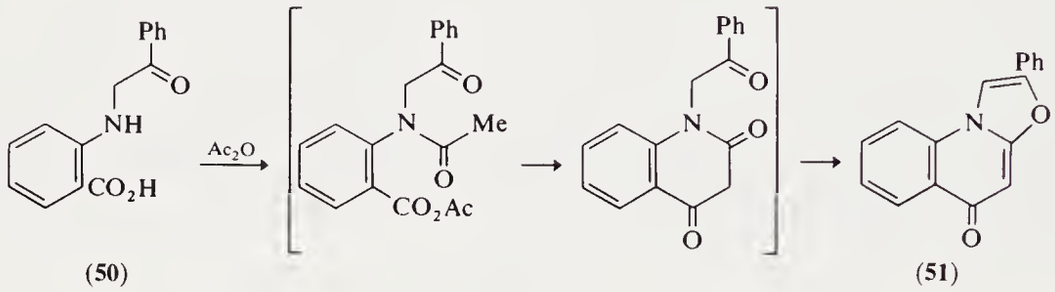
4.6.2.2.3 *Oxazolo*[b]-*fused systems*

Cyclic amides can be used similarly to the thioamides of the last section. 1-(2-Chloroethyl)-imidazolidin-2-one (**46**) with potassium hydroxide gave the tetrahydroimidazo[2,1-*b*]oxazole (**47**) ⟨57JA5276⟩.



(46) (47) (48) (49)

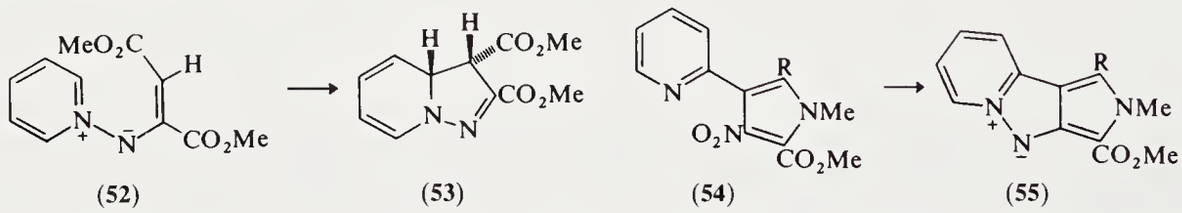
The 1-phenacyl-2(1*H*)-pyridinone (**48**) is cyclized to the oxazolo[3,2-*a*]pyridinium salt (**49**) by sulfuric acid ⟨67JHC66⟩. Sometimes the loss of a proton can give a neutral product as in the conversion of (**50**) into the ring-fused system (**51**) ⟨71JOC222⟩. For further examples see Section 3.3.3.4.1 and CHEC 4.29.



(50) (51)

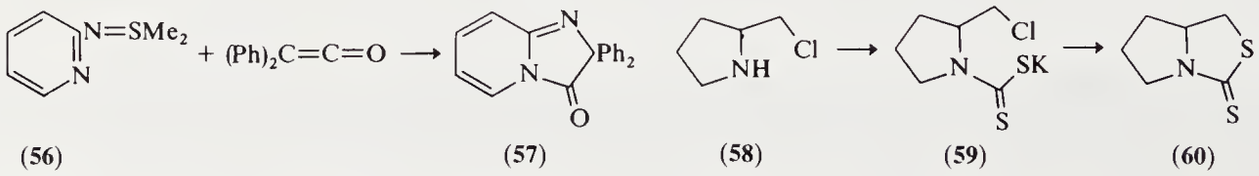
4.6.2.2.4 *Other systems*

1-Aminopyridinium iodide with dimethyl chlorofumarate forms a readily aromatized dihydropyrazolo[1,5-*a*]pyridine (**53**) *via* an initially formed 1:1 adduct (**52**); for a similar example see Section 3.2.3.12.4.iii. The 2-substituted pyridines (**54**) with triethyl phosphite yield the pyrrolopyrazoles (**55**) ⟨79JOC622⟩.



(52) (53) (54) (55)

With diphenylketene, the sulfimide (**56**) derived from 2-aminopyridine gives imidazo[1,2-*a*]pyridin-3-one (**57**) ⟨77H(8)109⟩. 2-Chloromethylpyrrolidine (**58**) with CS_2 and potassium carbonate forms the dithiocarbamate (**59**) which undergoes intramolecular alkylation on sulfur to give (**60**) ⟨63JOC981⟩.

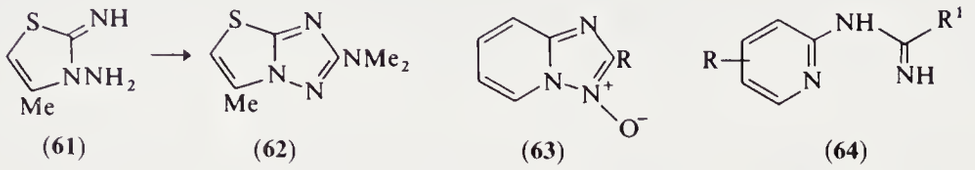


(56) (57) (58) (59) (60)

4.6.2.3 Two Other Heteroatoms

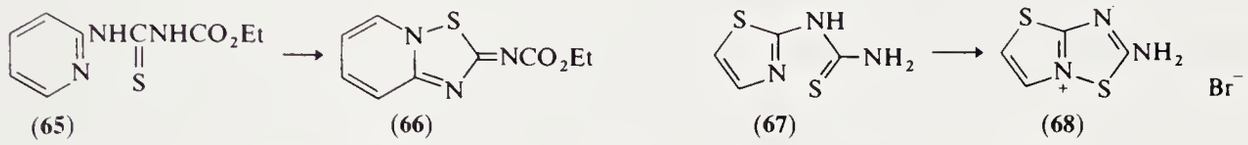
4.6.2.3.1 1,2,4-Triazolo[a]-, *1,2,4-thiadiazolo*[a]- *and 1,3,4-thiadiazolo*[b]-*fused systems*

The 1,2-diamino-4-methylthiazole (**61**) with phosgeniminium chloride $Cl_2C{=}NMe_2^+$ gives the thiazolo[3,2-*b*][1,2,4]triazole derivative (**62**) ⟨73AG(E)806⟩. Reaction of the sulfimide (**56**) with nitrile oxides RCNO forms [1,2,4]triazolo[1,5-*a*]pyridine 3-oxides (**63**) in good yield. This method is applicable to analogous pyrimidines and pyrazines ⟨76JCS(P1)2166, 78BCJ563⟩. Lead tetraacetate oxidation of (**64**) gives compounds of type (**63**) but without the *N*-oxide group.



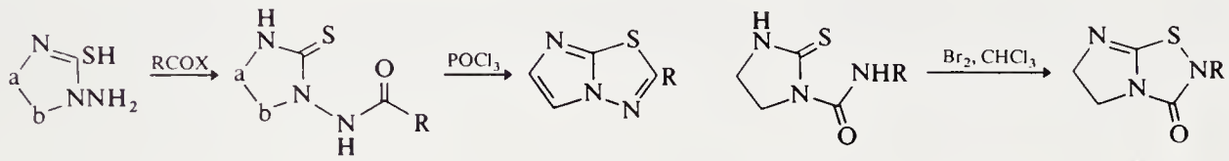
(**61**) (**62**) (**63**) (**64**)

Oxidative ring closure on to a ring nitrogen atom occurs readily as in the formation of the [1,2,4]thiadiazolo[2,3-*a*]pyridine (**66**) from the 2-pyridylthiourea (**65**) ⟨75JHC1191⟩. Similarly, bromine oxidation of 2-thiazolylthiourea (**67**) gives the 2-aminothiazolo[3,2-*b*][1,2,4]thiadiazolylium bromide (**68**) ⟨71JPR1148⟩.



(**65**) (**66**) (**67**) (**68**)

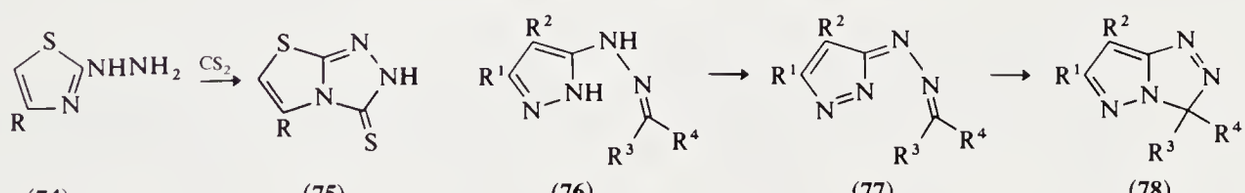
Reaction of an amino-substituted heterocyclic thiol such as (**69**) with acylating agents gives compounds (**70**), which are cyclized by $POCl_3$ to form, for example, imidazo[2,1-*b*][1,3,4]thiadiazoles (**71**) ⟨63LA(663)113⟩. Bromine oxidation of the cyclic thiourea (**72**) forms 2,3,5,6-tetrahydroimidazo[1,2-*d*][1,2,4]thiadiazol-3-ones (**73**) ⟨73JPR539⟩.



(**69**) (**70**) (**71**) (**72**) (**73**)

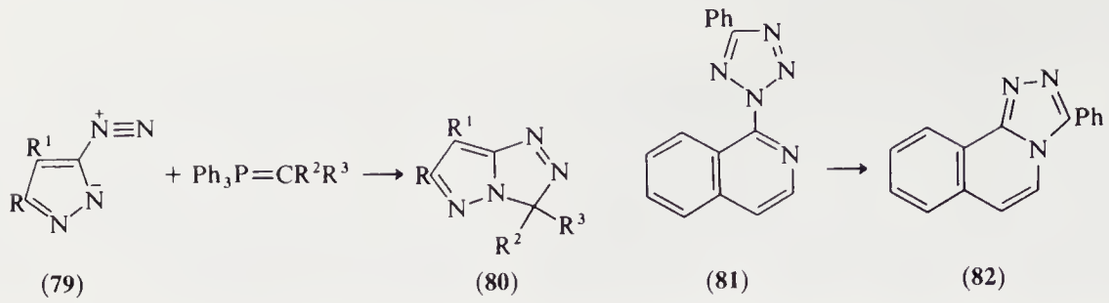
4.6.2.3.2 1,2,4-Triazolo[b]- *and 1,2,4-thiadiazolo*[c]-*fused systems*

α-Hydrazino nitrogen heterocycles are readily converted into 1,2,4-triazolo[*b*]-fused systems, as exemplified by (**74**)→(**75**) ⟨71JOC10⟩. Oxidation of the 2-pyrazolyl hydrazone (**76**) with $Pb(OAc)_4$ in CH_2Cl_2 gives, *via* azine (**77**), the 3*H*-pyrazolo[5,1-*c*]-1,2,4-triazole (**78**) ⟨79TL1567⟩.



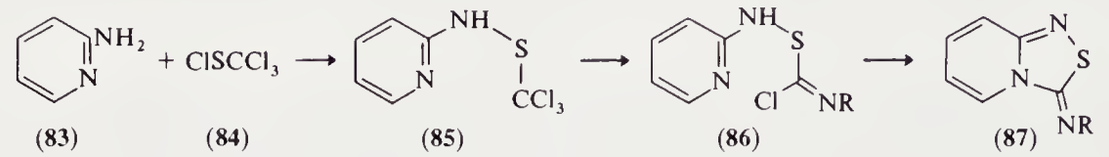
(**74**) (**75**) (**76**) (**77**) (**78**)

The diazopyrazole (**79**) with various phosphorus ylides afforded 3*H*-pyrazolo[5,1-*c*]-1,2,4-triazoles (**80**) by elimination of triphenylphosphine ⟨79TL1567⟩. Reaction of 1-chloroisoquinoline with 5-phenyltetrazole gives 3-phenyl-1,2,4-triazolo[3,4-*a*]isoquinoline (**82**) *via* intermediate (**81**) ⟨70CB1918⟩



(79) (80) (81) (82)

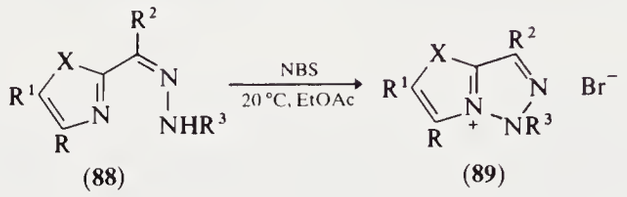
Trichloromethanesulfenyl chloride (**84**) converts 2-aminopyridine (**83**) into the intermediate sulfenamide (**85**) which with an aromatic amine cyclizes to (**87**), probably *via* the intermediate (**86**) ⟨75JOC2600⟩.



(83) (84) (85) (86) (87)

4.6.2.3.3 1,2,3-Triazolo[c]-fused systems

An example of synthesis by N—N bond formation is shown in the conversion (**88**)→(**89**).



(88) (89)

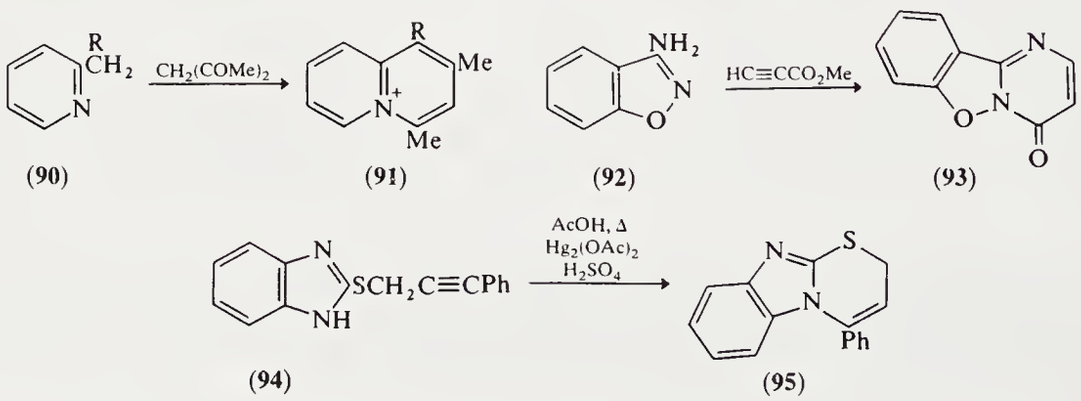
4.6.2.4 Three Other Heteroatoms: Fused Tetrazoles

α-Azido-azoles and -azines exist in ring–chain tautomeric equilibrium with fused tetrazoles: see Sections 3.4.1.2.3 and 3.2.3.6.4.

4.6.3 FORMATION OF A SIX-MEMBERED RING WITH ONE N ATOM AT A RING JUNCTION

4.6.3.1 Ring Formation Using a Three-carbon Fragment

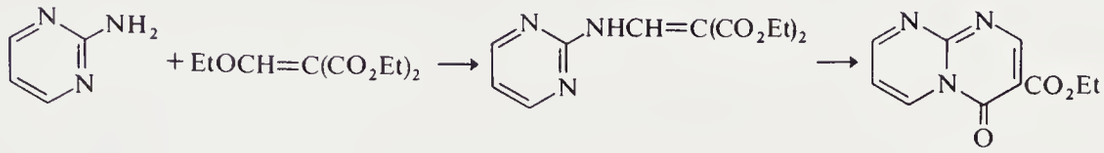
Six-membered rings are formed by reaction of a three-carbon fragment with an aza heterocycle containing any of (i) an α-methyl, (ii) an α-amino or (iii) a potential α-mercapto group. Examples of (i) and (ii), respectively, are (**90**)→(**91**) and the reaction of 3-aminobenzisoxazole (**92**) with methyl propiolate to form (**93**) (together with a regioisomer) ⟨72CB794⟩. Heating (**94**) with mercury(I) acetate and acid affords the 4-phenyl-2*H*-thiazino[3,2-*a*]benzimidazole (**95**).



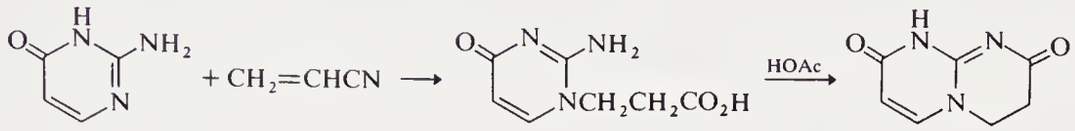
(90) (91) (92) (93)

(94) (95)

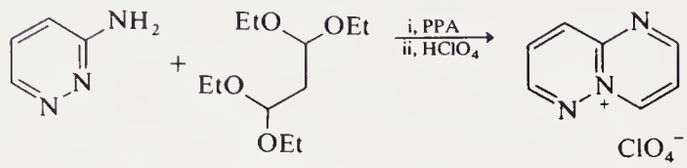
Reactions of this type have been used extensively for the preparation of diazinodiazines, and examples include the formation of compounds (**96**), (**97**), (**98**) and (**99**) by the routes shown.



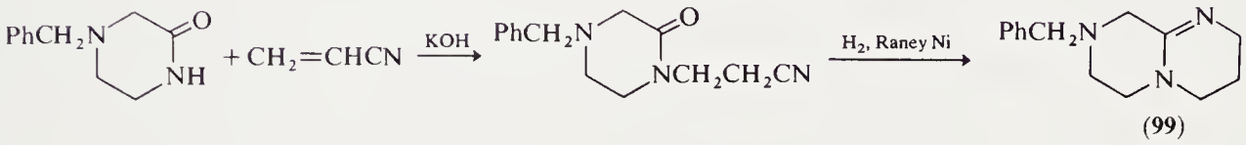
(**96**)



(**97**)



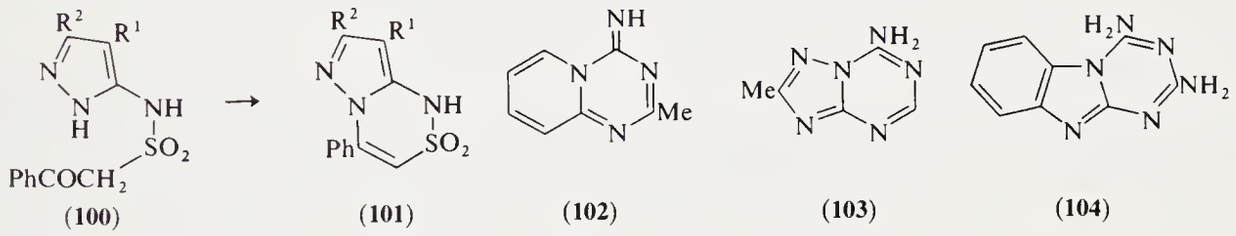
(**98**)



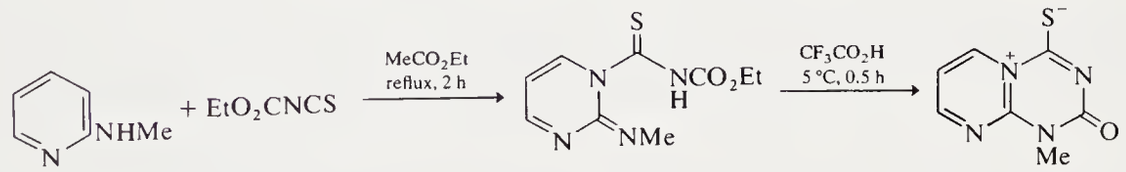
(**99**)

4.6.3.2 Other Ring Formation not Involving Cycloaddition Reactions

Methods analogous to those described in the last section, but using a CCS or CNC three-atom fragment, are illustrated by the syntheses of compounds (**101**), (**102**) [from 2-aminopyridine and MeC(OMe)=NCN], (**103**) [from 3-amino-5-methyl-1,2,4-triazole and CH(OEt)=NCN], (**104**) [from 2-aminobenzimidazole and cyanoguanidine], and the fused mesomeric 1,3,5-triazine betaine shown in Scheme 2.

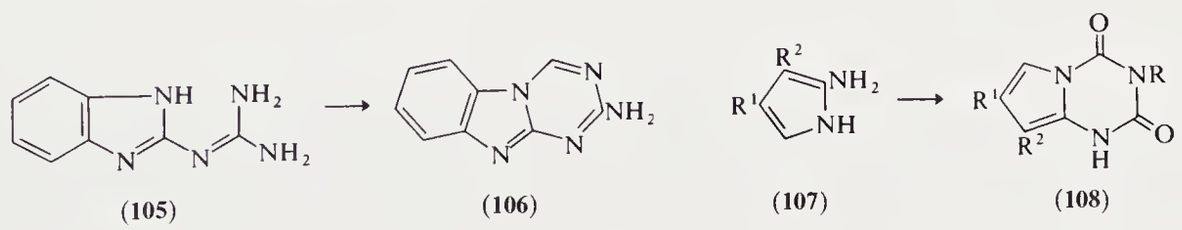


(**100**) (**101**) (**102**) (**103**) (**104**)



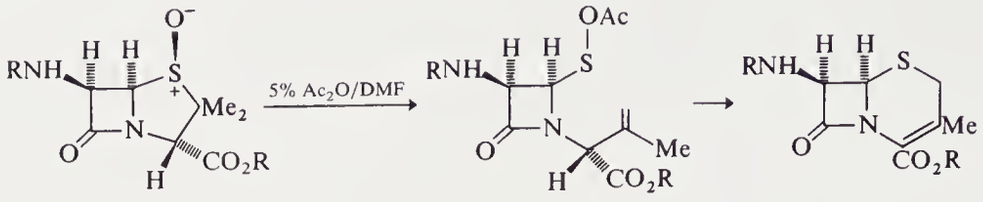
Scheme 2

Other syntheses involve insertion of a single ring atom, *e.g.* (**105**) + HCO_2Et → (**106**), or the use of two moles of RNCO for (**107**) → (**108**).



(**105**) (**106**) (**107**) (**108**)

Treatment of the sulfoxide (**109**) with 5% Ac_2O/DMF at 130 °C gives the deacetoxycephalosporin (Scheme 3).

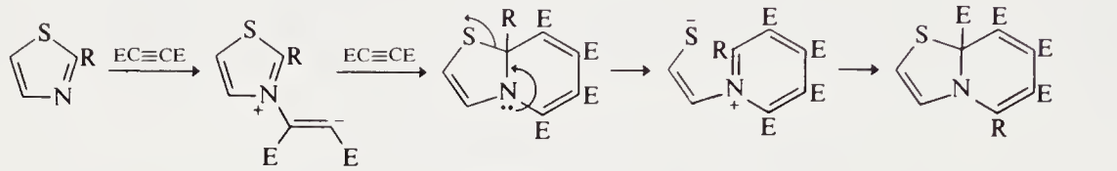


(**109**)

Scheme 3

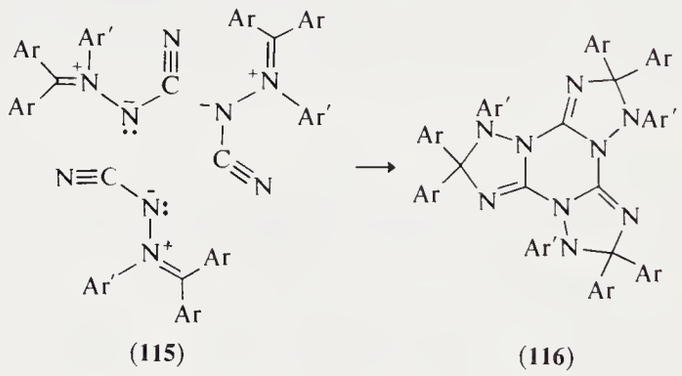
4.6.3.3 Cycloaddition Reactions

1,4-Dipolar cycloadditions lead to six-membered rings. Rearrangements may be encountered. Thiazole or 2-methylthiazole (**110**; R = H and Me) with DMAD forms an initial 1,4-dipolar species (**111**). Reaction of (**111**) with a second DMAD gives a 1:2 adduct, presumably (**112**). Ring opening to (**113**), followed by cyclization in the alternative mode, resulted in (**114**) ⟨78AHC(23)263⟩ (see also CHEC 4.19). For the similar reactions of pyridine with DMAD and pyridazine with maleic anhydride see Section 3.2.1.3.7.



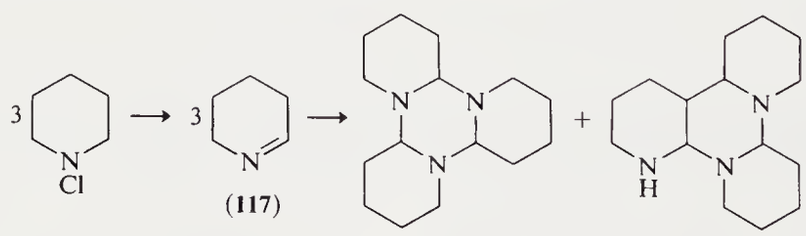
(**110**) (**111**) (**112**) (**113**) (**114**) E = CO_2Me

C,*C*,*N*$^{\alpha}$-Triaryl-*N*$^{\beta}$-cyanoazomethine imines (**115**) are trimerized on heating to (**116**) *via* a succession of three 1,3-dipolar cycloadditions, the third being intramolecular ⟨80AG(E)906⟩.



(**115**) (**116**)

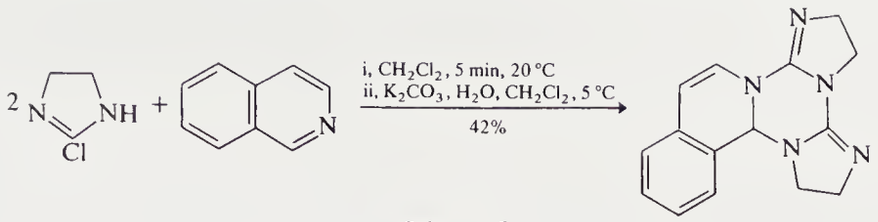
N-Chloropiperidone on heating with potassium hydroxide loses hydrogen chloride to give the intermediate (**117**), which forms a mixture of trimers (Scheme 4) ⟨59HC(13)1, p. 446⟩.



(**117**)

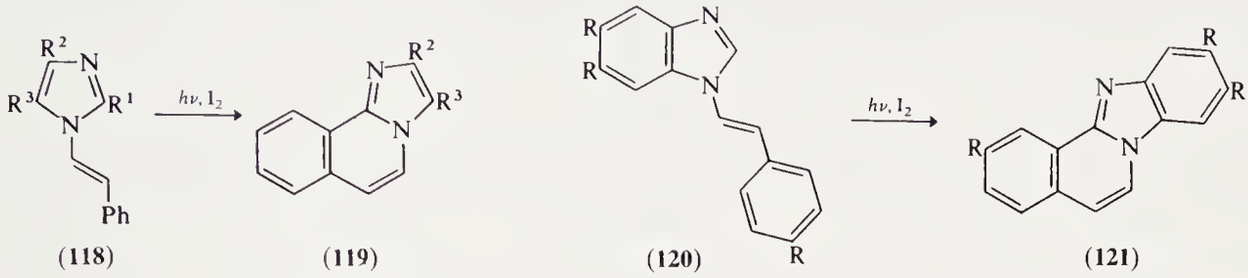
Scheme 4

The mixed 'trimerization' of heterocyclic compounds is a potentially valuable route to fused systems. The reaction of isoquinoline with 2-chloro-4,5-dihydroimidazole is a recent example (Scheme 5) ⟨81S154⟩.



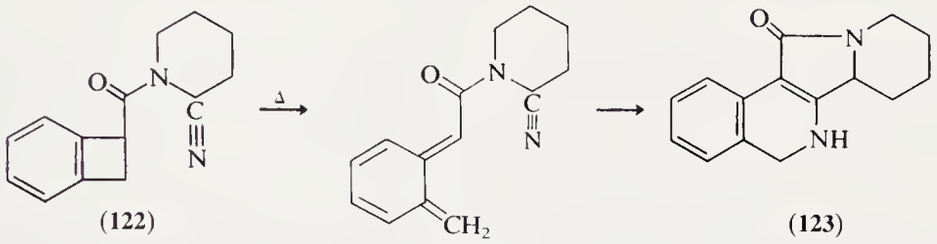
Scheme 5

Compounds with a ring junction N atom result from the photochemical cyclization of *cis*-1-styrylimidazoles. Irradiation of the imidazole (**118**; $R^1 = H$) in methanol in the presence of I_2 gave imidazo[2,1-*a*]isoquinoline (**119**) ⟨76JCS(P1)75⟩. *trans*-1-Styrylbenzimidazole (**120**) similarly formed successively the *cis* isomer and the benzimidazo[2,1-*a*]isoquinoline (**121**). For similar reaction of 1-styrylpyridinium, see Section 3.2.2.3.9.



(**118**) (**119**) (**120**) (**121**)

Intramolecular [4 + 2] cycloaddition reactions are illustrated by thermolysis of the benzocyclobutene (**122**) to the tetracyclic system (**123**), *via* trapping of a quinodimethane by the nitrile group (Scheme 6).



(**122**) (**123**)

Scheme 6

For [3 + 3] cycloaddition of azafulvalene ketenes see Section 3.3.3.3.6.

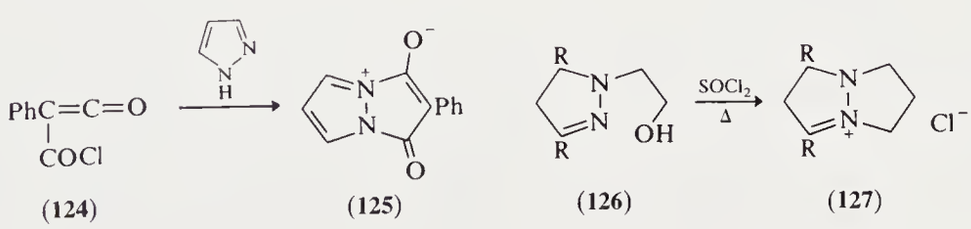
4.6.3.4 Other Methods

Azolealdehydes with an α-NH group dimerize (Section 3.4.3.4.4). Cyclic $\overset{+}{N}$—$\bar{N}$ links can be formed using nitrene intermediates (Section 3.4.3.4.2).

4.6.4 TWO NITROGEN ATOMS AT A RING JUNCTION

4.6.4.1 Five-membered Rings

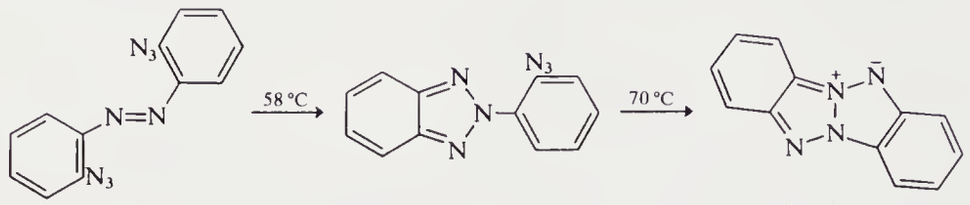
A wide variety of methods are available: the following examples are intended only to be illustrative. Reaction of pyrazole with (chlorocarbonyl)phenylketene (**124**) forms the zwitterionic pyrazolo[1,2-*a*]pyrazole (**125**) ⟨80JA3971⟩.



(**124**) (**125**) (**126**) (**127**)

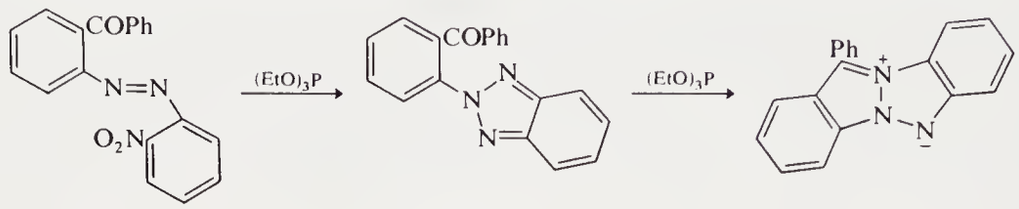
The pyrazoline (**126**) cyclized to the pyrazolinium salt (**127**) on heating with thionyl chloride ⟨68JOC3941⟩.

Heating 2,3′-diazidoazobenzene (**128**) at 58 °C formed (**129**); at 70 °C a second ring closed to give the tetraazapentalene (**130**) ⟨67JA2618⟩.



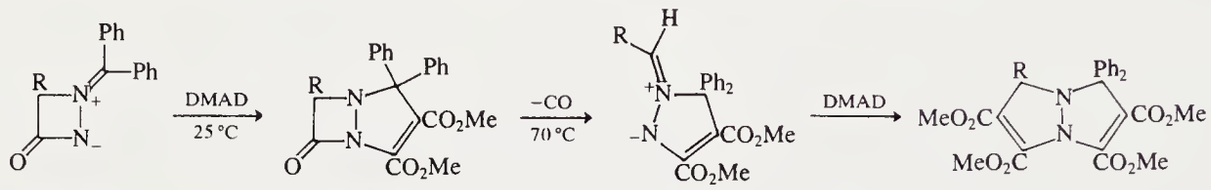
(**128**) (**129**) (**130**)

The substituted azobenzene (**131**) with triethyl phosphite gives the triazapentalene (**133**) *via* the 2-substituted benzotriazole (**132**) which undergoes a second deoxygenative cyclization ⟨74CL951⟩.



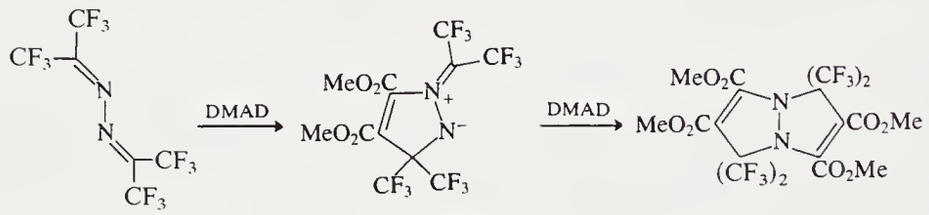
(**131**) (**132**) (**133**)

The betaine (**134**) reacts with DMAD to give product (**135**) which easily undergoes thermal fragmentation to (**136**) followed by another cycloaddition to form (**137**) ⟨81JA7743⟩.



(**134**) (**135**) (**136**) (**137**)

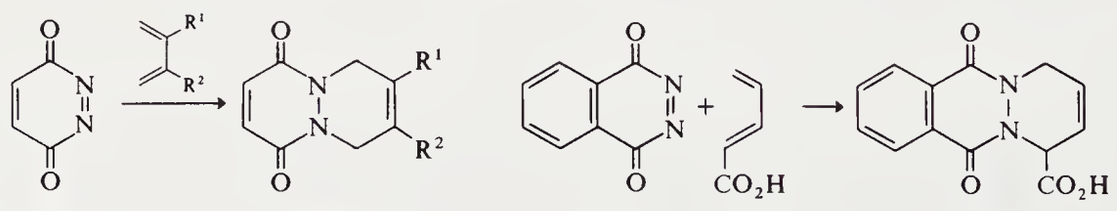
'Criss-cross' addition of azines also involves two successive 1,3-dipolar cycloadditions (Scheme 7) ⟨76S349⟩.



Scheme 7

4.6.4.2 Six-membered Rings

3,6-Pyridazinedione (**138**) readily condenses with butadiene, 2,3-dimethylbutadiene and coumalic acid to give the respective Diels–Alder adducts (**139**).



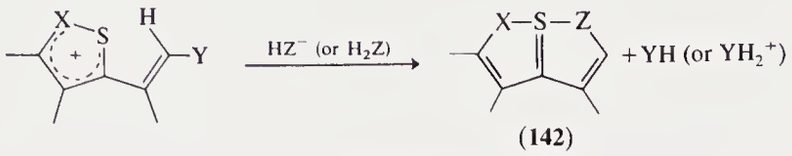
(**138**) (**139**) (**140**) (**141**)

Phthalazine-1,4-dione reacts similarly, *e.g.* (**140**)→(**141**).

4.6.5 SULFUR AT A RING JUNCTION

The best known compounds are of type (**142**). Available synthetic methods are discussed in CHEC 4.38.5; the following are illustrative. The method of Scheme 8 has been widely used (CHEC 4.38.5.2.2): X can be S or NMe; Y = OMe, SMe or NMe_2; Z = O, S, Se or NR.

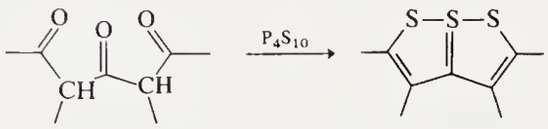
For related syntheses see Section 3.4.3.3.4.



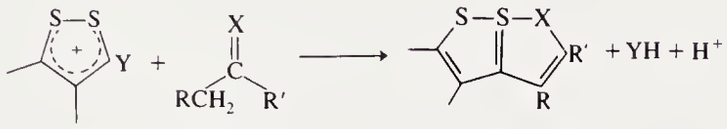
(**142**)

Scheme 8

1,6,6aλ^4-Trithiapentalenes are obtained from 1,3,5-triketones with P_2S_5, *e.g.* (**143**)→(**144**) ⟨71AHC(13)161⟩.



(**143**) (**144**)



X = O or S; Y = Cl or SMe

(**145**) (**146**)

1,2-Dithiolylium cations carrying a leaving group at the 3-position (**145**) react with active methylene compounds to give products (**146**) in which X = O or S ⟨80AHC(27)151⟩.

Subject Index

As described in the introductory material, the arrangement of this Handbook is such that the physical properties and reactions of particular types of compounds are very systematically treated, and information on them can usually be rapidly assessed by consultation of the detailed contents under the 'Structure' and 'Reactivity' sections, respectively. However, it is not as simple to access the *preparation* of particular heterocyclic compounds for reasons which are discussed in the 'Synthesis' section. A major aim of this index is to provide such information; entries referring to the synthesis of a given compound are therefore denoted with an asterisk.

It has not been possible, nor was it desirable, to index a compound or reaction at every mention in the text. Instead the essential features of compounds have been chosen, and individual compounds indexed specifically only where they are discussed in some detail.

JPC	J. Phys. Chem.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KGS	Khim. Geterotsikl. Soedin.
LA	Liebigs Ann. Chem.
M	Monatsh. Chem.
MI	Miscellaneous [book or journal]
MIP	Miscellaneous Pat.
MS	Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds', Wiley, New York, 1971
N	Naturwissenschaften
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi
NMR	T. J. Batterham, 'NMR Spectra of Simple Heterocycles', Wiley, New York, 1973
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PAC	Pure Appl. Chem.
PC	Personal Communication
PH	'Photochemistry of Heterocyclic Compounds', ed. O. Buchardt, Wiley, New York, 1976
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RRC	Rev. Roum. Chim.
RTC	Recl. Trav. Chim. Pays-Bas
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SH	W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds', Wiley, New York, 1977, parts 1 and 2
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
T	Tetrahedron
TH	Thesis
TL	Tetrahedron Lett.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
USP	U.S. Pat.
YZ	Yakugaku Zasshi
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe-Seyler's Z. Physiol. Chem.

JPC	J. Phys. Chem.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KGS	Khim. Geterotsikl. Soedin.
LA	Liebigs Ann. Chem.
M	Monatsh. Chem.
MI	Miscellaneous [book or journal]
MIP	Miscellaneous Pat.
MS	Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds', Wiley, New York, 1971
N	Naturwissenschaften
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi
NMR	T. J. Batterham, 'NMR Spectra of Simple Heterocycles', Wiley, New York, 1973
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PAC	Pure Appl. Chem.
PC	Personal Communication
PH	'Photochemistry of Heterocyclic Compounds', ed. O. Buchardt, Wiley, New York, 1976
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RRC	Rev. Roum. Chim.
RTC	Recl. Trav. Chim. Pays-Bas
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SH	W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds', Wiley, New York, 1977, parts 1 and 2
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
T	Tetrahedron
TH	Thesis
TL	Tetrahedron Lett.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
USP	U.S. Pat.
YZ	Yakugaku Zasshi
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe-Seyler's Z. Physiol. Chem.

HANDBOOK OF HETEROCYCLIC CHEMISTRY

ALAN R. KATRITZKY, FRS

Heterocyclic chemistry is the largest of the classical divisions of organic chemistry. Heterocyclic compounds are widely distributed in Nature, playing a vital role in the metabolism of living cells. Their practical applications range from extensive clinical use to fields as diverse as agriculture, photography, biocide formulation and polymer science. The range of known compounds is virtually limitless, encompassing a considerable spectrum of physical, chemical and biological properties.

This book provides a balanced, concise and informative account of heterocyclic chemistry that will be suitable for graduate or advanced undergraduate students and a convenient reference book for research workers, both specialists in the field and those whose expertise lies in other areas but who nevertheless need information on heterocyclic chemistry. The author is Chairman of the Editorial Board of the major treatise *Comprehensive Heterocyclic Chemistry*, a significant feature of which is the inclusion of special chapters on the structure, reactivity and synthesis of heterocyclic ring systems. The *Handbook of Heterocyclic Chemistry* is based on these special chapters. Illustrated throughout with thousands of clearly drawn chemical structures, the highly systematic coverage given to the subject makes this the most authoritative one-volume account of modern heterocyclic chemistry available.

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