COMPREHENSIVE HETEROCYCLIC CHEMISTRY

JOURNAL CODES FOR REFERENCES

For explanation of the reference system, see p. 629

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.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)

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.

COMPREHENSIVE HETEROCYCLIC CHEMISTRY

IN 8 VOLUMES

COMPREHENSIVE HETEROCYCLIC CHEMISTRY

The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds

Volume 2

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Part 2A

Six-membered Rings with One Nitrogen Atom

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Contents

Foreword

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 is 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. Over 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 vitamin; the photosynthesizing pigment chlorophyll; the oxygen transporting pigment hemoglobin, and its breakdown products the bile pigments; the hormones kinetin, heteroauxin, serotonin and histamine; together with 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 is 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.

Aims 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 ongoing 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 accessible manner in Chapter 1.03.

The approach and treatment throughout this work is 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 (Chapter 1.01).

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Volume 6 (Part 4B: Five-membered Rings with Two or More Oxygen, Sulfur or Nitrogen Atoms)

Volume 7 (Part 5: Small and Large Rings)

Volume 8 (Part 6: Indexes)

2.01

Structure of Six-membered Rings

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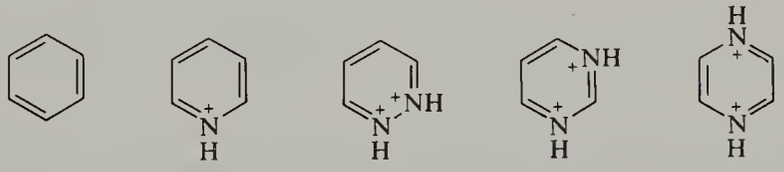
University of East Anglia

2.01.1 SURVEY OF POSSIBLE STRUCTURES: NOMENCLATURE

Aromatic six-membered heterocycles, isoelectronic with benzene, are widely distributed in nature, and in the world of synthetic chemistry. 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 is theoretically possible, but knowledge of this type of structure does not extend beyond 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. This makes a far wider range of possibilities available, since an extra positive charge is not incorporated with each substitution. However, there is a limit to the number of carbon atoms which can be replaced in this way. Fragmentation of the six-membered ring to three triple-bonded species (C_2H_2, HCN and/or N_2) can be very advantageous thermally, particularly if more than one nitrogen molecule per ring is produced. This imposes a limitation on the number of stable forms. Thus the monocyclic azines which are known (see Figure 1) 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 Chapter 2.21). No pentazines are known. It is apparent from Figure 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).

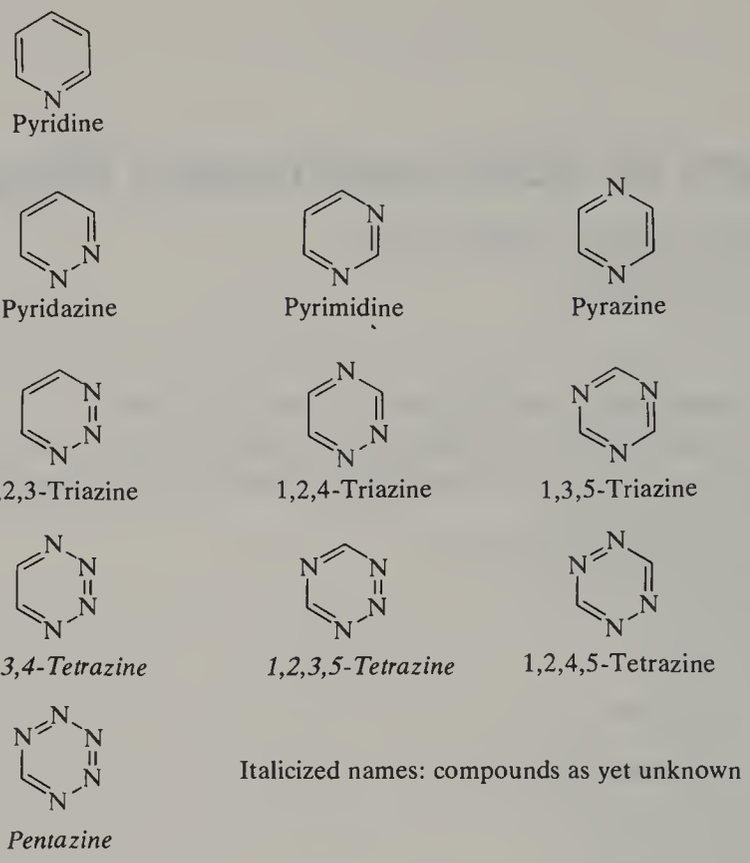
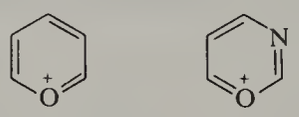


Figure 1

Although all the rings in Figure 1 contain six π-electrons, the accumulation of electronegative nitrogen atoms in the polyaza structures leads to hydrolytic as well as thermal instability. This is noticeable in pyrimidine, and marked in the triazines and tetrazine. Some stability can be conferred by appropriate substitution, as we shall outline later.

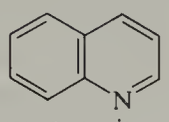
Further pursuit of the isoelectronic substitution principle leads to the identification of a further class of cation formed by replacing the aza-nitrogen by an oxonia group (O^+). There is here no possibility of 'cancelling' the charge by further proton removal. Therefore the fundamental heteroaromatic rings containing an oxonia-oxygen are few, and the pyrylium ion (**6**) and some of its aza and diaza analogues, *e.g.* the 1,3-oxazinium ion (**7**), are the only examples in the monocyclic series. Some of the corresponding sulfur analogues, with S in place of O, are also known.

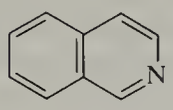


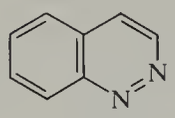
A number of sulfur-containing systems are characterized by the presence of the formally tetravalent element in the ring. These are the 'thiabenzenes', and with just the single heteroatom in the ring (C_5S rings) they are very unstable, non-planar structures which are largely ylidic in character (Chapter 2.25). Aza substitution results in stabilization. Six-membered rings with several nitrogen and sulfur atoms are known (see Chapter 2.28); bonding in these compounds seems to be similar to that found in the inorganic sulfur nitrides.

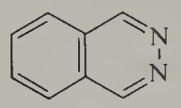
When two fused six-membered rings (naphthalene analogues) are considered, possibilities become very numerous, partly on account of the reduced symmetry of naphthalene, compared with benzene, and also because of the larger number of positions available for substitution. Thus, there are two monoazanaphthalenes, quinoline (**8**) and isoquinoline (**9**), four benzodiazines [cinnoline (**10**), phthalazine (**11**), quinazoline (**12**) and quinoxaline(**13**)], with the two nitrogen atoms in the same ring, and six naphthyridines (*e.g.* (**14**), named and

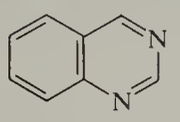
numbered in a systematic way) with the nitrogens in different rings. Of the higher poly-azanaphthalenes which have been prepared (examples with up to six nitrogen atoms are known), the important pteridine system (**15**) should be noted. Both the benzotriazines are known, but 1,2,3,4-benzotetrazine is not.

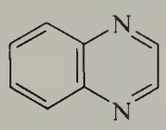

(**8**) Quinoline

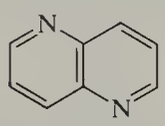

(**9**) Isoquinoline

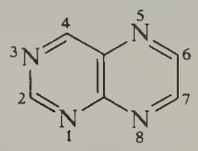

(**10**) Cinnoline


(**11**) Phthalazine

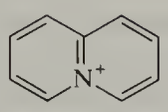

(**12**) Quinazoline

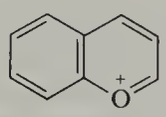

(**13**) Quinoxaline

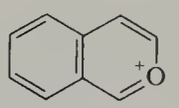

(**14**) 1,5-Naphthyridine

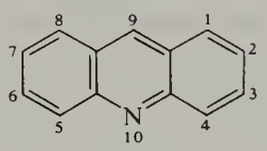

(**15**) Pteridine

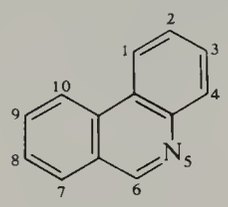
Azonia substitution at a naphthalene bridgehead position gives the quinolizinium ion (**16**). Oxonia substitution, elsewhere, forms the 1- and 2-benzopyrylium ions (**17**) and (**18**). The two most well-known monoaza systems with three aromatic fused rings are acridine (**19**), derived structurally from anthracene, and phenanthridine (**20**), an azaphenanthrene. The better-known diaza systems include phenazine (**21**) and 1,10-phenanthroline (**22**), while systems with three linearly fused pyridine rings are called anthyridines, *e.g.* the 1,9,10-isomer (**23**).

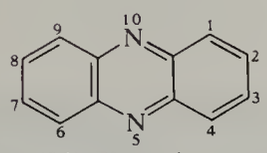

(**16**) Quinolizinium

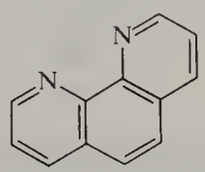

(**17**) 1-Benzopyrylium

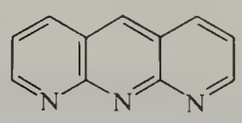

(**18**) 2-Benzopyrylium


(**19**) Acridine

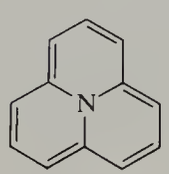

(**20**) Phenanthridine

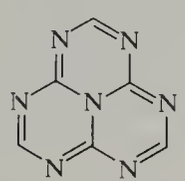

(**21**) Phenazine


(**22**) 1,10-Phenanthroline


(**23**) 1,9,10-Anthyridine

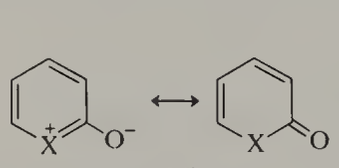
Heterocycles structurally based on the phenalene ring system form an interesting class, frequently possessing distinctive colours. With nitrogen as the central atom we have the unstable 9b-azaphenalene (**24**), which has only fairly recently been prepared and is still comparatively little studied ⟨76JCS(P1)341⟩. The cyclazine nomenclature is commonly applied to this and related compounds: thus, (**24**) is (3.3.3)cyclazine. With further aza substitution, in positions alternant to the central atom, their stability increases; the heptaazaphenalene (**25**) is (thermally) a very inert compound, derivatives of which, *e.g.* the triamine, have been known since the early days of organic chemistry (see Chapter 2.20).


(**24**)

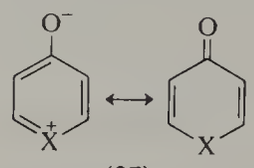

(**25**)

A positively charged heteroatom can be balanced by a negatively charged substituent, and if they are oriented favourably relative to each other the charges may formally cancel. Thus, the 2- and 4-pyridone structures (**26**, **27**; X = NH) and the corresponding pyrones

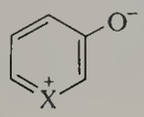
(**26**, **27**; X = O) (we use an abbreviated and informal nomenclature here—long-established and widely understood) are generated. These systems have complete π-conjugation, and possess 'aromatic' stabilization in some degree, although precisely to what extent is difficult to quantify. The isomeric structures (**28**; X = NH, O) are also known, but they are chemically more reactive, behaving as 1,3-dipoles in cycloaddition reactions, and being prone to dimerization and rearrangement. Benzo-fused analogues of these compounds are also long-known and well investigated, as is indicated by the profusion of trivial names by which they are, or have been, known. Thus, the 2*H*-1-benzopyran-2-ones (**29**) are the coumarins, the 4*H*-1-benzopyran-4-ones (**30**) are the chromones and the 2-phenyl derivatives (**30**; R = Ph) of the chromones are the flavones. The dibenzopyrones (**31**) are known as xanthones.



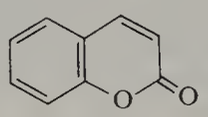
(**26**)



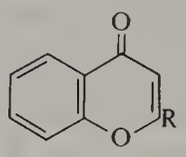
(**27**)



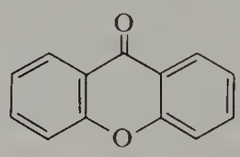
(**28**)



(**29**)

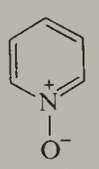


(**30**)

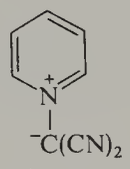


(**31**)

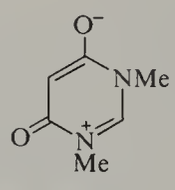
Interesting structures can be formed by combinations of ring and side-chain substituents in special relative orientations. As indicated above, structures (**28**) contain the elements of azomethine or carbonyl ylides, which are 1,3-dipoles. Charge-separated species formed by attachment of an anionic group to an azonia-nitrogen also are 1,3-dipoles: pyridine 1-oxide (**32**) is perhaps the simplest example of these; the ylide (**33**) is another. More complex combinations lead to '1,4-dipoles', for instance the pyrimidine derivative (**34**), and the 'cross-conjugated ylide' (**35**). Compounds of this type have been reviewed by Ramsden ⟨80AHC(26)1⟩.



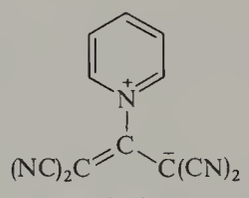
(**32**)



(**33**)

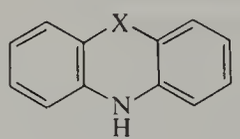


(**34**)

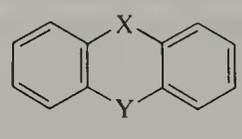


(**35**)

The potential for complete 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. This gives a total π-electron count of eight—a recipe for 'antiaromaticity' and hence instability. Nevertheless, many such systems are known, particularly when the heteroatoms are oxygen or sulfur. A discussion of the factors tending to stabilize these compounds would be out of place here; we simply note that the rings are often not planar, being folded (heteroatoms 1,4-) or puckered (1,2-), and that the best-known examples are the dibenzo-fused systems phenothiazine (**36**; X = S), phenoxazine (**36**; X = O), thianthrene (**37**; X = Y = S), phenoxathiin, or phenoxthionine (**37**; X = S, Y = O) and dibenzo-*p*-dioxin (**37**; X = Y = O). The tendency towards more 'systematic' nomenclature along this sequence is no doubt a reflection of the progressively diminishing importance of the compounds.



(**36**)

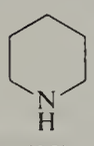


(**37**)

Of the legion of partially saturated six-membered ring heterocycles, an idea of their stability, or lack of it, can normally be gained by consideration of the thermodynamic stability of the various components which can be identified in them. Thus, those rings which contain ester or amide functions can be expected to possess the chemical reactivity and the

thermodynamic stability of these. (The fact that they are constrained into a six-membered ring forces these groups into conformations which they tend not to favour in open-chain compounds, but this is not of any great significance.)

Some of the partially and fully reduced heterocyclic six-membered rings are sufficiently important to have trivial names with which the reader should be familiar. Thus hexahydropyridine (**38**) is known as piperidine, and tetrahydro-1,4-oxazine (**39**) is morpholine. Tetrahydropyridines are also sometimes referred to as piperideines, with the position of the double bond denoted by a Δ, but this system is obsolescent (at the least).



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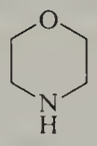


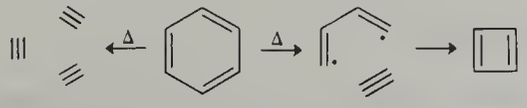
(39)

Although most ring systems are numbered according to a fairly straightforward set of rules (see Chapter 1.02), there are several exceptions, and the IUPAC handbook ⟨B-79MI20100⟩ or *Chemical Abstracts* should always be consulted in cases of doubt. Acridine, for instance, now has its 'meso' positions numbered 9 and 10 (see structure **19**). (At least two other systems have been widely used in the past, leading to a great deal of confusion which still hangs over this area of chemistry.) This method follows the same pattern as in anthracene, which is also 'non-systematic'. Phenazine, however, is numbered systematically, as in structure (**21**). On the other hand, phenanthridine (**20**) is numbered in the systematic fashion as indicated, although phenanthrene still keeps to the traditional method (starting with 1 at '4' in structure (**20**), and running anticlockwise, to give the central ring the 9 and 10 positions). Monocyclic systems are not exempt from confusion, either; rings were formerly arranged in such a way as to give 'corresponding' positions in pyrimidines, purines and pteridines the same numbers. In recent years the pyrimidines and pteridines have followed conventional 'least numbers' rules, but tradition still reigns with the purines (see Chapter 4.09).

Ruthless adherence to full systematic nomenclature throughout these volumes would serve little useful purpose. While it is necessary for the *Chemical Abstracts* indexes to avoid colloquial forms, most of our contributors seem to agree that insistence on the use of, *e.g.* '4(1*H*)-pyridinone' at every point, rather than the traditional but less precise '4-pyridone', produces a pedantic effect on the English style. So old-fashioned forms like 'pyridone' coexist here with systematic names, the choice being dictated by the individual authors of the chapters.

2.01.2 THERMODYNAMIC ASPECTS: STABILITY AND THEORETICAL CALCULATIONS

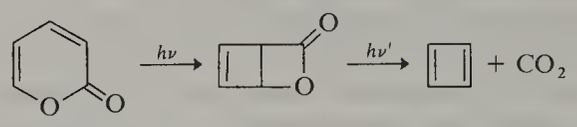
An indication of the stabilities of chemical structures can be gained simply by inspection of the compounds which are known to exist. It is apparent, from Section 2.01.1, that the presence of several nitrogen atoms substituting CH groups in aromatic ring systems is not conducive to stability, as a general rule. A distinction must be drawn between a compound's thermodynamic instability, relative to its products of decomposition formed in the absence of any other reagent, and its hydrolytic instability, or tendency to break down in the presence of water. Thus, 1,3,5-triazine requires quite high temperatures to decompose it to hydrogen cyanide, but water attacks it very rapidly, giving formamide and other products. The fused derivative (**25**) is also thermally quite stable, but hydrolytically unstable. When nitrogen atoms are adjacent, the very stable dinitrogen fragment can be produced. Although a concerted decomposition into three fragments is theoretically allowed, the extrusion of nitrogen and reorganization of the remaining four-atom chain has been observed in several instances (Scheme 1). Another thermodynamically stable fragment which may be eliminated



CH or N at angles and extremities

Scheme 1

is carbon dioxide. Here, however, chemists have usually resorted to photochemical ring contraction first, and photoelimination of the CO_2 fragment (equation 1).



(1)

Heats of combustion can give useful comparative data on the thermodynamic stabilities of heterocyclic compounds. For a useful short account the review of Pihlaja and Taskinen ⟨74PMH(6)199⟩ may be consulted. In practice, attempts to derive resonance energies for the aromatic heterocyclic systems have led to values which have been treated with scepticism even by their originators. The main problem (apart from the necessary sacrifice of a fairly large quantity of pure material) lies in the fact that the resonance energies arise as differences between two rather large numbers, one (the empirical heat of formation) being known to a fair degree of accuracy from the experimental data, the other (the 'theoretical' heat of formation) being arrived at by summation of a number of bond energies, all derived from other work on simpler compounds. The latter value is subject to a considerable degree of uncertainty. Some facts do however emerge from this sort of data. In a comparison of the isomeric diazines pyridazine, pyrimidine and pyrazine, Tjebbes found their heats of formation to be respectively 4397.8, 4480.2 and 4480.6 kJ mol^{-1} ⟨62ACS916⟩. The fact that pyridazine is almost 83 kJ mol^{-1} less stable than the other two is certainly a significant one. Unfortunately the data are not available to allow further comparisons between other series, such as the triazines, or the various diazanaphthalenes.

Molecular orbital calculations are dealt with by other contributors at varying length in other sections of this work. The principles involved do not differ in significant detail, as regards the various subdivisions of heterocyclic compounds (*i.e.* by ring size) which are used here. To some extent we share the cynicism expressed by the author of Chapter 2.04, in his introductory section. Theoretical calculations have tended to follow experimental results (or, at least, those that have been published have done so), and on occasions when the results have been reversed as a result of new findings, the calculations have usually been sufficiently agile to reverse their predictions also, by application of greater degrees of sophistication. The great value of MO calculations is their ability to indicate in which direction useful and/or interesting lines of research may lie.

2.01.3 THERMODYNAMIC ASPECTS: MOLECULAR SHAPE AND CONFORMATION

It would be out of place here to attempt a detailed description of the methods available for determining the geometry of molecules. For volatile compounds, gas-phase measurements can be performed using electron diffraction, while those which possess a permanent dipole moment are usually amenable to microwave spectroscopy. Crystalline compounds generally yield to X-ray or neutron diffraction. Although intermolecular forces can introduce some distortions, the large volume of data which have been provided by X-ray crystallography makes it a reliable source of information, especially when results from several related compounds can be compared. In recent years the faster computation methods which have become available have made results from this technique much more easily obtained. X-Rays have made their impact on heterocyclic chemistry since their early days, however; it is 60 years since the structure of hexamethylenetetramine was confirmed by their use. Because of the cumbersome and expensive apparatus required (the source of radiation is an atomic pile), there are far fewer structural results obtained by neutron diffraction. Since neutrons are more strongly diffracted by hydrogen atoms than are X-rays, they give more reliable data on the location of these atoms.

2.01.3.1 Fully Unsaturated Rings

The benzene ring has a fully symmetrical (D_{6h}) planar hexagonal carbon framework. Heteroatom substitution upsets this symmetry, but except in certain special cases, as for instance the 'thiabenzenes', the planarity of the ring is preserved. Although it is known

that the benzene ring can be deformed fairly substantially without losing its aromatic character, the electron orbital overlap which provides the bonding framework of the ring is at its best (*i.e.* of lowest energy), according to LCAO theory, when the π-orbitals are parallel, and this requires the ring to be planar.

In Figure 2 the bond lengths and internal bond angles are given for some of the simple azines. Gas-phase electron diffraction, microwave spectroscopy, or the two techniques in combination, provided the results on compounds which were sufficiently volatile but with insufficient tendency to crystallize at accessible temperatures; X-ray diffraction provided the remainder.

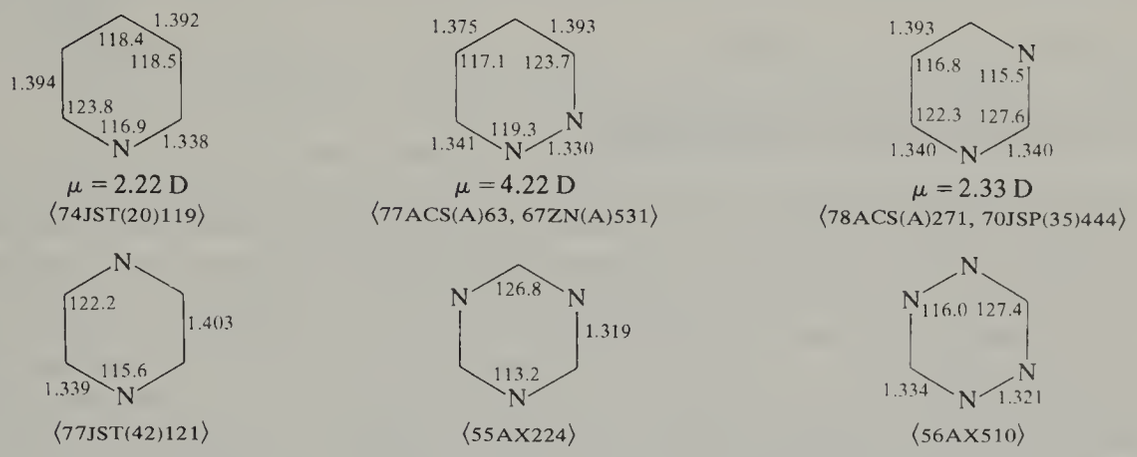


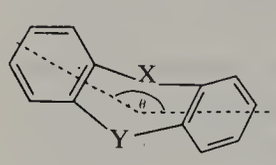
Figure 2 Molecular dimensions and dipole moments of some simple azines

The C—N bond length is slightly (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 towards the centre 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 centre of gravity than the carbons. An explanation in simple hybridization terms which has been advanced is that the lone pairs are held in orbitals which have slightly more than one third *s* character (as in pure sp^2), because of the electronegativity of the nitrogen atoms. This gives more *p* character to the hybrid orbitals forming the C—N bonds, thus decreasing the angle between them. The widening of the angles at the carbon vertices is concentrated at the carbons adjacent to the nitrogen. However, it should be emphasized that these are comparatively minor deviations from a completely regular hexagon.

Very few data are available on pyrylium or thiopyrylium salts, and these 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°). The short (133 pm) C—O bond lengths may be the deciding feature here, but it is probably premature to speculate, in the absence of data on the unsubstituted system. Thiopyrylium salts are characterized by long C—S bonds (*ca.* 172 pm) and a small CSC angle of *ca.* 104°. The geometry is similar to that shown by the phosphorins (phosphabenzenes) ⟨68AG(E)811⟩.

With two O, S or NR groups and two C=C double bonds in a ring, the systems are not aromatic, and there is no reason to expect them to be planar. In fact, the simple systems are little known, and, except for 1,4-dithiin, it is necessary to look for data from fairly heavily substituted or fused-ring systems. The most extensive studies have been made on the dibenzo-fused compounds, in which the presence of a sulfur atom in the central ring seems to ensure non-planarity of the system. Thianthrene (**40**; X = Y = S) and its various sulfoxides and sulfones have a fairly sharp dihedral angle between the planes of the benzene rings (θ = 128° in thianthrene ⟨63AX310⟩). Phenoxathiin (**40**; X = S, Y = O) and phenothiazine (**40**; X = S, Y = NH) are also non-planar (θ = 136° and *ca.* 158°, respectively) ⟨66AX429, 68CC833⟩, but dibenzodioxin (**40**; X = Y = O) is apparently planar (θ = 180°) ⟨78AX(B)2956⟩. Phenoxazine (**40**; 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 (**41**; X = O and S), respectively), planarity is found as expected. The same effect is seen with the alloxazines (**42**), which are planar, and the dihydroalloxazines (**43**), which, according to both X-ray and UV spectral studies, are not.



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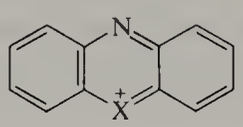

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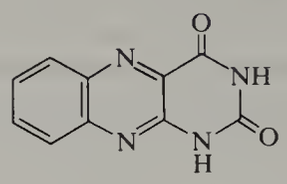

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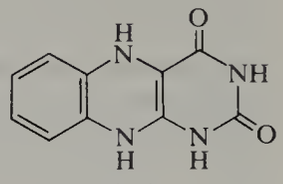


(43)

2.01.3.2 Partially and Fully Reduced Rings

Reduced six-membered heterocyclic systems have been studied extensively by a full range of physicochemical techniques. 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; the conformational 'energy profile' therefore contains some deep pockets which accommodate all but the vibrationally highly excited molecules, and the physicochemical studies of their conformational exchange have occupied the attentions of many research groups in the past two decades. Besides the techniques (X-ray, electron and neutron diffraction, and microwave spectroscopy) which, in principle at least, can provide all the structural dimensions of a molecule, the details of molecular conformations are often conveniently accessible by less direct methods. For instance, the coupling constant parameters from ^{1}H NMR spectroscopy provide an estimate of dihedral angles, and thus assist in building a model of the system. Vibrational and rotational spectroscopy, and dipole moment measurements, may also give information on molecular symmetry which allows a distinction to be made between various conformers. Solution and gas-phase measurements do not always give the same answers as crystal structure determinations, since the forces between molecules which are present in crystals may be sufficient to disturb a finely balanced equilibrium or to distort a flexible molecule from its normally preferred shape in free space.

The overall picture of the many results which have been obtained with hetero-substituted cyclohexane rings is a very consistent one. Cyclohexane itself in its lowest energy conformation adopts the so-called 'chair' conformation, as depicted in Figure 3 by the two outer formulae (a, b). These are contained in 'energy wells' *ca.* 42 kJ mol^{-1} deep. Another conformation, of low abundance in cyclohexane at normal temperatures, but which is important in some substituted derivatives, is the 'twist' form (c, d). This is *ca.* 22 kJ mol^{-1} less stable than the chair forms, and it lies on the lowest-energy pathway between them.

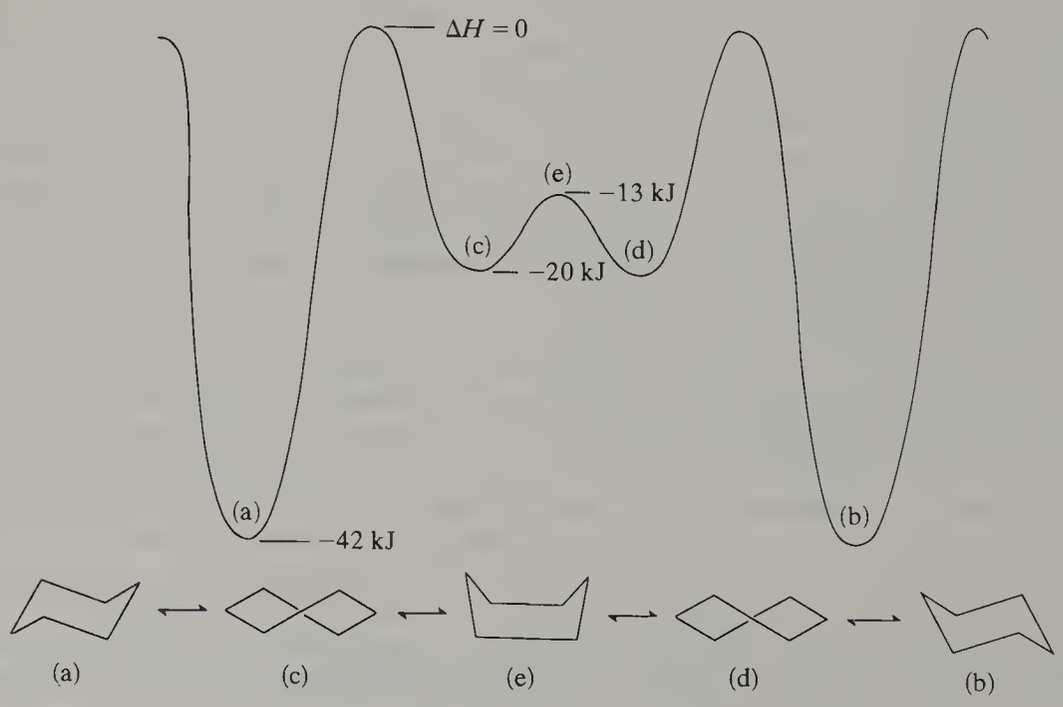
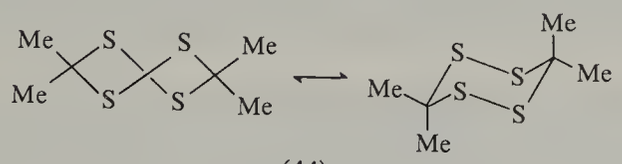


Figure 3 Shapes and relative energies of cyclohexane conformations

The twist form is also called the 'flexible' form, because without angle strain a left-handed twist (c) can be converted into a right-handed one (d), by way of a third form *ca.* 7 kJ mol^{-1} higher in energy (and actually not strictly an intermediate, since it occupies a maximum on the energy profile) which is the 'boat' form (e).

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. Crabb and Katritzky ⟨84UP20100⟩ have provided an up-to-date and full account of the results in this area, to which the reader should refer.

One interesting exception to the generalization that chair forms predominate in this series is shown by the tetrathian (**44**), which prefers the twist form in the solid phase, and also in CS_2 solution at 0 °C; both chair and twist forms coexist in solution, with a free energy difference of *ca.* 3.5 kJ between them ⟨67JA5978, 68JA2450⟩.



(**44**)

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). The reader is referred to the relevant monograph chapters for details. Noteworthy points are as follows:

(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 to the conformations of carbohydrates ⟨B-71MI20100, B-83MI20100⟩.

(3) Since a nitrogen atom 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 predominantly occupies an axial site. Solvation can, however, considerably alter this picture.

2.01.4 SPECTROSCOPIC STUDIES

2.01.4.1 NMR Spectra

The account we give here of the NMR spectroscopy of heterocyclic six-membered rings is necessarily a very sketchy one, since this spectral technique has been so widely used. It has proved invaluable, for many years, in the identification and characterization of new compounds, and it is also a subject of study in its own right. Fortunately, there exist many detailed monographs on the subject, some of which are listed in the references. We hope that the most important aspects are covered here, but would caution the reader against using the data quoted without checking against the original work, or at least the specialized monographs. For one thing, it has not been possible to ensure that data drawn from different sources are strictly comparable. Solvent effects can be quite large, particularly in proton spectra, where the range of chemical shift covered is rather a small one. To eliminate the effects of solute association, extrapolation of the observed data to infinite dilution in carbon tetrachloride is desirable, but all too often this is not feasible. Deuterochloroform is a more powerful, and for other reasons also a more suitable, solvent, particularly for ^{13}C spectroscopy, but its polarity inescapably affects solute parameters. Even if a 'universal solvent' were known, which would allow all organic compounds to be run under standard conditions, its solvating power would imply strong interactions with the solute molecules, and reduce the value of any theoretical model used to explain data correlations in terms of the isolated molecules.

2.01.4.1.1 ^1H spectra

The ^1H NMR spectra of aromatic six-membered heterocycles have been measured extensively. The considerable amount of data which were available by 1972 were compiled by Batterham in an excellent critical monograph ⟨B-73NMR⟩, which provides the basis for the general account which follows here.

(i) Chemical shifts

The protons on the benzene ring are generally supposed to experience a small deshielding effect due to the aromatic ring current, which brings the chemical shift of the benzene protons to δ 7.24 p.p.m. It is not possible (or at any rate not easy) to separate the effects arising from changes in the ring current from the other effects (inductive, field, anisotropic, *etc.*) which heteroatom substitution produces on the chemical shifts of ring protons, and it seems to be usual to assume that the same ring current persists in the polyazabenzenes as in benzene itself. It should be noted that the 'ring current' concept is by no means universally accepted, notwithstanding the detailed amount of theory which has been built around it ⟨*cf.* B-73NMR, p. 11⟩.

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 *ortho* and *meta* effects of a single nitrogen atom. (This particular phenomenon is attributed to the presence of two electron lone pairs on adjacent atoms, and numerous other effects arising from this are known, and can be found detailed in the appropriate monograph chapters.) Tables 1 and 2 summarize the chemical shifts of the protons in various aza heterocycles. For further details, and for a discussion of the effects of other substituents, the monograph of Batterham should be consulted.

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

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

[a] Measured in $CDCl_3$ (remainder in CCl_4).
[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 2 ^1H Chemical Shifts of Protons on the Heterocyclic Rings of Simple Benzazines (*cf.* naphthalene, column 1)

Position	$\delta(^1H)$ (p.p.m. TMS) (Position of N atoms indicated)							
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

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.

(ii) 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 they are of intermediate value (*ca.* 6.5 Hz).

Coupling constants between protons in saturated and partially saturated six-membered rings have frequently been used to provide information on ring conformations. The Karplus equation, one form of which is $^3J = A\cos^2\phi$, is an empirical relationship connecting the vicinal (three-bond) coupling J(H—C—C—H) with the dihedral angle (ϕ) between the two CH bonds, and, suitably modified for the presence of electronegative elements if necessary, it has proved very valuable in determining the geometry of slowly (low-temperature measurements) and rapidly (high temperature) inverting six-membered systems. When a molecule is in rapid equilibrium between conformations, a measured coupling constant is a time-average of the coupling constants appropriate for the several conformations (with their ϕ values) involved. Thus, for an inverting system of type (a) $\rightleftharpoons$ (b) (Figure 3), J_{cis} is the time-average of $J_{ax-eq'}$ and $J_{eq-ax'}$, while J_{trans} averages $J_{ax-ax'}$ and $J_{eq-eq'}$. Lambert has pointed out that the ratio R, given by J_{trans}/J_{cis}, should be independent of the electronegativities of the adjacent elements X and Y, since their effects are proportionately the same on both J_{cis} and J_{trans}, and that the R values can be used as a guide to molecular shapes and distortions ⟨71ACR87⟩.

The 'direct' coupling constants (D_{ij}) of pyridine, obtained from a spectrum of the molecule in a nematic liquid crystal solvent, are listed in Batterham's monograph ⟨B-73NMR, p. 10⟩. These data provide information about the geometry of the molecule, as the couplings are proportional to the inverse cube of the distance (r_{ij}) between the nuclei.

The one-bond ^{13}C–^{1}H couplings are dealt with in the next section.

2.01.4.1.2 ^{13}C spectra

Application of ^{13}C NMR spectroscopy to heterocyclic chemistry has developed very rapidly during the past 15 years, and the technique is now used almost as routinely as ^{1}H NMR spectroscopy. There are four main areas of application of interest to the heterocyclic chemist: (i) elucidation of structure, where the method can be particularly valuable for complex natural products such as alkaloids and carbohydrate antibiotics; (ii) stereochemical studies, especially conformational analysis of saturated heterocyclic systems; (iii) the correlation of various theoretical aspects of structure and electronic distribution with chemical shifts, coupling constants and other NMR derived parameters; and (iv) the unravelling of biosynthetic pathways to natural products, where, in contrast to related studies with ^{14}C-labelled precursors, stepwise degradation of the secondary metabolite is usually unnecessary.

As with any other technique, there are problems associated with ^{13}C NMR spectroscopy, and three in particular are important with respect to its application to heterocyclic chemistry. First, and by no means insignificant, the location of published data for even the small number of heterocyclic compounds which have been studied so far can be tedious and time-consuming. This problem should ease, however, as more comprehensive compilations and 'atlases' of spectral data, including computerized data banks, become available. Second, many heterocyclic compounds have negligible solubility in any solvent that can be used for NMR measurements, and hence the spectra cannot be recorded. Again, this problem should ease as 'magic angle of spin' instruments become more widely available, thus enabling the spectra of solid samples to be recorded. Finally, largely as a consequence of the highly polar nature of most heterocyclic compounds, ^{13}C chemical shift values can vary quite substantially depending on the nature of the solvent used in the experiment.

(*i*) *Aromatic systems*

(*a*) *Chemical shifts.* Chemical shift data for a number of monocyclic, unsubstituted six-membered heteroaromatic compounds are given in Table 3. Two general trends are immediately obvious from these data. First, in general, and in accordance with theoretical calculations and observed reactivity patterns, 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. Second, 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.*

Table 3 ^{13}C 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)							
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

Table 4 ^{13}C 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 *N*H-keto form.

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 4. Fusion of an aromatic or heteroaromatic ring to an azine changes the electronic distribution in the azine portion of the resultant molecule. The chemical shifts of remaining ring carbon atoms in the azine portion of the molecule are consequently different from those in the parent azine, although the difference is usually less than 10 p.p.m. Shift data for a number of common condensed azine systems are given in Figure 4.

Protonation of azines results in shielding of the α carbon atoms and deshielding of the β and γ carbon atoms (Table 5), particularly the latter, and these effects have been accounted for in terms of additivity parameters. The upfield protonation parameter for the γ 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.

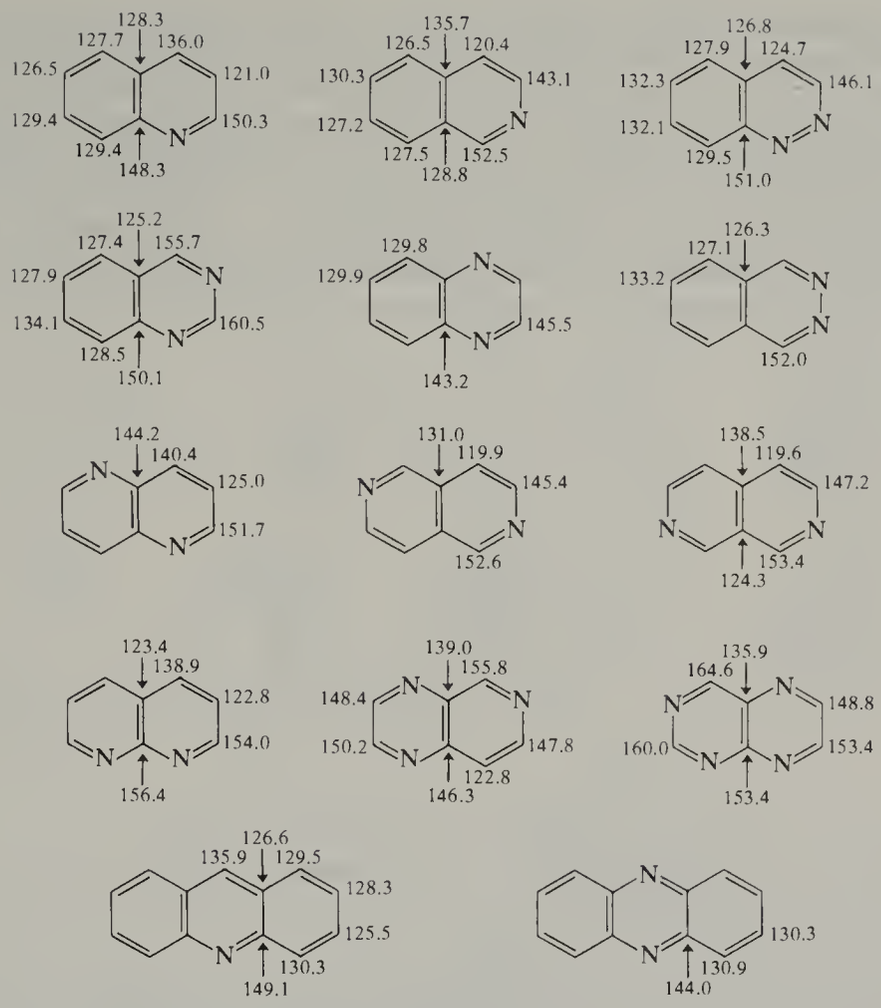


Figure 4

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 5). A further important general trend in the azines arises on *N*-oxidation, which

Table 5 ^{13}C 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

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 (Figure 5). The corresponding conjugate acids of the *N*-oxides have chemical shifts very similar to those of the protonated parent heterocycles.

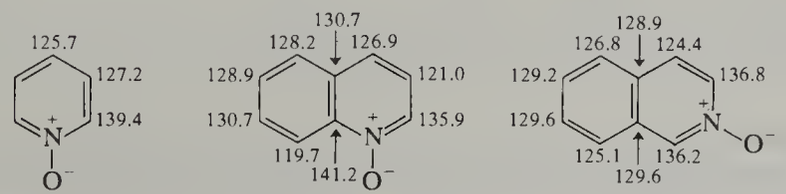


Figure 5

The azines have been the most intensively studied of the six-membered heteroaromatic systems. It is obvious from the nevertheless not unsubstantial amount of data available on the 'less aromatic' oxygen and sulfur systems, especially the pyrones and thiopyrones, that these latter compounds 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 Figure 6.

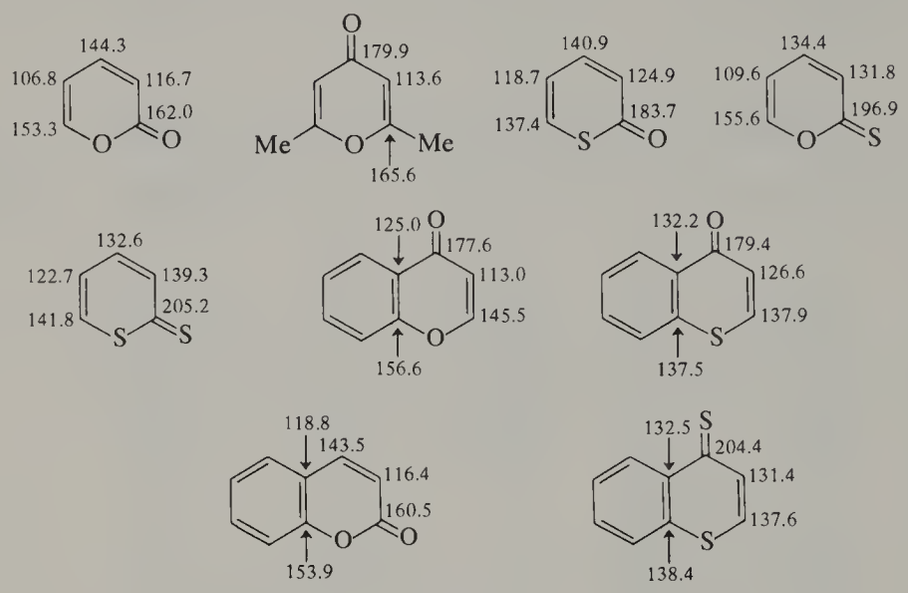


Figure 6

(*b*) *Coupling constants.* In contrast to ^{1}H NMR spectroscopy, measurement and interpretation of ^{13}C–^{1}H coupling constants is far from routine. This is at least partly due to the fact that, in conjunction with other spectroscopic and chemical information, ^{13}C chemical shift data and simple signal multiplicities are often sufficient for unambiguous structure assignment. Spectra run under fully or partially proton-decoupled conditions are more intense, and easier to analyze, than those in which full proton coupling is present. In many other cases, however, such as biosynthetic studies, stereochemical and mechanistic investigations, and structure elucidation of complex natural products, use of ^{13}C–^{1}H and, possibly, ^{13}C–^{13}C coupling constants may be necessary for complete interpretation of spectral data. Single frequency proton decoupling, for example, which often reveals longer range couplings, can be very useful in distinguishing between carbon atoms of similar chemical shift. Single-bond ^{13}C–^{1}H coupling constants for the six-membered heteroaromatic compounds lie in the approximate range 150–220 Hz, the magnitude varying with substituent electronegativity. Longer range couplings are much smaller (up to *ca.* 12 Hz), and the values are difficult to predict. Data for simple azines are summarized in Table 6.

Table 6 One-bond ^{13}C–^{1}H Coupling Constants (Hz) in the Simple Monocyclic Aromatic Azines (*cf.* 159 Hz for benzene)

Position	*J* (Hz) (Position of N atoms indicated)						
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

(*ii*) *Saturated systems*

A large amount of data are available on the ^{13}C spectra of saturated six-membered ring systems. The subject has been reviewed in detail by Eliel and Pietrusziewicz ⟨79MI20101⟩.

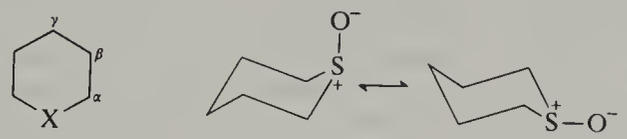
A paper by Lambert *et al.* ⟨76JA3778⟩ lists the chemical shifts of the α, β and γ-methylene carbon atoms of a very wide range of compounds of type (**45**); here we summarize the data for the compounds relevant to this volume (see Table 7).

Table 7 ^{13}C Chemical Shifts (δ, p.p.m. from TMS) in Saturated Six-membered Rings (**45**)[a]

X in (**45**)	*Shift of C at position* 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 27.2, and the signals of the α, β and γ carbons of tetrahydrothiopyran (**45**; 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 (**46**) (the preferred conformation) or equatorial (**47**): 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.



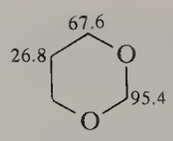
(**45**) (**46**) (**47**)

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 (**45**; X = NH) the α carbon signal is shifted by about 20 p.p.m., to *ca.* δ 47.7, while in *N*-methylpiperidine (**45**; 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 (**45**; X = NH). The nitroso compound (**45**; 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 (**45**; 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. Apart from the case of two α oxygen atoms—in 1,3-dioxane (**48**) the shift of C-2 is δ 95.4 instead of δ 108 which a double shift of 40 p.p.m. would require—predictions of shift made on this basis are usually accurate to within 5 p.p.m. and are generally much closer than this. Observed shifts for a few representative examples are shown in structures (**48**)–(**52**).

Many studies have been made of substituent effects in saturated heterocyclic six-membered rings. For a detailed discussion the review of Eliel and Pietrusziewicz should be consulted ⟨B-79MI20101⟩. Particularly noteworthy in studies of conformation and configuration



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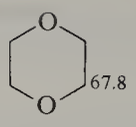

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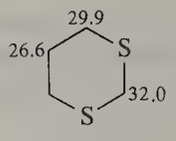

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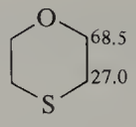

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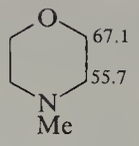
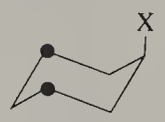


(52)

is the so-called 'γ-gauche effect'. The operation of this effect is to induce an upfield (screening) shift of the ^{13}C signal from a ring carbon *meta* to an axial substituent (structure **53**). The amount of shielding varies with the substituent atom. The shielding experienced by the γ carbon atom caused by an electronegative heteroatom *para* to it (structure **54**) is also a manifestation of the γ-gauche effect.



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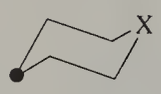


(54)

One-bond couplings ($^1J_{CH}$) in saturated systems do not seem to have been investigated extensively. The value 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.

2.01.4.1.3 Nitrogen NMR spectra

Because of the importance of nitrogen in heterocyclic chemistry it would be reasonable to expect the nitrogen NMR of such compounds to be well developed. However, experimental difficulties have hindered progress in this area. Both the stable nitrogen isotopic nuclei have magnetic moments, but the predominant isotope (^{14}N, 99.64% natural abundance) also has an electric quadrupole moment, and as a result of this the NMR signals are usually very broad, sometimes so much so as to be missed altogether. The ^{15}N isotope has a spin of $\frac{1}{2}$ and does not suffer from this disadvantage, giving sharp lines as a rule. But it is of very low natural abundance (0.36%, *i.e. ca.* one third that of ^{13}C, relative to ^{12}C), and furthermore, like the ^{14}N nucleus, it is of low sensitivity (*ca.* 0.1% of that of the proton). The Overhauser effect, which on decoupling of attached protons enhances the signals from the ^{13}C nuclei, can, unless precautions are taken, actually diminish ^{15}N signals. Although advances in experimental technique have solved many of these problems, it is still not a routine matter to obtain nitrogen resonance data on heterocyclic systems. Much of the early data were obtained with ^{14}N spectra, but now ^{15}N measurements at natural abundance are more common, and this technique is less likely to lead to errors arising through the large linewidth of the ^{14}N signals.

Good reviews of the various aspects of nitrogen NMR appear in the monograph of Witanowski and Webb ⟨B-73MI20100⟩; most relevant to the organic chemist is the chapter on the nitrogen chemical shifts in organic compounds. A more recent volume on ^{15}N spectroscopy by Levy and Lichter is also useful ⟨B-79MI20102⟩.

Some nitrogen chemical shifts relating to azines are given in Table 8. More detailed information can be found in the review of Witanowski *et al.* The following trends and observations are noteworthy:

(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 8 Nitrogen 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 ⟨80HCA504⟩.
[b] Screening constants, p.p.m. 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⟩, and it would be unwise to rely on this generalization.)

The couplings of other magnetic nuclei to nitrogen have been studied; the reader should refer to Axenrod's chapter in the monograph of Witanowski and Webb for details ⟨B-73MI20100⟩. 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⟩. Since ^{14}N has a spin number $I = 1$, coupling to a proton (when observed) gives rise to a triplet in the proton spectrum, with coupling constant related to the corresponding coupling to ^{15}N by the equation $J(^{14}N) = -0.713\,J(^{15}N)$. The proportionality constant is the ratio of the magnetogyric constants for the two nuclei, and is negative (this is of theoretical, but seldom of any practical, significance).

2.01.4.1.4 Other nuclei

Fluorine and phosphorus occasionally appear attached to, or as part of, heterocyclic rings. However, very little systematic attention has been paid to them, in the area of the azines, and it would not be appropriate to detail the work here. With other nuclei (^{2}H, ^{3}H, ^{29}Si, *etc.*) information is still more scarce, and reference should be made to the specialized reviews in this area.

2.01.4.2 Nuclear Quadrupole Resonance

Atomic nuclei which possess spin quantum numbers greater than $\frac{1}{2}$ have quadrupole moments also, and direct transitions between nuclear quadrupolar energy levels can be observed under favourable conditions. The nucleus of greatest interest to the heterocyclic chemist is that of nitrogen. Unfortunately, its quadrupole moment is rather low, and spectra are difficult to obtain, even in the most favourable cases. Chlorine as a substituent has been far more fully studied, and the resonances have been used as a probe of electronic interactions between the chlorine atom and the heterocyclic nucleus, in a number of cases. There is still, however, a great paucity of data on NQR spectra of heterocyclic molecules, and the great majority of the authors of the specialist reviews in this volume have been obliged to omit mention of the technique altogether. We refer the reader who wishes to learn more about the subject to the brief review by Lucken ⟨63PMH(2)89⟩.

2.01.4.3 IR and Raman Spectra

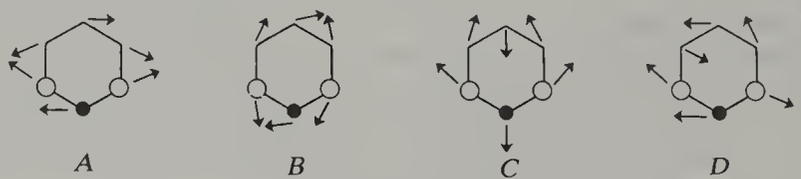
Work on the vibrational spectra of the six-membered aromatic heterocycles has been well summarized by Bellamy ⟨B-75MI20100⟩, who refers to detailed reviews by Katritzky and Ambler ⟨63PMH(2)161⟩ and Katritzky and Taylor ⟨71PMH(4)265⟩. Systematic studies of the IR spectra of substituted pyridines were made in the 1950s and 1960s, when it was established: (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 (called 'ring-breathing' by Bellamy) for pyridines and pyrimidines are listed in Table 9, together with the corresponding bands of a monosubstituted benzene. More vibrations are possible for the quinolines and isoquinolines, and seven or eight bands in the region 1650–1350 cm^{-1} have been described for these compounds.

Table 9 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] Vapour phase. [c] Various media.



A *B* *C* *D*

Heteroatoms indicated by filled circles (pyridines) or open circles (pyrimidines)

A great deal of attention has been paid to the IR spectra of six-membered heterocycles containing one or more carbonyl groups in the ring. Although in these cases (for instance, the pyridin-2- and -4-ones, the pyrones and pyrimidones) one of the higher-frequency bands in the 1500–1700 cm^{-1} region can usually be assigned to the carbonyl stretching vibration, 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. Simple 2-pyrones show the most unambiguous carbonyl bands (at *ca.* 1730 cm^{-1}).

Assignments have been suggested for the absorptions of many of the saturated heterocyclic six-membered rings ⟨63PMH(2)161, p. 240, 71PMH(4)265, p. 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 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.

2.01.4.4 UV and Related Spectra

Although the electronic spectra of organic compounds are simple to obtain, and therefore have been recorded as a matter of routine for many years, the information they reveal is meagre, in comparison to other forms of spectroscopy, and furthermore, while the basic principles are well enough understood, the detailed interpretation of the spectra is frequently uncertain. However, empirical correlations and qualitative explanations have been of value in this area, as in others, and it is at this level that this section is aimed. UV spectroscopy is of particular value in the field of natural product chemistry, in which an alkaloid, for instance, can usually be assigned to its structural class simply by examination of its absorption spectrum and comparison with those of others. We direct the reader's attention to treatments by Murrell ⟨B-63MI20100⟩ and Mason ⟨63PMH(2)1⟩ of the theoretical aspects. Jaffé and Orchin ⟨B-62MI20100⟩ give, *inter alia*, semiempirical descriptions of the spectra of some aza-substituted polyacenes. An extensive listing of the UV maxima of a wide variety of heterocycles has been compiled by Armarego ⟨71PMH(3)67⟩.

The spectra of saturated heterocycles are generally fairly featureless, with amine $n \rightarrow \sigma^*$ absorptions and those transitions associated with sulfur showing up weakly, while saturated ethers are usually transparent down to 210 nm.

The aromatic 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 they are sometimes obscured by the longer-wavelength $\pi \rightarrow \pi^*$ bands. In hydrogen bonding solvents they are further weakened, and shifted hypsochromically (to shorter wavelengths) from their positions in hydrocarbon solvents. The $n \rightarrow \pi^*$ transitions are frequently difficult to locate, except when two aza-nitrogen atoms, each with a lone pair of electrons, are adjacent. In these cases the two filled non-bonding orbitals are considered to interact, forming a higher-energy and a lower-energy orbital (see Figure 7). Transitions from the higher of these orbitals into the lowest vacant π^* level thus require less energy than if the lone pairs were separated. As a result 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 colour. Here the multiple aza substitution lowers the lowest π^* (π_4) orbital considerably, thus narrowing the gap between it and the non-bonding levels. Table 10 gives the positions of the $n \rightarrow \pi^*$ absorptions of a number of the simpler aza-aromatics.

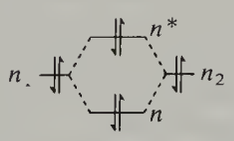


Figure 7 The splitting of the adjacent non-bonding orbitals in pyridazine

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 10 lists the principal bands in the spectra of some representative

Table 10 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), 5.42 (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⟩.

monocyclic systems, with those of benzene added for comparison. In the aza derivatives of the higher polyacenes, UV spectral comparisons have frequently been used as an indication of structural correspondence ⟨58HC(12)551⟩.

The UV spectrum of a complex conjugated molecule is usually observed to consist of a few broad band systems, often with fine structure, which may be sharpened up in non-polar solvents. Such a spectrum can often be shown to be more complex than it superficially appears, by investigation of the magnetic circular dichroism (MCD) spectrum, or by introduction of dissymmetry and running the optical rotatory dispersion (ORD) or circular dichroism (CD) spectrum. These techniques will frequently separate and distinguish overlapping bands of different symmetry properties ⟨71PMH(3)397⟩.

Of interest, and occasional importance (in whiteness enhancers, for instance), are the fluorescent properties of heterocyclic compounds. Fluorescence is quite frequently found in the compounds relevant to this volume; the acridines and acridones show it particularly often, but it appears in a number of very diverse systems. The fluorescence and phosphorescence of heterocyclic molecules have been reviewed by Schulman ⟨74PMH(6)147⟩.

2.01.4.5 Photoelectron Spectra

Photoelectrons are those electrons which are produced when an energetic photon of radiation strikes a molecule, and the analysis of the spectrum of energies which they possess gives rise to the photoelectron spectrum. Since electrons are in general fairly firmly bound within molecules, the exciting radiation must be in the UV region of the spectrum, even when peripheral, or valence shell, electrons are ejected. For the lower-lying core electrons still more energetic radiation is needed, and for this purpose X-rays are used. Thus two main types of PE spectroscopy can be defined: UPS or ultraviolet photoelectron spectroscopy, which probes the valence shell electrons, and XPS or X-ray photoelectron spectroscopy, which is mainly concerned with the low-lying core electrons. The latter type is also known as ESCA, which stands for electron spectroscopy for chemical analysis. It is useful for this purpose (chemical analysis) because the energies of the core electrons are very characteristic of the atoms from which they arise, regardless of their chemical combination. It is UPS that provides the results of greatest interest to the heterocyclic chemist. A useful introductory description of the technique is given by Heilbronner *et al.* ⟨74PMH(6)1⟩, who list the various heterocyclic molecules studied by the method up to 1973. We also refer the reader to Chapter 2.04 by Johnson in this volume, which provides a fuller description of PE spectroscopy than the present one, particularly as it relates to the pyridines, and to Ballard's text ⟨B-78MI20100⟩.

The six-membered aromatic azines have received a great deal of attention, and their UPS spectra are probably as well understood as any. Most authors assign the most readily ionized level of pyridine to 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.

PE spectroscopy has also been applied to the study of the conformational equilibria of saturated heterocyclic six-membered rings, and in particular of hexahydropyridazines. The

results, obtained by Nelsen *et al.* ⟨73JA2013⟩, are discussed in Heilbronner's review ⟨74PMH(6)1⟩, and need not be repeated here.

PE spectra are nearly always obtained from gas-phase samples, although solution techniques are available ⟨76MI20100, 82MI20100⟩. It is amenable for application even to transient species, and at both high and low temperatures. It must however be observed that the results, and in particular their interpretation, are not so readily accessible to the majority of organic chemists as are those of, for instance, NMR or IR spectroscopy. Perhaps for this reason they tend to be treated with some caution, except by the main practitioners in the field. Comparison of assignments, even in the fundamental case of pyridine, for instance ⟨74PMH(6)1, B-78MI20100⟩, reveals discrepancies over which agreement would be desirable.

2.01.4.6 Microwave Spectra

This particularly valuable technique for studying molecules which possess permanent dipole moments in the vapour phase has been reviewed on many occasions. For its application to heterocyclic compounds the excellent account by Sheridan ⟨74PMH(6)53⟩ should be consulted.

Microwave spectroscopy yields several types of information of value to the organic chemist. Firstly, there are the molecular dimensions, which are usually obtainable to a good degree of accuracy by comparison of the moments of inertia of the molecule and its various isotopically substituted species. Then, by study of the effects of an electric field on the spectrum (the Stark effect) the magnitude and direction of the dipole moment can be obtained, again with accuracy unattainable by other methods. The information provided about 'molecular force fields' is also valuable in conformational studies, being able to probe energy barriers far lower than those accessible by NMR methods. The Zeeman effects, produced on the spectrum by the application of a magnetic field to the sample, and the nuclear quadrupole coupling effects, are mainly of interest to the specialist in these areas.

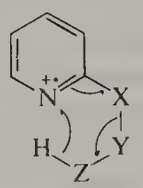
2.01.5 MASS SPECTROMETRIC STUDIES

The behaviour of the simple azines and their benzo analogues on electron impact under mass spectrometric conditions is now known to be much more complex than had been previously suspected and a variety of fascinating processes has been observed. 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 are also common, and the ease with which these various processes occur means that great care must be exercised in the interpretation of results from studies of fragmentation mechanisms using labelled compounds. There is a wide variety of textbooks and reviews on mass spectrometry available. Budzikiewicz, Djerassi and Williams devote several chapters to heterocyclic compounds ⟨B-67MI20100⟩, and two reviews by Spiteller are worthy of attention ⟨66AHC(7)301, 71PMH(3)223⟩.

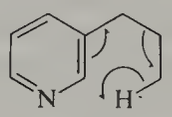
The mass spectra of the aromatic six-membered heterocycles and their benzo analogues reflect the stability of the ring systems, with the molecular ion in many cases also being the base peak. Fragmentation of the azines by loss of HCN ($M-27$) is the common pathway and for pyridine the $M-27$ ion is the only fragment of any significance in the spectrum apart from the molecular ion. Fragmentation by successive losses of molecules of HCN is common 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 thiopyrylium salts, due partly no doubt to the involatility of the compounds; elimination of CO or CS is the major fragmentation pathway.

Substituent effects are in some instances predictable and/or easily rationalized, but are more subtle in other cases. *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.* (**55**), and this is a general process. Retro-ene reactions with 3- and 4-substituted azines, *e.g.* (**56**), are generally of little significance.

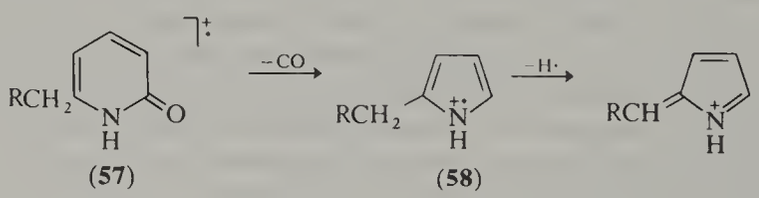


(**55**)

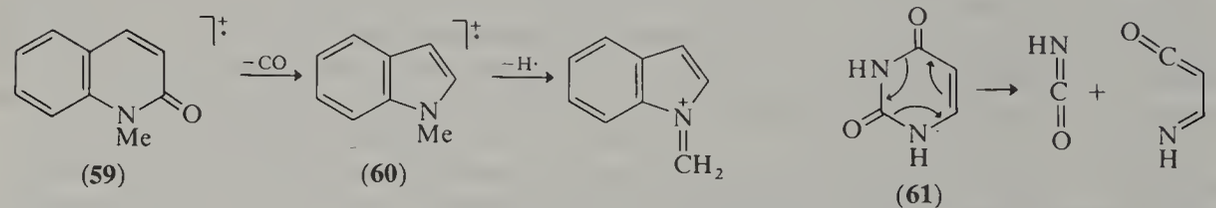


(**56**)

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.* (**57**) → (**58**) and (**59**) → (**60**), but with compounds such as uracils and their benzo analogues, the 1-substituted 4-quinazolinones and quinazolinediones, the retro-Diels–Alder fragmentation is favoured, *e.g.* (**61**), 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 appears to be common. Amino groups are usually eliminated as HCN.



(**57**) (**58**)

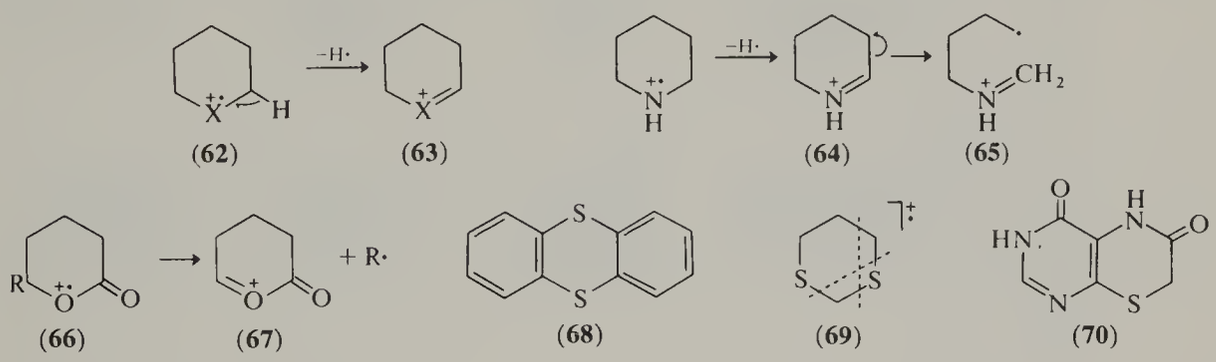


(**59**) (**60**) (**61**)

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-hydroxycoumarins, 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 the monocyclic dihydroheterocycles.

The fully saturated heterocyclic systems have not so far been studied in great detail and in many instances the fragmentation pathways and the structures of the fragment ions are not known with any degree of certainty. Loss of hydrogen atoms from α carbons, (**62**) → (**63**), and β-cleavage, (**64**) → (**65**) and (**66**) → (**67**), 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. In some instances the mode of cleavage is fairly straightforward: thianthrene (**68**), for example, fragments by two successive losses of sulfur atoms to give the biphenylene radical cation, and two of the major fragments from 1,3-dithiane (**69**) are $(M-CH_2S)^{+\cdot}$ 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 (**70**), for instance, fragments with loss of COS.

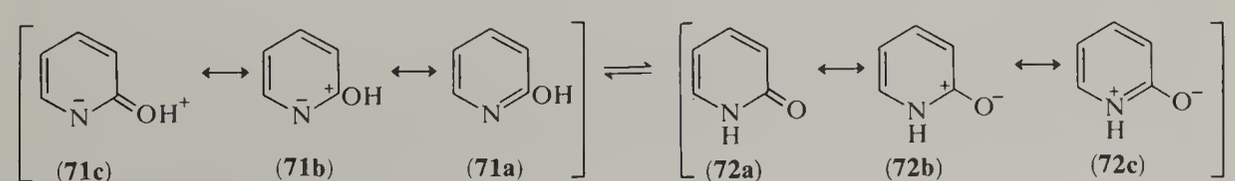


(62) (63) (64) (65) (66) (67) (68) (69) (70)

2.01.6 TAUTOMERISM

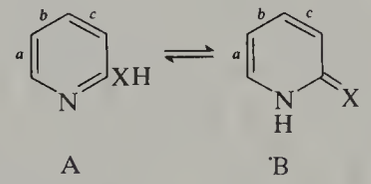
The tautomerism of six-membered heterocycles has been referred to elsewhere (Section 2.01.1), in connection with the variety of aromatic structures available to heterocyclic compounds. In this section we consider the matter in more detail. For a fuller discussion the reader should consult the monograph by Elguero *et al.* ⟨76AHC(S1)⟩ which thoroughly covers work on the subject up to 1976.

Table 11 summarizes the main results on the tautomerism of mono-hydroxy-, -mercapto-, -amino- and -methyl-azines and their benzo derivatives, in water. At first sight the equilibrium between 2-hydroxypyridine (**71**) and pyridin-2-one (**72**) is one between a benzenoid and a non-benzenoid molecule respectively (**71a** ⇌ **72a**). However, the pyridinone evidently has a continuous cyclic *p*-orbital system, containing six π-electrons, the usual aromatic count, if the carbonyl group contributes none. This assumption implies the formula (**72b**), from which by redistribution of electrons we arrive at (**72c**), which has the same benzenoid system as (**71a**). Further canonical forms (**71b**, **71c**) can be drawn of (**71**) which correspond to the 'non-benzenoid' forms of (**72**). The elusive property of 'aromaticity' is therefore possessed by both tautomers, although not necessarily by both equally. When the carbonyl oxygen of (**72**) is replaced by less electronegative atoms, as in the imine tautomers of amino heterocycles, or the methylene tautomers of methyl derivatives, the tendency towards polarization in forms corresponding to (**72b**) and (**72c**) is considerably less, and the amino and methyl tautomers are therefore favoured in most instances.

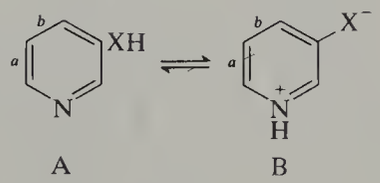


(71c) (71b) (71a) (72a) (72b) (72c)

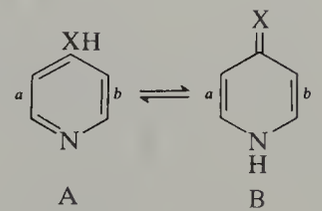
Table 11 Tautomeric Equilibria of some Monofunctional Azines and Benzazines[a]



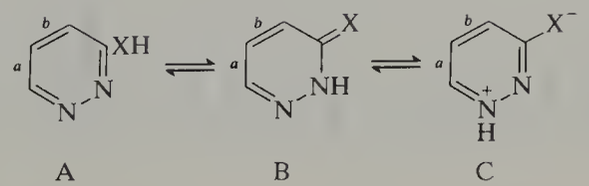
X =	O	S	NH	CH_2
Parent	B (3.0)	B (4.7)	A (*ca.* 6)	A (13.3)
Benzo[*a*]	B (3.9)	B (5.1)	A (4.3)	A (9.4)
Benzo[*b*]	B (low)	B (3.0)	—	—
Benzo[*c*]	B (4.8)	B (5.8)	A (3.8)	A (9.5)
Dibenzo[*a*,*c*]	B (3.9)	—	A (2.8)	A (high)



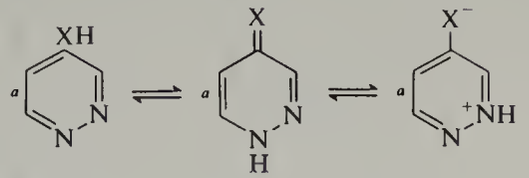
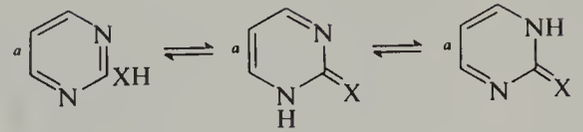
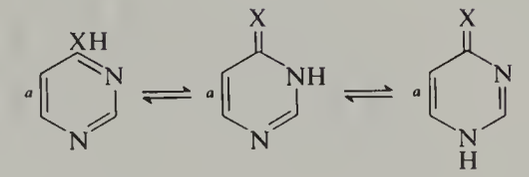
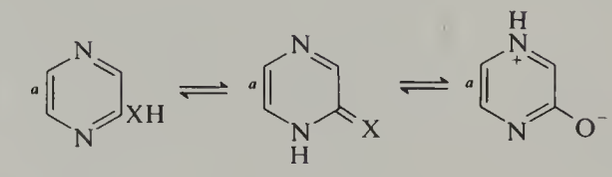
Parent	B (0.1)	B (2.2)	A	A
Benzo[*a*]	A (*ca.* 1)	B (1.5)	A	A
Benzo[*b*]	B (*ca.* 0.5)	—	A	A



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



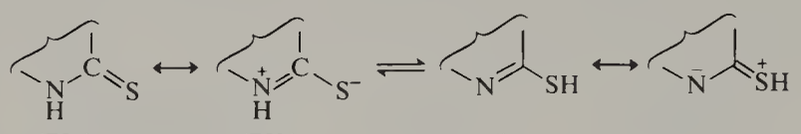
Parent	B (4.3)	B	A	
Benzo[*a*]	B (2.6)	—	A (8.3 *vs.* B)	
Benzo[*b*]	B	B	A	

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

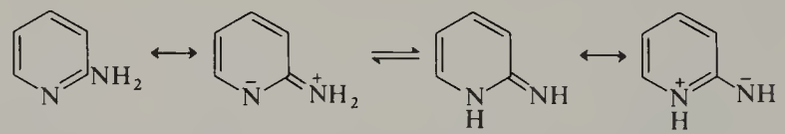
Since polar solvents would be expected to stabilize polar forms, a retreat towards the hydroxy tautomer (**71**) would be predicted in solvents less polar than water, and in the vapour phase. This is borne out in practice: at equilibrium both 2- and 4-hydroxypyridine (as well as the 3-hydroxy compound, which even in water exists as an approximate 1:1 mixture of OH and NH forms) exist as such, rather than as the pyridinones. However, the 2- and 4-quinolinones remain in the NH (keto) forms, even in the vapour phase. Hydrocarbon or other solvents of very low polarity would be expected to give results similar to those in the vapour 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 ⟨77ACR186, 78JOC177⟩.

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 (**73a** ↔ **73b**) is strongly polarized towards the form (**73b**), on account of the generally weak C=S π-bond in (**73a**). This tends to increase the acidity of the proton on the nitrogen atom, and as a result the tautomerism of thiol–thione equilibrium constants in heterocyclic systems carrying these functions favours the thione form over the thiol (**74**) to an extent only slightly greater than that found in the hydroxy–oxo equilibria. In the vapour phase, 2- and 4-pyridinethiols predominate over the thiones ⟨76JA171⟩.

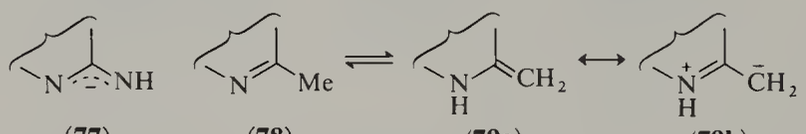


(**73a**) (**73b**) (**74**)

In amine–imine systems (**75** ⇌ **76**) the mobile proton can in principle be located at either of the two basic nitrogen sites in the anion (**77**). Since the canonical form with aromatic (benzenoid) structure is polar in the imine (**76b**) and non-polar in the amine (**75a**), the amine structure should be favoured, particularly in non-polar solvents. This seems generally to be the case, although solvent and medium effects do not appear to have been investigated; the results available at the present time refer mainly to aqueous and other polar solvents.



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



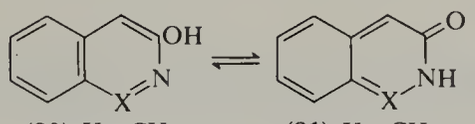
(**77**) (**78**) (**79a**) (**79b**)

The tautomerism of a methyl group α or γ to a ring nitrogen (**78** ⇌ **79**) is still less favourable than that of the amine; simple valence and electronegativity considerations of the type employed above suggest that there is little aromaticity associated with the methylene tautomer (**79**). These tautomers are therefore present to only a very small extent at equilibrium. However, because ionic bond-making and bond-breaking processes between carbon and hydrogen are much slower than between nitrogen or oxygen and hydrogen, the methylene tautomers can sometimes be produced, and kept for long enough for their spectra to be obtained, before they decay to the corresponding methyl compounds ⟨*e.g.* 82TL1943⟩.

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 towards alternative forms. Substituents may also favour 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 **79b**).

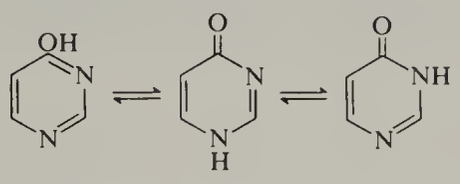
Benzo-fusion to a heterocyclic ring involved in tautomerism has the effect of steering the equilibrium in directions which tend to retain the full aromaticity of the benzene ring.

Thus, while the 3-hydroxyisoquinoline–3-isoquinolinone equilibrium (**80** ⇌ **81**) and that of the cinnoline derivatives (**82** ⇌ **83**) favour the keto forms (**81**, **83**), 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.

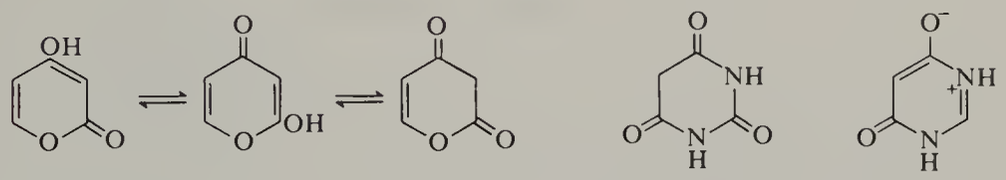


(**80**) X = CH (**81**) X = CH
(**82**) X = N (**83**) X = N

Extra nitrogen heteroatoms in the ring provide alternative sites for the tautomeric proton. 4-Hydroxypyrimidine, for instance, can exist as such (**84**), or in the 1*H*- (**85**) or 3*H*- (**86**) pyrimidone forms. In the hydroxypyrone (**87**), the 2-hydroxy form (**88**) is possible, and, since aromaticity is not very strong in the pyrones, the diketo structure (**89**) may also be important. The general tendency in compounds of these types is for the forms with amide or ester groups (**86**, **87**) to be preferred over the vinylogous amides or esters (**85**, **88**). In compounds with several potential hydroxy groups, *e.g.* barbituric acid (**90**), non-aromatic structures, with interrupted cyclic conjugation, are commonly favoured. In polar media the dipolar 4,6-pyrimidinedione molecule (**91**), with two CO—NH groups, is the predominant tautomer.

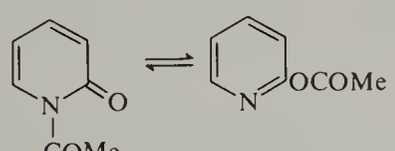


(**84**) (**85**) (**86**)

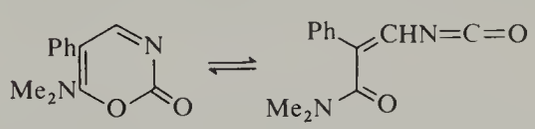


(**87**) (**88**) (**89**) (**90**) (**91**)

Other forms of tautomerism are much less commonly encountered in heterocyclic six-membered rings. Like protons, acyl groups can occupy alternative positions, on a ring atom or a substituent (*e.g.* **92** ⇌ **93**), and their migration from one position to another is frequently rapid enough for the reaction to be considered as a tautomeric shift. Ring–chain tautomerism is unusual in fully 'aromatic' systems—an example is in the oxazinone (**94**), which ring-opens reversibly on heating ⟨78CC902⟩, although in dihydro systems, for instance in dihydropyridines, electrocyclic ring opening occurs, frequently as a prelude to rearrangement.



(**92**) (**93**)



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

2.02

Reactivity of Six-membered Rings

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2.02.1 INTRODUCTION

In this chapter we summarize the reactivity of the six-membered heterocyclic compounds. We describe first the aromatic compounds, where 'aromatic' is defined as fully conjugated round the ring, and then the partially and fully saturated compounds. Within each of these sections we discuss first the reactivity at the ring atoms, then the reactivity of substituent groups.

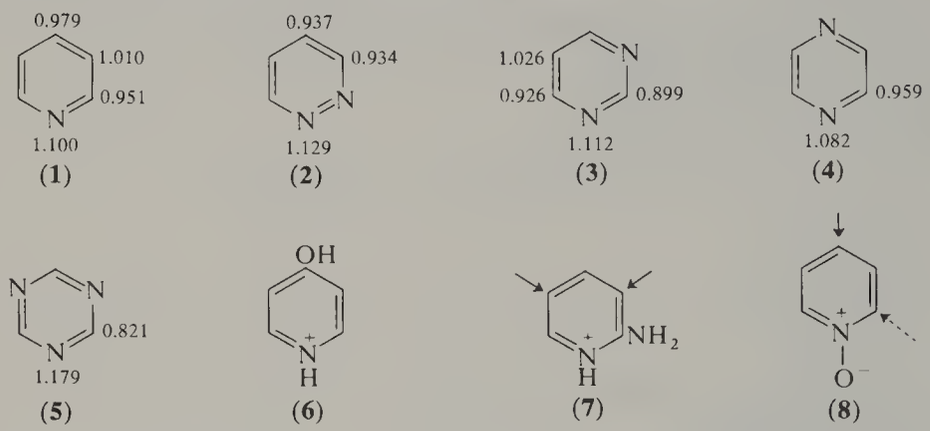
The reactions and reactivity patterns of heterocyclic compounds are rich and varied; they are also in very many instances predictable with a high or complete degree of accuracy. The heterocyclic or natural product chemist can therefore, for example, plan multistage syntheses in the reasonably secure knowledge that individual steps will proceed as expected. The objective of the chapter is to give the general and non-specialist reader a 'feel' for these reactions and reactivity patterns in the area of six-membered heterocycles.

2.02.2 REACTIVITY AT THE RING ATOMS: AROMATIC COMPOUNDS

2.02.2.1 General Survey

Reactivity at the ring atoms in the six-membered aromatic compounds is generally quite predictable on the basis of three major factors: the charge distribution within the ring, the

electronic (mesomeric, inductive) effects of substituent groups, and steric effects, the last normally being least important. Typical π-electron charge distributions for some simple azines are given in (**1**)–(**5**), and explain the facile reaction of the ring nitrogen atoms in these π-deficient heterocycles with electrophiles. Pyrylium and thiopyrylium salts clearly *cannot* behave analogously. An obvious corollary of this ease of reaction of electrophiles with ring nitrogen atoms is that electrophilic heteroaromatic substitution of the π-deficient heterocycles, including pyridinium, pyrylium and thiopyrylium salts, is exceptionally difficult. Thus, nitration, sulfonation, halogenation, metallation, *etc.*, of pyridine require drastic conditions and yields of the expected 3-substituted products are very low. Under the conditions necessary to effect substitution the nitrogen atom is essentially quantitatively converted into the pyridinium form and, like other pyridinium, pyrylium and thiopyrylium salts, this results in a profound deactivation of the ring carbon atoms. These effects carry over to the benzo analogues, where electrophilic substitution of the benzazines takes place in the benzo-fused ring. The situation with chromones, coumarins and the thio analogues, however, is rather more complicated. Electrophilic substitution often takes place in the benzo-fused ring. It may, however, occur preferentially in the heteroring; for example, 4-hydroxycoumarins undergo facile electrophilic substitution at the 3-position.

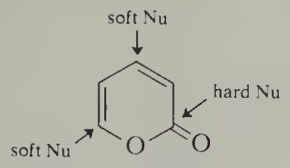


The effects of ring substituents on electrophilic heteroaromatic substitution follow predictable general trends, *i.e.* electron-releasing substituents, especially hydroxy (**6**) and amino (**7**) α or γ to a ring nitrogen atom, facilitate reaction, while electron-withdrawing substituents act in the opposite sense. Of particular importance in this respect are *N*-oxides (**8**), which react at ring carbon with various types of electrophiles under moderate conditions and the overall substitution reactions often proceed in good to excellent yield.

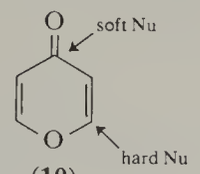
As expected from electron distribution data, nucleophilic attack at ring carbon atoms α and γ to the heteroatoms is a reaction characteristic of the π-deficient heterocyclic systems. The ease with which nucleophilic addition to the ring takes place depends primarily on two major factors, namely, the number and type of substituent groups present on the ring and the number of heteroatoms in the ring. The latter factor is, of course, particularly important with respect to the azines, especially in the chemistry of the polyaza heterocyclic systems. Pyridine, for example, is virtually unaffected by potassium hydroxide at 300 °C, pyrimidine is unstable to hot alkali, while 1,3,5-triazine is completely decomposed by cold water. The very important and widespread phenomenon of covalent hydration of polyaza heterocycles is a classic illustration of the great ease with which these compounds undergo nucleophilic attack. As expected, pyridinium, pyrylium and thiopyrylium salts undergo even more facile nucleophilic attack at positions α and γ to the heteroatom. The effects of substituent groups on the ease of reaction with nucleophiles follow the expected general trends, *i.e.* electron-withdrawing groups facilitate reaction while electron-donating groups suppress it.

Pyrones and thiopyrones react very readily with a variety of nucleophiles, but here the situation is complicated not only by the carbonyl group, but by the fact that these compounds show elements of both aromatic and aliphatic character. Pyran-2-one (**9**) can in principle react with nucleophiles at the 2-, 4- or 6-position and examples of each type of reaction are known. There is an approximate correlation with the hard and soft acid and base hypothesis, in that hard nucleophiles such as HO^- generally react at the 2-position while soft nucleophiles such as hydride ion generally react at the 6-position. Reactions at the 4- and 6-positions can, of course, be rationalized mechanistically simply as examples of conjugate addition. A similar situation obtains with pyran-4-ones (**10**), where reaction can in principle occur at the 2- or 4-position. Hard nucleophiles generally react at the 2-position,

soft nucleophiles at the 4-position. Nucleophilic addition to both pyran-2- and -4-ones is very often followed by ring cleavage to give either acyclic products or, as with ammonia for example, a new heterocyclic system by recyclization of the ring cleavage product.

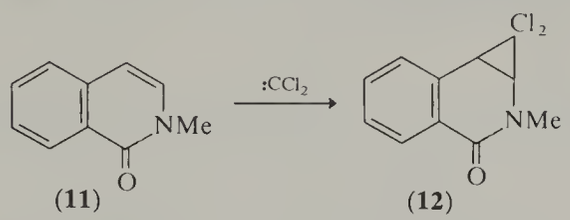


(9)



(10)

Reactions of ring atoms with radicals and electron-deficient species such as carbenes have been studied to a certain extent, but by no means as intensively as with electrophiles. The products from reactions of the azines with radicals depend primarily on the nature of the experimental conditions and the source of the radicals. The 2-position in pyridine is the most reactive to radicals, generally followed by the 3-, and this trend is even more pronounced when acid is either present or generated during the reaction. Vapour-phase bromination of pyridine, for example, gives mainly 2-bromo- and 2,6-dibromo-pyridine. Intramolecular radical substitution of pyridines is of some importance as a route to polycyclic heterocyclic derivatives. Reaction of the aromatic six-membered heterocycles with carbenes has not been studied in any great detail, and in general the reactions are unexceptional. Reaction of 2-methylisoquinolin-1(2*H*)-one (**11**) with dichlorocarbene, for example, gives the fused cyclopropane (**12**) in excellent yield (equation 1).

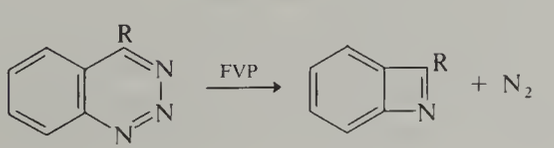


(11) (12) (1)

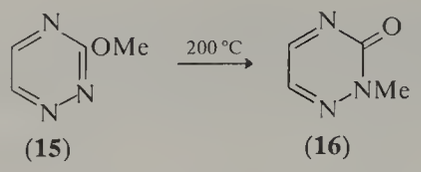
2.02.2.2 Thermal and Photochemical Reactions Involving No Other Species

This is a rather substantial area of chemistry of the six-membered heterocyclic compounds and one in which, while a few general trends are discernible, there is also an enormous diversity of behaviour depending on the ring system. Consequently, there can be no detailed discussion in this chapter, and the reader is referred to the monograph chapters for information on individual ring systems.

Pyrylium and thiopyrylium salts are very stable thermally and there has been little study of their reactions on thermolysis or photolysis. The following details are therefore restricted to the azines, study of the thermolysis of which is also somewhat restricted. This situation should, however, change with the increasing application of flash vacuum pyrolysis (FVP) in organic chemistry, because while the majority of azines and their derivatives are stable to temperatures up to 300 °C, temperatures up to 1000 °C are readily accessible with FVP. It appears that a minimum of three nitrogen atoms is required in the ring before thermal fragmentation occurs to any significant extent. 1,2,4,5-Tetrazines, for example, decompose both thermally and photochemically to give nitriles and nitrogen, while FVP of 1,2,3-benzotriazines (**13**) gives the benzazetes (**14**; equation 2). The 4-one derivatives decompose similarly to give the corresponding benzazetones and it has been claimed that tris(dimethylamino)-1,2,3-triazine also gives the azete; trimethyl- and triphenyl-1,2,3-triazine, however, give nitrogen, a nitrile and the appropriate acetylene. [2-Methyl-1,2,4-triazin-3(2*H*)-one (**16**) is obtained when 3-methoxy-1,2,4-triazine (**15**) is heated to 200 °C (equation 3).] Pyridazine (**17**) is isomerized to pyrimidine (**18**) at 300 °C (equation 4), probably *via* a mechanism closely related to that discussed below for photochemical ring isomerization, and gas-phase photolysis is required to generate nitrogen and vinylacetylene.



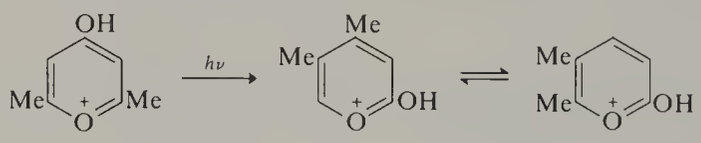
(13) (14) (2)



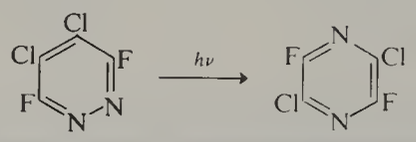
(15) (16) (3)

(17) (18) (4)

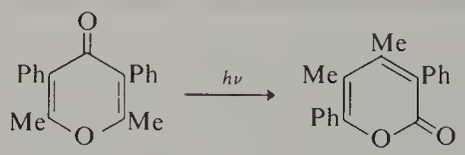
Photoisomerization of substituted benzenes *via* prismane, benzvalene, *etc.* intermediates was demonstrated some 20 years ago, and in 1975 Barltrop and Day suggested a scheme to account for all possible permutations about a six-membered ring, irrespective of the precise mechanism of the rearrangement ⟨75CC177⟩. They listed 12 possible 'permutations' about a six-membered ring which, together with standard mechanistic considerations, can be used to provide reasonable explanations for many reactions which had previously baffled mechanistic photochemists. The six-membered heterocyclic systems provide possibly the clearest cases where, as a consequence of heteroatom and side-chain substitution, the permutation pattern can be followed in full, and reactions such as those depicted in equations (5) and (6) can be rationalized (for further examples with pyridazines see ⟨82JOC398⟩). Pyran-4-ones, especially highly substituted derivatives, undergo photorearrangement to the corresponding pyran-2-ones (equation 7).



(5)

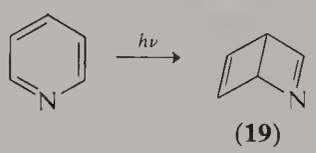


(6)

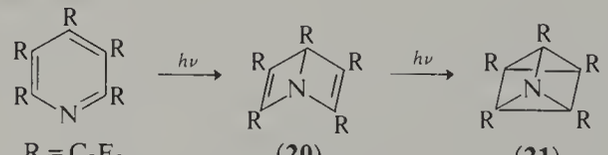


(7)

Irradiation of the six-membered heterocycles can, as mentioned above, lead to valence bond isomerization. Pyridine gives only one of the two possible Dewar pyridines, namely (**19**; equation 8). Derivatives of the alternative Dewar pyridine have been prepared as outlined in equation (9) and compound (**20**) in turn is converted on further irradiation into the azaprismane derivative (**21**).

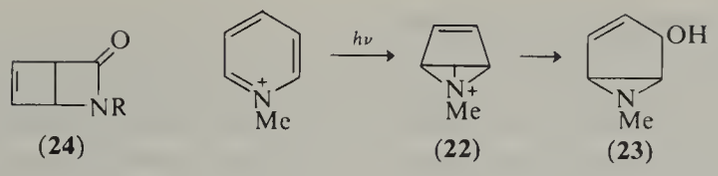


(19) (8)



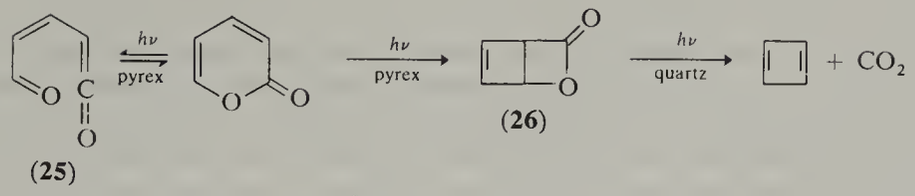
$R = C_2F_5$ (20) (21) (9)

It has been suggested that the azabenzvalene derivative (**22**) is an intermediate in the phototransformation of *N*-methylpyridinium chloride into the fused aziridine (**23**; equation 10). Irradiation of 2-pyridone derivatives gives the azabicyclo[2.2.0]hexane derivatives (**24**) in good yield; this reaction, followed by cleavage of the C=C bond, has been used as a route to β-lactams. Photochemically induced valence bond isomerization of pyran-2-one can follow two pathways: at temperatures close to absolute zero and using pyrex equipment a photoequilibrium with the ketene (**25**) is set up, but at 77 K a bicyclic lactone (**26**) is formed in high yield. When irradiated through quartz, this loses carbon dioxide to give cyclobutadiene (equation 11).



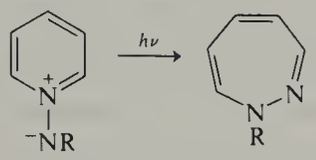
(10)

(24) (22) (23)



(11)

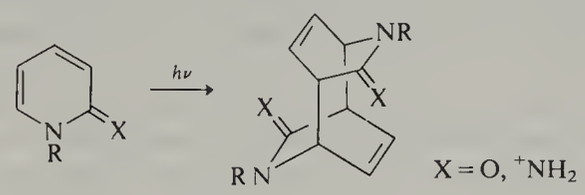
(25) (26)



(12)

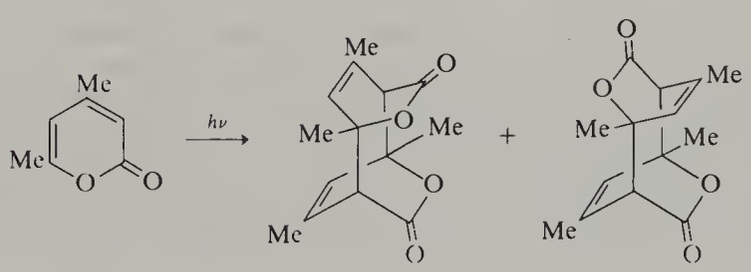
The irradiation of pyridine *N*-oxides and *N*-imines usually proceeds through ring expansion and incorporation of the *N*-substituent into the ring (equation 12). It has frequently been postulated that oxaziridines and diaziridines are intermediates in these reactions, but these suggestions have also been disputed. Certain other photochemical transformations of substituted pyridines proceed in very much the expected manner, and ring expansions and ring contractions are also observed with certain derivatives; in general, however, the yields in such processes are low and they are, consequently, of little synthetic significance.

An unusual photochemical reaction of 2-pyridones, 2-aminopyridinium salts and pyran-2-ones is photodimerization to give the so-called 'butterfly' dimers. These transformations are outlined in equations (13) and (14). Photodimerization by [2+2] cyclization is also a common and important reaction with these compounds. It has been the subject of particular study in pyrimidines, especially thymine, as irradiation of nucleic acids at *ca.* 260 nm effects photodimerization (*e.g.* equation 15); this in turn changes the regular hydrogen bonding pattern between bases on two chains and hence part of the double helix structure is disrupted. The dimerization is reversed if the DNA binds to an enzyme and this enzyme–DNA complex is irradiated at 300–500 nm. Many other examples of [2+2] photodimerization are known and it has recently been shown that 1,4-dithiin behaves similarly (equation 16) ⟨82TL2651⟩.

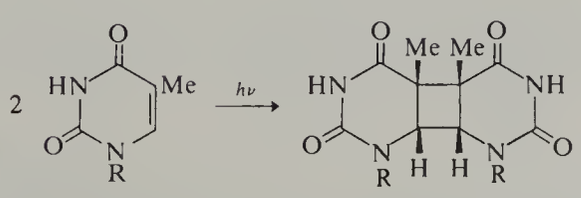


(13)

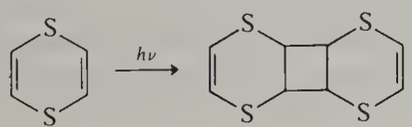
$X = O, {}^{+}NH_2$



(14)



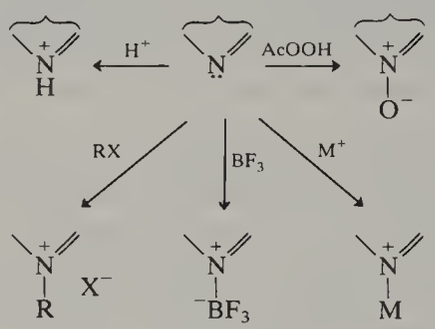
(15)



(16)

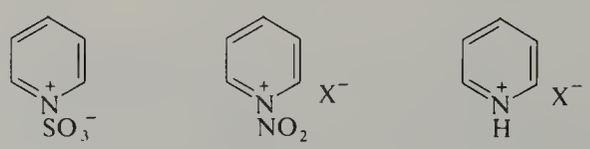
2.02.2.3 Reactivity Towards Electrophiles

The six-membered π-deficient nitrogen heterocycles react at ring nitrogen with a wide variety of electrophiles including protic and Lewis acids, peracids, alkyl halides and tosylates, halogens and transition metal ions (Scheme 1). In other words, these compounds behave as typical tertiary amines, although the facility with which a particular reaction takes place obviously depends to a considerable extent on the basicity of the ring nitrogen atom. This in turn is influenced by two major factors, namely, the presence of substituent groups at ring positions and the presence of additional heteroatoms in the ring system. Thus, electron-releasing groups in pyridine tend to increase the basicity of the ring nitrogen atom, especially where more effective resonance is possible in the cation than in the neutral molecule, while electron-withdrawing groups exert the opposite effect. The pK_a of pyridine, for example, is 5.17 while that of 4-methylpyridine is 6.02 and that of 4-aminopyridine is 9.2. The effect of introduction of one or more additional heteroatoms into the ring system is generally much more pronounced. Thus, the pK_a of pyrimidine is 1.3 and that of pyrazine is 0.6. These effects must obviously be given careful consideration when experimental conditions are being devised for important preparative processes such as the formation of quaternary salts or *N*-oxides. Pyridine is readily oxidized to pyridine *N*-oxide with peracetic acid or MCPBA, for example, but efficient conversion of pentachloropyridine to the *N*-oxide requires a much more powerful oxidant such as peroxytrifluoroacetic acid.



Scheme 1

The reactions of ring nitrogen atoms with electrophiles are of fundamental importance, not only in heterocyclic chemistry as such but in many aspects of general synthetic organic chemistry. Quaternary salts, the nitrogen ylides derived from them and the *N*-oxides are classes of compound with richly developed chemistry, outlines of which are given later; detailed discussions of these topics are, of course, given in the individual chapter monographs. Familiar applications of pyridine electrophile reagents to organic synthesis include the use of pyridinium-1-sulfonate (**27**), *N*-nitropyridinium salts (**28**), pyridinium hydrobromide dibromide (**29a**) and pyridinium chlorochromate (**29b**) as reagents for sulfonation, nitration, bromination and oxidation under mild and relatively non-acidic conditions. Even more widely exploited has been the use of pyridine, substituted pyridines and other π-deficient heterocyclic systems as catalysts in acylation and related reactions. During the last few years in particular, the use of 4-dialkylaminopyridines as acylation catalysts has become very widespread; these compounds are more than 10 000 times more basic than pyridine and, consequently, even the most unreactive of hydroxy groups can be acylated effectively when 4-dialkylaminopyridines are used as catalysts. Pyridinium, pyrylium and thiopyrylium salts are, of course, already positively charged at the heteroatom and, consequently, no further reaction with electrophiles is possible at that centre.

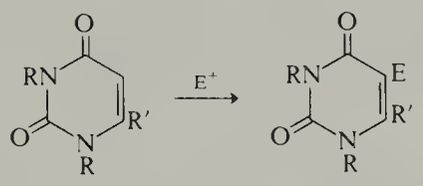


(**27**) (**28**) (**29**) **a**; X = Br_3
b; X = $ClCrO_3$

In contrast to the ease of reaction of ring nitrogen atoms in π-deficient six-membered heterocycles with electrophiles, electrophilic heteroaromatic substitution at carbon of the unsubstituted compounds proceeds only under very drastic conditions and yields of products are usually very poor. This is also true with pyridinium, pyrylium and thiopyrylium salts,

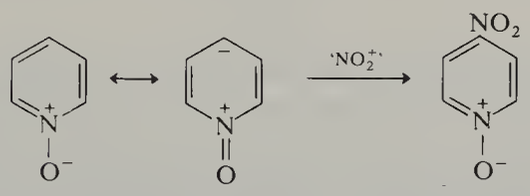
where direct electrophilic substitution is virtually unknown. The reactivity of pyridine in such reactions is frequently likened to that of nitrobenzene, and, as expected from electron distribution data, when substitution occurs, it does so at the 3-position. Sulfonation can be carried out in acceptable (70%) yield, but most other reactions (*e.g.* nitration) give poor yields or fail completely. Friedel–Crafts alkylation and acylation, for example, are unknown in the simple azines.

The effects of substituent groups, as indicated in the general survey, are largely predictable, powerful electron-donating groups in particular facilitating the process of electrophilic substitution. Thus, 2- and 4-pyridone and 2- and 4-aminopyridine undergo electrophilic substitution under moderate conditions, and both mono- and di-substituted products can be obtained in good yield; substitution occurs at the positions *ortho* and *para* to the activating groups, first at the 3-position in the pyridones, and mixtures of monosubstituted products are often obtained. 2- and 4-Aminopyridines undergo nitration in most cases *via* the *N*-nitroamines. Nitration, nitrosation, azo coupling, halogenation, sulfonation and the Mannich reaction have all been studied in some detail, especially nitration and halogenation, and many important synthetic procedures have been developed. In the pyrimidines, for example, nitrosation, nitration and azo coupling of suitably activated substrates are very important procedures for the introduction of nitrogen functionality at the 5-position (equation 17).



$E = NO_2^+, NO^+, ArN_2^+$ (17)

The reactions of azine *N*-oxides with electrophiles at ring carbon atoms are very important. Pyridine *N*-oxide is nitrated in good yield under fairly moderate conditions ($H_2SO_4/HNO_3/100\,°C$) (equation 18; in general only a very small amount of the 2-nitro isomer is formed) and a wide range of substituted derivatives behave analogously. With quinoline *N*-oxides the orientation of nitration (*i.e.* at the 4-position or in the benzo-fused ring) depends on the reaction temperature. Similar substitutions are known for halogenation, but the reactions of *N*-oxides with electrophiles can proceed by much more complicated pathways, depending on the nature of the electrophile and on structural and electronic features in the *N*-oxide substrate. In a mechanistic sense, however, these reactions involve reaction of a nucleophile with a ring carbon atom and are discussed in Section 2.02.2.4. Electrophilic substitution of the azine *N*-oxides has been thoroughly reviewed ⟨B-71MI20200⟩.

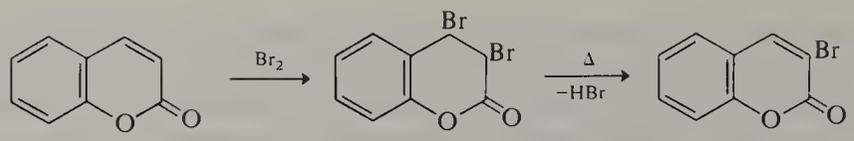


(18)

Reaction of the benzo-fused six-membered heterocycles with electrophiles can obviously take place at the benzo-fused ring or at the heteroring, and again substituent effects are all important. In the absence of powerful electron donor substituents in the heteroring, electrophilic substitution normally occurs first in the benzo-fused ring. Appropriately situated oxygen and nitrogen substituents, however, direct substitution to the heteroring, as summarized in structures (**30**) and (**31**). Moreover, there are many instances known, especially with the oxygen and sulfur heterocycles, where 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 (19).

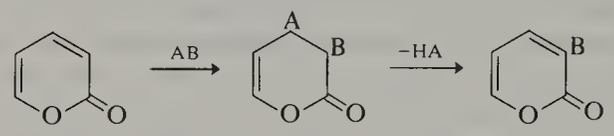
(**30**) (**31**)

$E^+ = NO_2$, Br, CH_2NR_2, *etc.*

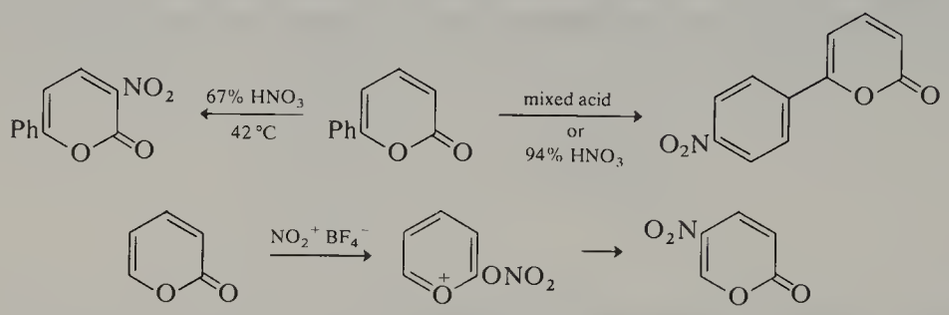


(19)

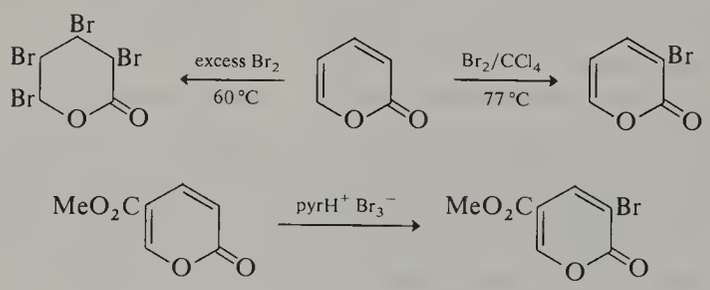
The addition–elimination mechanism is also very common in the monocyclic oxygen and sulfur heterocycles (*e.g.* equation 20), a fact frequently cited as evidence for their low aromaticity. Pyran-2-ones can react with electrophiles at the 3- and 5-positions and pyran-4-ones at the 3-position (they also react at the carbonyl oxygen atom, but this is classified as a substituent reaction). Moreover, while the position of substitution can often be predicted on the basis of charge distribution and substituent effects, the choice of experimental conditions can also profoundly affect the outcome of the reaction, as illustrated in Schemes 2 and 3.



(20)



Scheme 2

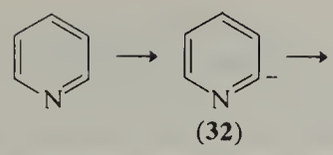


Scheme 3

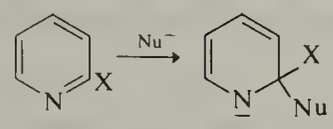
Oxidation of the six-membered aromatic heterocycles at ring carbon atoms by electrophilic reagents is of little synthetic utility, as opposed to *N*-oxidation and the oxidation of substituent groups. The azines are generally very resistant to oxidation by reagents other than peracids—as mentioned earlier, reagents comprising pyridine in conjunction with inorganic oxidants are widely used for the oxidation of functional groups in synthetic organic chemistry. Oxidation of quinoline and isoquinoline with potassium permanganate under vigorous conditions gives mixtures of products and both the benzo-fused ring and the heteroring are attacked. The pyridinedicarboxylic acids and (in the case of isoquinoline) phthalic acid or phthalimide are formed in modest yield. Ozone cleaves pyridines to give mixtures of products corresponding to both possible Kekulé forms; 3,4-dimethylpyridine, for example, gives a mixture of glyoxal, pyruvaldehyde and butane-2,3-dione.

2.02.2.4 Reactivity Towards Nucleophiles

As mentioned earlier, nucleophilic attack at ring carbon atoms α and γ to a heteroatom is a reaction characteristic of the π-deficient six-membered heterocycles. Within this context we do not regard hydrogen atoms attached to ring carbon atoms as substituent groups, and hence proton removal to generate a carbanionic centre is classified as a reaction at a ring carbon atom. There are thus six major reaction types, summarized in equations (21)–(26) in terms of the initial mechanistic steps.


products (21)

(32)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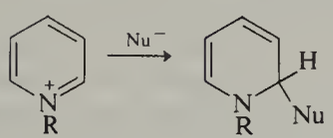
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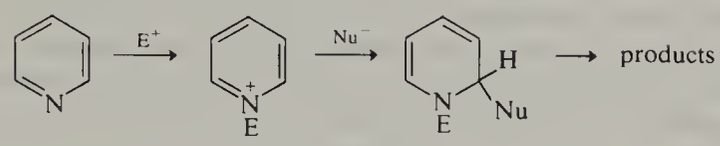
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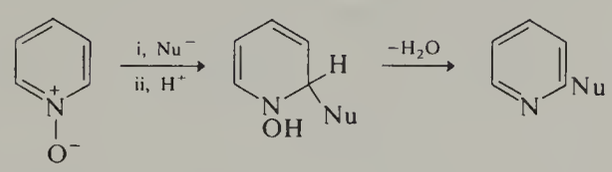
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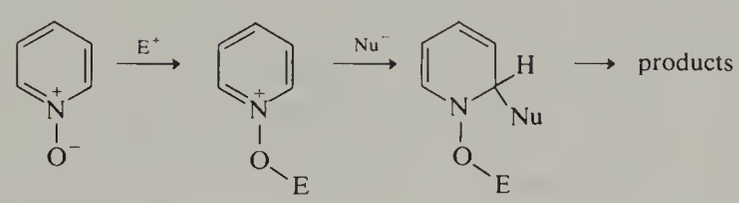
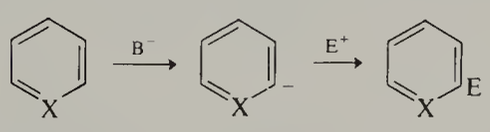
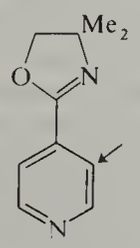
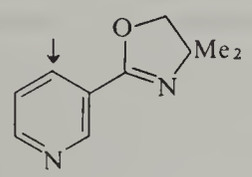

products (26)

Treatment of pyridine with $NaOD/D_2O$ at elevated temperatures results in eventual replacement of all hydrogen atoms by deuterium. This process presumably involves deprotonation followed by rapid deuteration of the intermediate negatively charged species (*cf.* equation 21) in a sequential manner. Azine *N*-oxides are deuterated in a similar way, positions adjacent to the *N*-oxide exchanging particularly rapidly. Controlled deprotonation of ring carbon atoms α and γ to the heteroatom can be accomplished by the use of strong, non-nucleophilic bases and the intermediate carbanions may be trapped by electrophiles (equation 27). The yields in these reactions are in most cases only moderate, however. As expected, deprotonation occurs more easily if the heteroatom is positively charged.


(27)

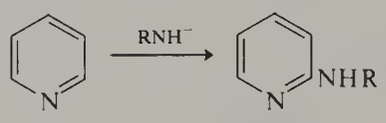
There has been considerable recent interest in the generation of carbanions such as (**32**), and especially in the use of functional groups to 'direct' the lithiation reaction. Most studies have been concerned with simple pyridine derivatives and it is already clear that the overall course of reaction depends critically on the nature of the directing group, the organolithium reagent used and the experimental conditions. Meyers has examined the effect of the oxazoline group in directing lithiation and shown that the 2-(4-pyridyl) derivative (**33**) is metallated, as expected, at C-3 with methyllithium while the 3-isomer (**34**) reacts at C-4 with lithium tetramethylpiperidide ⟨82JOC2633⟩. Reaction of (**34**) with alkyllithiums, however, gave only the 4-substituted dihydropyridines in excellent yield. 3-Pivaloylaminopyridine also undergoes metallation at C-4 with butyllithium, but does not react


(33)


(34)

with methyllithium or LDA ⟨82S499⟩. By contrast, treatment of 3-ethoxy- or -butoxy-pyridine with butyllithium in the presence of TMEDA results in apparently exclusive metallation at the 2-position ⟨82S235⟩. Other examples involving the use of tertiary amides as directing groups have been summarized ⟨82ACR306⟩ and this is a research area which will obviously be a subject of much study in the future. Reactions of the heterolithium derivatives are discussed in Section 2.02.3.8.

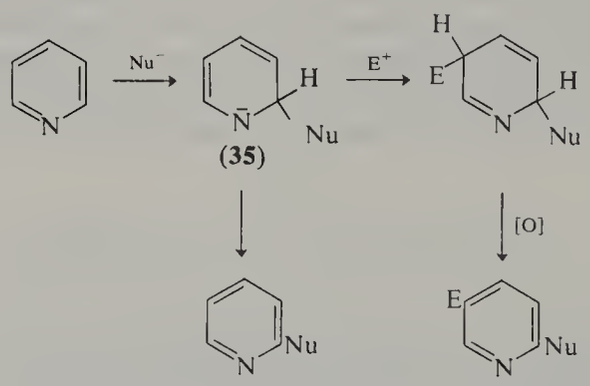
Only very powerful nucleophilic reagents such as HO^-, NH_2^-, RLi, LAH, *etc.*, react effectively at the ring carbon atoms of simple pyridines (*cf.* equation 22), and even then forcing conditions may be required. Oxidation of pyridine to 2-pyridone with potassium hydroxide, for example, requires a temperature of *ca.* 300 °C. Nevertheless, some of these reactions can be of very considerable synthetic importance, especially the classical Chichibabin reaction for the preparation of 2-amino, alkylamino and hydrazino heterocycles (equation 28). The sequence of substitution is C-2, then C-6 and finally C-4. The Chichibabin reaction also requires rather vigorous conditions and often proceeds in only moderate yield; the simplicity of the approach, however, is such that it often represents the method of choice for the preparation of the requisite substituted heterocycle.



(28)

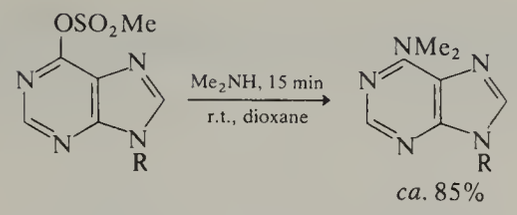
R = H, alkyl, NH_2

Reaction of nucleophiles with the polarized N=C bond of azines proceeds *via* dearomatization and formation of the corresponding 1,2-adduct. With alkyllithiums, for example, it is possible to isolate the dihydro products by careful neutralization of the reaction mixtures; these are, in general, rather unstable, however, and can easily be reoxidized to the fully aromatic compounds (Scheme 4). The dihydro adducts formed in these direct nucleophilic addition reactions can also be utilized for the introduction of substituent groups β to the heteroatom. Thus, reaction of (**35**) with one of a number of electrophiles, followed by oxidation of the intermediate dihydro product, constitutes a simple and, in many cases, effective method for the introduction of substituent groups at both the 2- and 5-positions of the pyridine ring (Scheme 4). Use of LAH in this sequence, of course, results in the formation of 3-substituted pyridines.



Scheme 4

One obvious reason why the above types of reaction proceed only with very powerful nucleophiles and often require very vigorous conditions is that hydride ion is a very poor leaving group and hence rearomatization of the intermediate dihydro compounds is a high energy process. Clearly, introduction of good leaving groups α and γ to the ring nitrogen atom should facilitate substitution, and this is as found. Halogens, alkoxy and tosyloxy groups, thioethers, sulfoxide and sulfone groups, and nitro groups are all, in appropriate combinations, readily displaced by a wide range of common nucleophiles, including hydroxide, alkoxide, sulfide, cyanide and borohydride ions, amines, carbanions and Grignard reagents. This is, in fact, the classical and still very widely used approach to the preparation of derivatives of the azines with specific functional groups α or γ to the ring nitrogen atoms. Surprisingly, there have been relatively few studies of the ease of reaction *versus* the nature of the leaving group, although the data which are available clearly indicate that the nature of the leaving group can exert a profound influence. The examples given in equations (29) and (30) illustrate how careful selection of the leaving group can result in highly efficient nucleophilic displacement reactions under mild conditions ⟨77CC447, 79JCR(S)125⟩. See also Section 2.02.3, in which the reactions of substituent groups are discussed.



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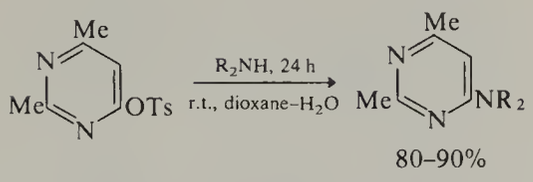
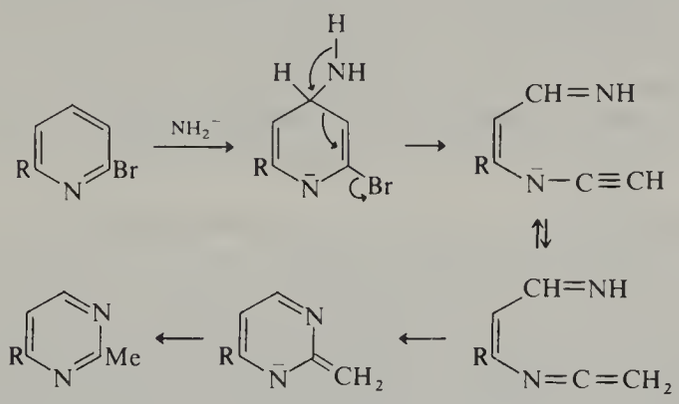
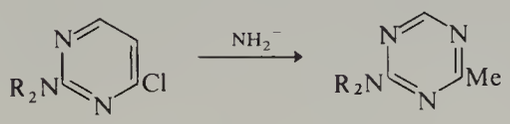


(30)

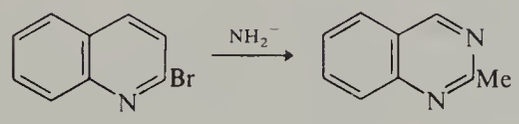
The other major factors which affect the ease of addition of nucleophiles to the π-deficient six-membered heterocycles are the presence of substituent groups and the number of heteroatoms in the ring and, in each case, the trends are as expected. Thus, electron-withdrawing groups facilitate reaction and electron-donating groups tend to retard reaction. Introduction of further heteroatoms also facilitates reaction—as mentioned earlier, 1,3,5-triazine is decomposed by cold water. This latter effect in particular can often lead to quite complicated reaction pathways, especially with the polyazines, and these are frequently described as ANRORC reactions (*A*ddition of *N*ucleophile, *R*ing *O*pening, *R*ing *C*losure). Typical examples are summarized in Scheme 5 and equations (31)–(33) (the last being an example—rather unusual in simple pyridine systems— of the Dimroth rearrangement).



Scheme 5



(31)



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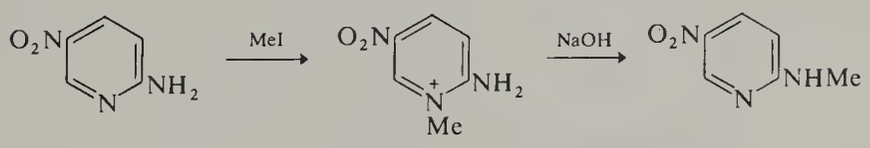
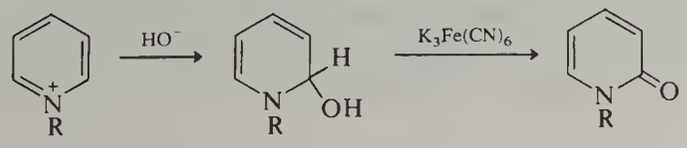


(33)

Nucleophiles react particularly easily with quaternized azines and with pyrylium and thiopyrylium slats (*cf.* equation 23); typical examples, including the well-known reaction of pyridinium salts with hydroxide in the presence of potassium ferricyanide to give 2-pyridones, are summarized in equations (34)–(36) (note the rather unusual orientation of addition in the last case; reaction normally occurs essentially exclusively α to the heteroatom if the position is free or occupied by a leaving group).



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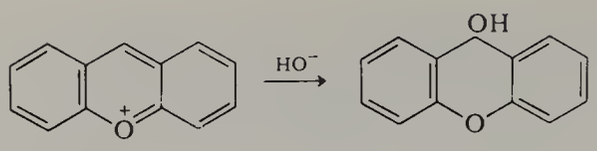

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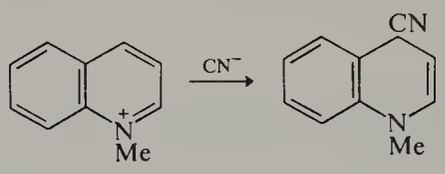
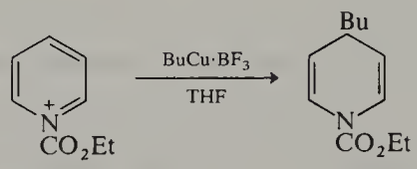


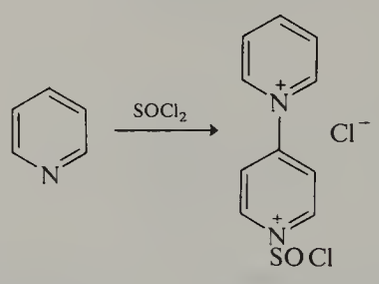
(36)



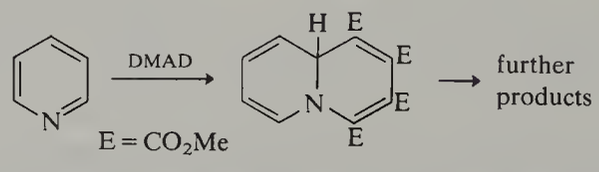
(37)

There has been much recent interest in the reactions of pyridinium salts with organometallic reagents, especially in the development of methods for the effective control of regioselectivity of addition. Most of the earlier work with Grignard and organocadmium reagents resulted mainly in 1,2-addition, but more recent studies have shown that a considerable degree of regioselectivity for either 1,2- or 1,4-addition can be obtained, and that the nature of the quaternizing group and the organometallic nucleophile is crucial. Lithium dialkylcuprates add preferentially at the 4-position of acylpyridinium salts ⟨74CJC3563⟩ while $RCu{\cdot}BF_3$ reagents give good yields of almost exclusively 1,4-dihydro derivatives (equation 37) ⟨82TL429⟩. Excellent 1,4-regioselectivity for Grignard additions to pyridinium salts has also been described ⟨82JOC4315⟩ and these and related methods ⟨*e.g.* 82TL1709⟩ are attractive procedures for the synthesis of 2- and/or 4-substituted pyridines and their dihydro derivatives.

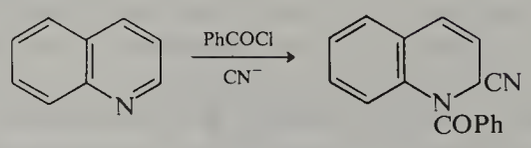
Nucleophilic additions to quaternized nitrogen heterocycles can also be readily carried out in many cases where the quaternization is carried out *in situ*; that is, the overall reaction proceeds by initial reaction of the ring nitrogen atom with an electrophilic species, followed by reaction at ring carbon with a nucleophile. Halogenation of quinoline and isoquinoline in the presence of Lewis acids gives almost exclusively the 5- and 8-halo derivatives; in the absence of Lewis acids, however, reaction occurs at the heterocyclic ring *via* initial reaction at ring nitrogen and the 3- and 4-halo derivatives are formed in good yield by an addition–elimination sequence. Mercuration follows a similar type of pathway and other examples of this (rather heterogeneous) general type of reaction are shown in equations (38)–(40), the last illustrating the formation of a well-known type, the Reissert compounds.



(38)



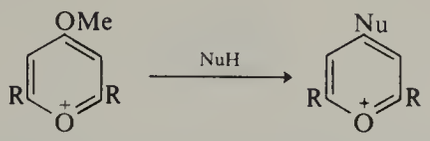
(39)



(40)

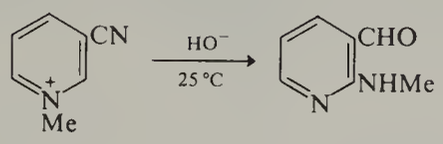
The effects of substituent groups in the reactions of the cationic heterocycles with nucleophiles are entirely as expected. Appropriately situated substituent groups which can function as leaving groups can be displaced (*e.g.* equation 41), and ANRORC reactions are very common (*e.g.* equations 42 and 43). The latter type of reaction is of particular

importance in pyrylium chemistry; the reaction has been widely exploited as a route to other heterocycles, especially pyridinium salts and, though much less commonly, also to benzenoid derivatives (Scheme 6).



(41)

NuH = R'OH, R'SH, R'_2NH



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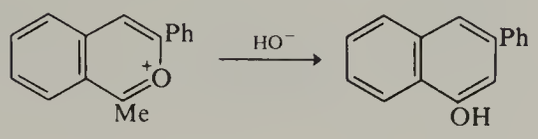

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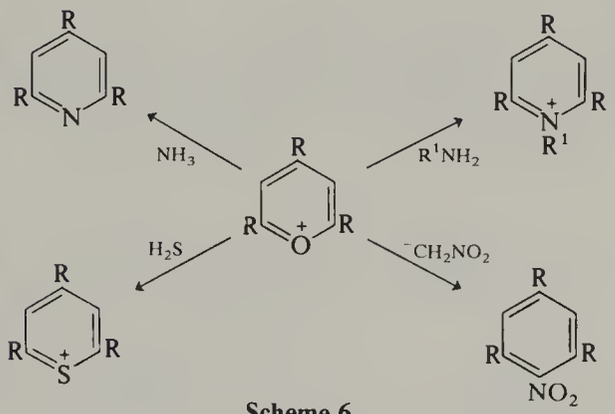
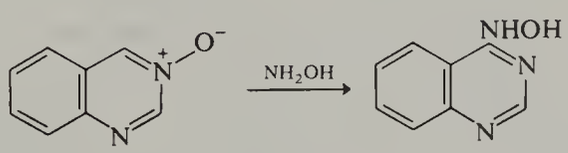
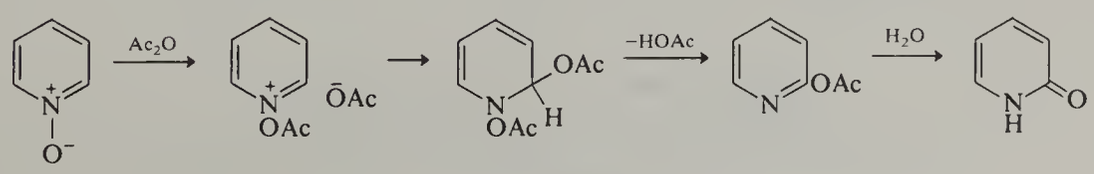


Scheme 6

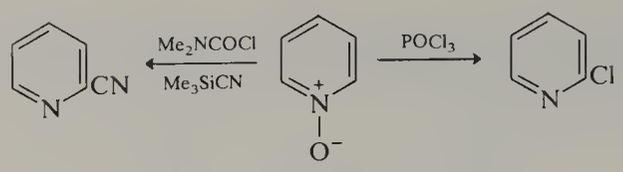
The reactions of *N*-oxides with nucleophiles at ring carbon are of very considerable interest and importance, and, from a mechanistic point of view, two common reaction pathways are discernible. The first, summarized in equation (25), involves addition of the nucleophile followed by rearomatization with loss of water from the dihydro intermediate. Treatment of quinazoline 3-oxide with hydroxylamine, for example, gives 4-hydroxylaminoquinazoline (equation 44). The second common pathway, the initial steps of which are shown in equation (26), involves initial reaction of the oxygen of the *N*-oxide with an electrophile followed by addition of the nucleophile at ring carbon. This can result in overall substitution α to the *N*-oxide function, as illustrated in the two important examples shown in Schemes 7 and 8. In these reactions the *N*-oxide oxygen atom is lost. In a number of other, rather more complicated reactions, however, the *N*-oxide function is retained and substitution occurs β to the heteroatom; two examples are shown in Schemes 9 and 10. It may also happen that the oxygen of the *N*-oxide group becomes incorporated into the final substituent group. Reaction of pyridine *N*-oxide with the imidoyl halide (**36**), for example, results in initial formation of the adduct (**37**); intramolecular nucleophile addition to the carbon–nitrogen bond gives (**38**) which rearomatizes as shown to generate the arylaminopyridine derivative (**39**; Scheme 11).



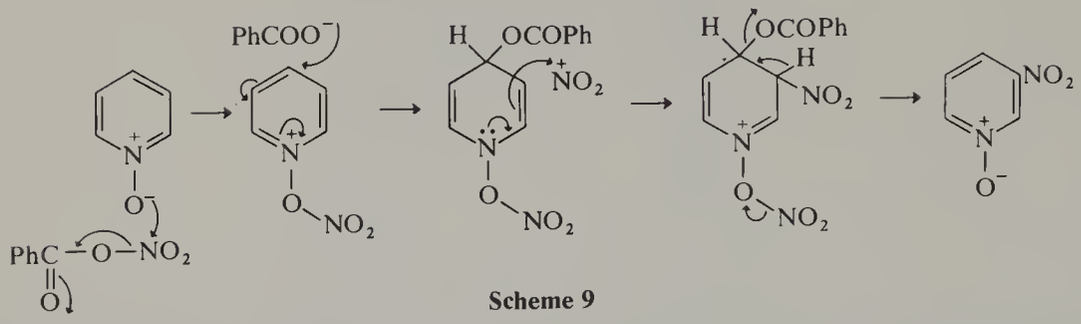
(44)



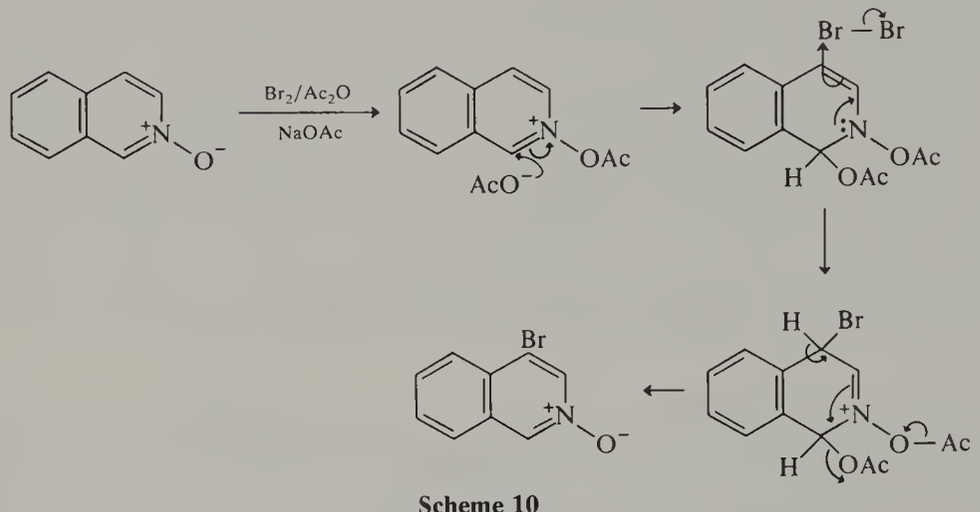
Scheme 7



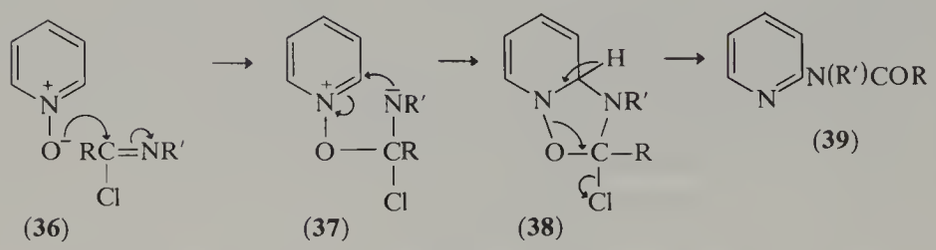
Scheme 8



Scheme 9



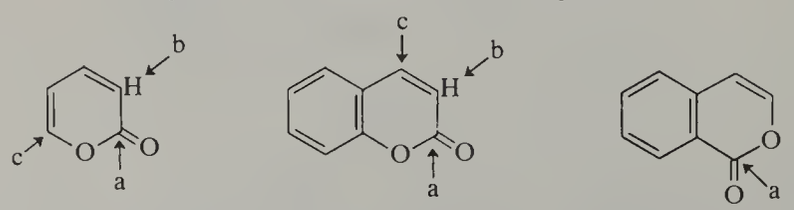
Scheme 10



Scheme 11

Pyridones are normally resistant to nucleophilic attack at ring carbon atoms, but the pyrones react rather readily. There is a useful correlation between the position of attack and the hardness or softness of the nucleophile, and the situation for the pyrones is summarized in Schemes 12 and 13. Representative transformations illustrating these concepts are shown in equations (45)–(51). ANRORC reactions are also very common and examples are given in equations (52)–(55).

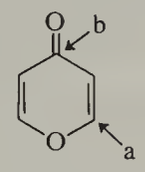
Pyran-2-ones: reactions with nucleophiles



a: hard nucleophiles, HO^-, RNH_2, RMgX, RLi
b: LDA
c: soft nucleophiles, CN^-, H^-(LAH), CH_2N_2

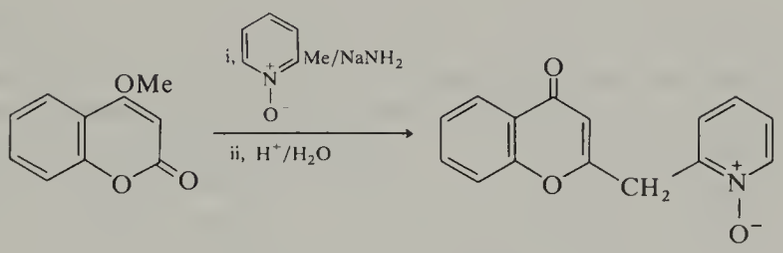
Scheme 12

Pyran-4-ones: reactions with nucleophiles

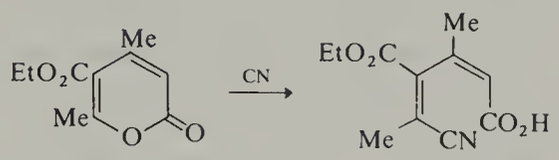


a: HO^-, RNH_2 (basic conditions), hard carbanions
b: RMgX, RNH_2 (acidic conditions), soft carbanions, H^-(LAH)

Scheme 13



(45)



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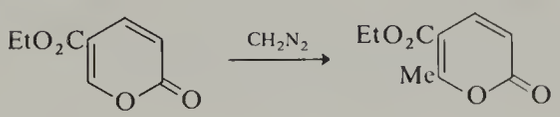
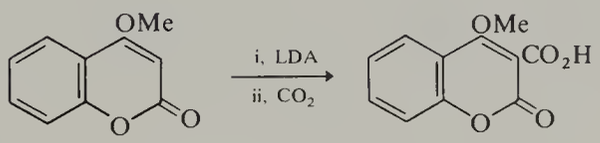


(47)



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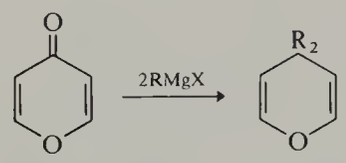
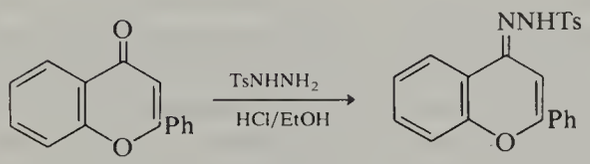
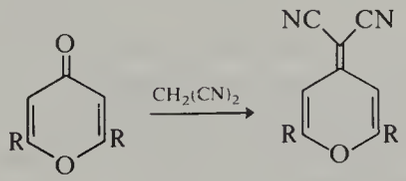


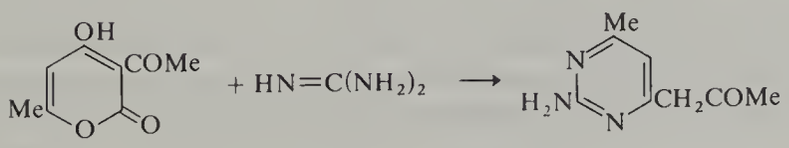
(49)



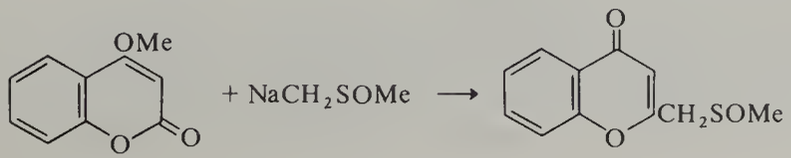
(50)



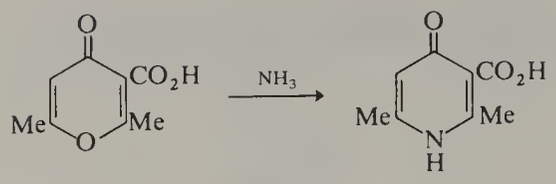
(51)



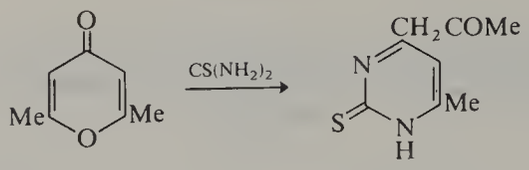
(52)



(53)

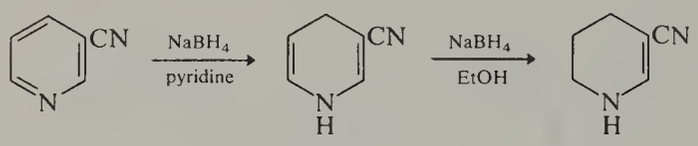


(54)

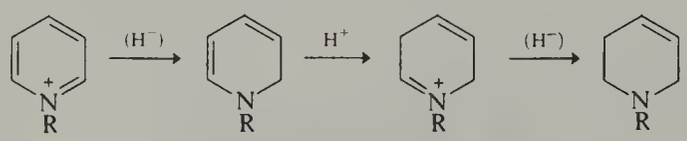


(55)

Chemical reduction of the six-membered heterocycles is usually reasonably straightforward and can be used for the preparation of di-, tetra- and hexa-hydro derivatives. As expected, the ease of reduction by nucleophilic reagents increasés if the ring is substituted with electron-withdrawing groups, or if the heteroatom is positively charged. Treatment of pyridine with LAH gives a mixture of 1,2- and 1,4-dihydropyridines in the form of an LAH complex, but the dihydro heterocycles have not been isolated. The more powerful LAH/$AlCl_3$ reagent reduces pyridines to a mixture of piperidines and tetrahydropyridines. Quinoline gives the 1,2-dihydro compound with LAH. Pyridine itself is unaffected by sodium borohydride but electron-withdrawing substituents, especially at the 3- and 5-positions, greatly facilitate reaction with hydride reducing agents (equation 56). Mixtures of 1,2- and 1,4-dihydro products are usually formed, but use of a protic solvent leads to tetrahydro derivatives (Scheme 14). One-electron reduction with sodium in ethanol or liquid ammonia has been used for the reduction of pyridines to piperidines, but tetrahydro and even dihydro derivatives are often isolated as unwanted by-products. For full details of these reactions the reader is referred to Chapter 2.04.

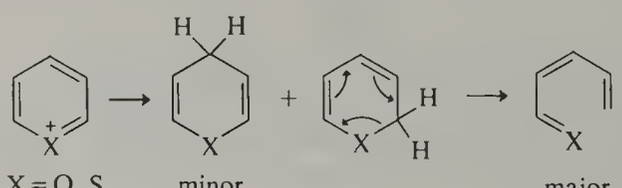


(56)



Scheme 14

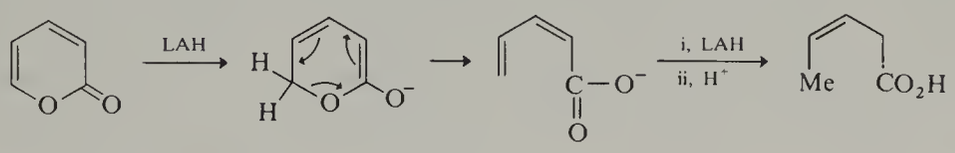
Reduction of cationic heterocycles is a very facile reaction and sodium borohydride is almost always the reagent of choice. With monocyclic pyrylium and thiopyrylium salts attack occurs preferentially at the 2-position and the product undergoes valence bond isomerism to give ring-opened products; small amounts only of the 1,4-dihydro products are formed (equation 57). The benzo and dibenzo analogues are also easily reduced, but here valence bond isomerism is not a favourable process. In contrast to these reactions, which are of little synthetic utility, reduction of pyridinium salts, especially with sodium borohydride, is a valuable procedure for the preparation of reduced pyridines. The extent of reduction depends on both the reaction conditions and the nature of any substituent groups present. Attack at the 2-position is generally predominant, but mixtures of dihydro adducts are by no means uncommon with simple pyridines. In non-protic solvents and at pH > 7 reduction usually stops at the dihydro stage, but in protic solvents and at pH 2–5, further reduction as outlined in Scheme 14 leads to 1,2,3,6-tetrahydro derivatives. Quinolinium and isoquinolinium salts behave similarly, and the borohydride reduction of 1-substituted 2-methyl-3,4-dihydroisoquinolinium salts is a routine operation in the synthesis of 1,2,3,4-tetrahydroisoquinoline alkaloids. Sodium dithionite reduces pyridinium salts,



(57)

especially those carrying electron-withdrawing groups at the 3- and 5-positions, to dihydropyridines. This reaction, which can be used for the conversion of NAD to NADH, gives preponderantly the 1,4-dihydro products, but small amounts of 1,2- and/or 1,6-dihydropyridines are also normally obtained.

Chemical reduction of pyrones can lead to a variety of products depending on the nature of the reducing agent and the reaction conditions. Reaction of pyran-2-ones with LAH, for example, proceeds *via* nucleophilic addition at the 6-position and gives ring-opened products by valence bond isomerism followed by further conjugate addition of hydride ion (equation 58). Pyran-4-ones similarly give different products depending on the nature of the reaction conditions. Reduction of 2-ethylchromone with sodium borohydride at room temperature, for example, results in both conjugate addition of hydride ion at the 2-position and reduction of the 4-oxo function to give the chromanol. If LAH at −78 °C is used, the reaction stops at the conjugate addition stage and the product is the chromanone. In general, however, the reactions of the oxygen and sulfur heterocyclic systems with reducing agents have not been studied in great detail.



(58)

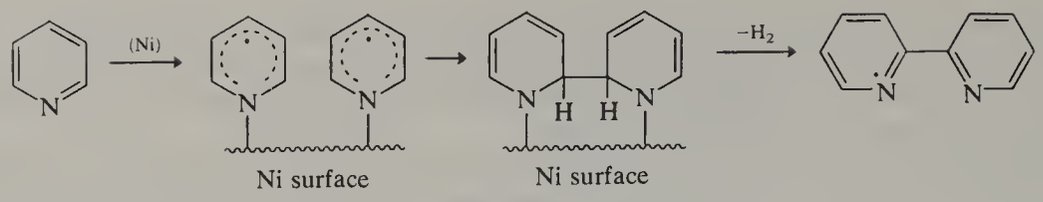
2.02.2.5 Reactivity Towards Free Radicals

Radical substitution of the six-membered heterocycles has not been studied in anything like the same detail as electrophilic and nucleophilic substitution, and most interest has been devoted to simple pyridines. Even so, a large number of investigations have been carried out and general trends are discernible. Alkylation with a wide range of alkyl radicals and arylation, especially phenylation, have been most thoroughly studied. Free radical alkylation of pyridine results in substitution at all three possible positions, with preference for substitution at the 2-position. The distribution of isomers does, however, vary according to the reaction conditions. Thus, under non-acidic conditions typical isomer distributions for alkylation are: 2-isomer *ca.* 60%, 3-isomer 20–25%, 4-isomer 15–20%. Under acidic conditions, on the other hand, there is a significant increase in the proportion of the 2-isomer produced and yields as high as 93% have been recorded together with approximately 7% of the 4-isomer. Under other conditions used to generate the methyl radical typical distributions are: 2-isomer 76–78%, 3-isomer 2.7–2.9%, 4-isomer 19–21%; overall yields, however, are often poor. Free radical arylation also results in substitution at all 3-positions and while substitution at the 2-position is still preferred, the amount of 3-aryl-substituted pyridine tends to be higher than in the case of free radical alkylation. These results indicate that the phenyl is less nucleophilic than the methyl radical. Free radical alkylation of isoquinoline, quinoline and quinolinium ions, and acridine, has also been studied in some detail; in most cases, however, the yields are very poor, and disubstitution (2,4-) is common with quinoline. There has been very little study of free radical alkylation and/or arylation of the oxygen and sulfur heterocycles.

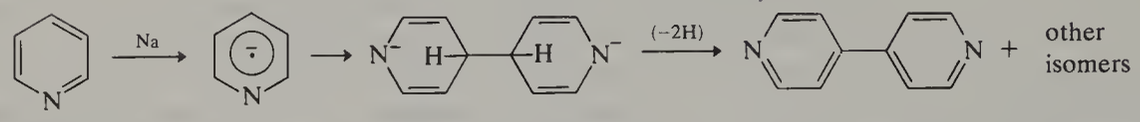
Free radical acylation of pyridines generally results in predominant or exclusive formation of the 2- and 4-substituted isomers, and carbamoylation, carboxylation and halogenation show similar product distributions. In certain of these reactions, most notably carbamoylation, synthetically significant yields of substitution products can be realized, but in many cases while quoted yields can look impressive, actual conversions can be very low ⟨74AHC(16)123⟩.

One commercially very important type of radical reaction of pyridines involves treatment of pyridine with certain metals such as sodium, zinc or Raney nickel. This results in formation of the corresponding radical anion which can undergo oxidative dimerization as outlined in Schemes 15 and 16, to give both 2,2′- and 4,4′-bipyridyl. Quaternization of these bipryidyls then gives the corresponding diquaternary salts, two of which in particular, diquat and paraquat, are manufactured on a large tonnage scale for use as weedkillers.

Another type of reaction which occurs at a metal surface and which is most conveniently discussed in this section is catalytic hydrogenation. Pyridine is reduced rather more easily than benzene, and quinoline and isoquinoline give the 1,2,3,4-tetrahydro derivatives.

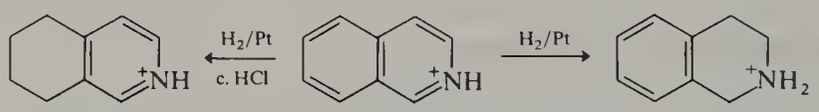


Scheme 15



Scheme 16

Pyridinium salts and pyridones also undergo catalytic hydrogenation reasonably smoothly, although there are numerous examples to illustrate that the product formed can depend on the nature of the catalyst used. Platinum-catalyzed hydrogenation of isoquinoline normally reduces the pyridine ring, but in the presence of an excess of hydrochloric acid the reagent preferentially attacks the benzene ring and forms 5,6,7,8-tetrahydro derivatives (equation 59). Generally speaking, however, catalytic reduction of the azines has not been investigated in great detail and is not a very widely used preparative procedure.

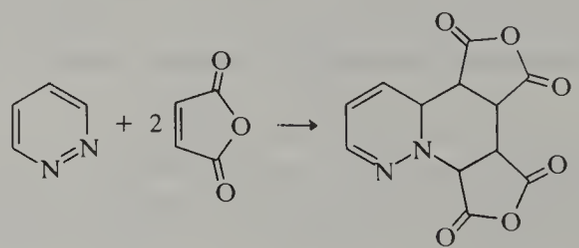


(59)

The oxygen and sulfur heterocycles, including pyrylium and thiopyrylium salts, are readily reduced catalytically. Moreover, it is usually possible to control the degree of reduction; both pyran-2- and -4-ones can readily be reduced to dihydro derivatives, in the former case the 5,6-dihydro compound. Examples of catalytic reduction of the oxo substituents to either the corresponding alcohol or to the methylene group are known, but these reactions normally occur only under pressure.

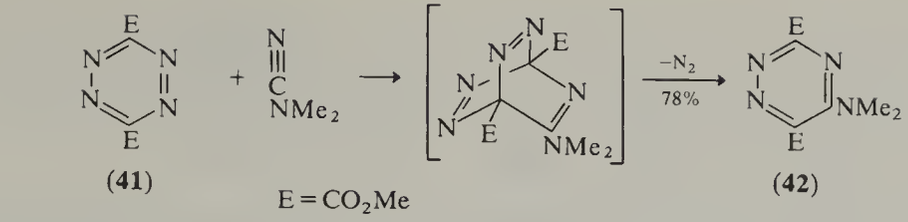
2.02.2.6 Reactions with Cyclic Transition States

In this section we deal with two important processes, the Diels–Alder reaction and Claisen rearrangements, as opposed to reactions discussed in Section 2.02.2.2 such as photoisomerization, some of which, strictly speaking, can be properly interpreted as proceeding *via* cyclic transition states. Diels–Alder reactions of the six-membered heterocycles are fairly common; in most cases the heterocycle functions as the diene component, but in some instances it participates as the dienophile. Pyridazine, for example, reacts readily at room temperature with maleic anhydride to give the 2 : 1 adduct (**40**; equation 60). Some triazines and tetrazines also readily undergo Diels–Alder reactions, and in many instances the possibility of loss of molecular nitrogen or a nitrile from an intermediate adduct results in facile aromatization and an overall ring transformation. These reactions are almost all of the 'inverse electron demand' type, as illustrated in the transformation of the 1,2,4,5-tetrazine (**41**) into the 1,2,4-triazine (**42**; equation 61) (for a recent review see Chapter 2.21 and ⟨82T3087⟩). This general approach can be modified by incorporation of a leaving group into the dienophile, as outlined in equation (62) ⟨82JOC895⟩. This procedure, which can give excellent yields of substituted and annelated pyridines, goes under very mild conditions, does not require prior formation of enamine, and in some instances needs only a catalytic amount of pyrrolidine.



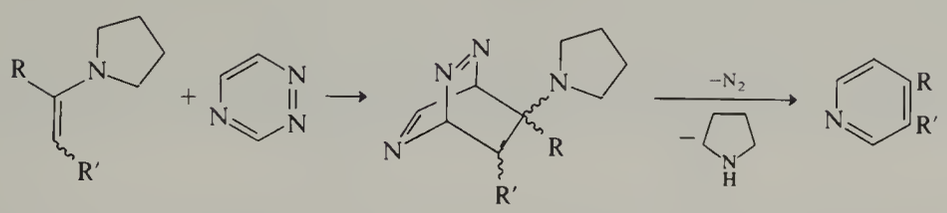
(60)

(40)



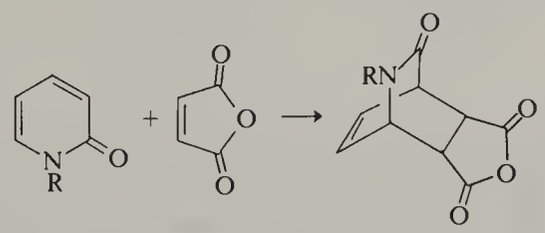
(41) (42)

$E = CO_2Me$ (61)

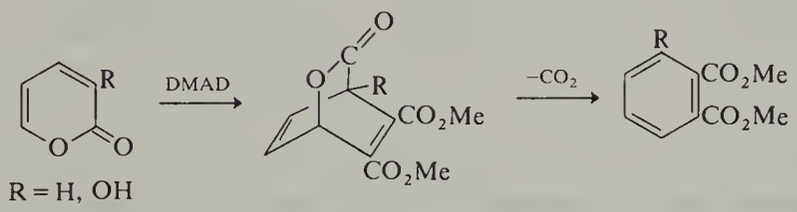


(62)

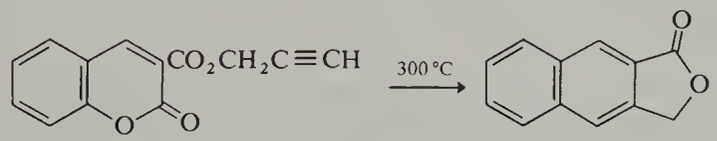
Intermolecular cycloaddition reactions involving 2-pyridones are also well known (*e.g.* equation 63), as are those of pyran-2-ones (equation 64). Here the heterocycles function as the diene components and loss of an isocyanate or carbon dioxide can lead ultimately to aromatic products. This is particularly important in the case of the pyran-2-ones and the reaction has been quite widely used for the synthesis of both aromatic compounds and cyclohexadienes. The benzo-fused heterocycles do not undergo cycloaddition so readily, as aromaticity must necessarily be lost in adduct formation; reaction can, however, occur under forcing conditions (equation 65) but yields are generally only moderate. A few other intramolecular Diels–Alder reactions are known with six-membered heterocycles, but this aspect has not been studied intensively. Examples of reactions in which the heterocyclic compounds function as dienophiles are shown in equations (66)–(68). The betaines derived from 3-hydroxypyridinium salts and some benzo-fused analogues undergo 1,3-dipolar cycloaddition reactions (*e.g.* equation 69) to give products which can readily be converted into tropones and tropolones. These reactions have been investigated in considerable detail.



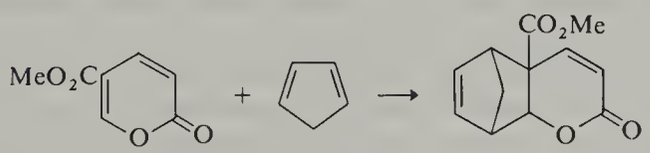
(63)



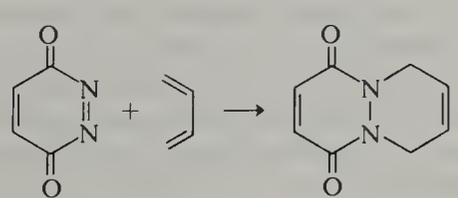
R = H, OH (64)



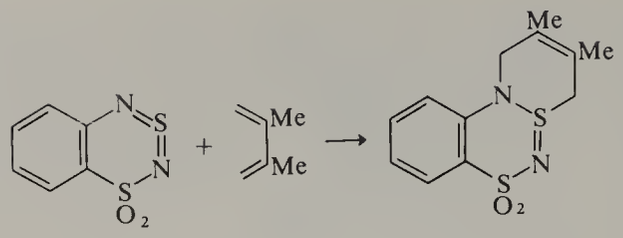
(65)



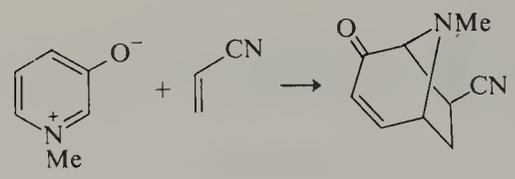
(66)



(67)

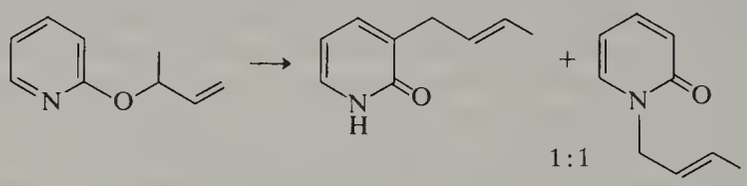


(68)

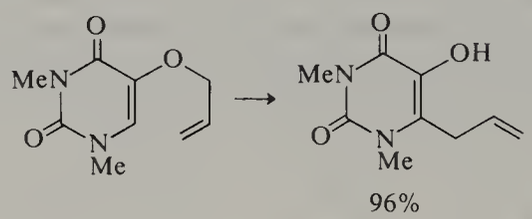


(69)

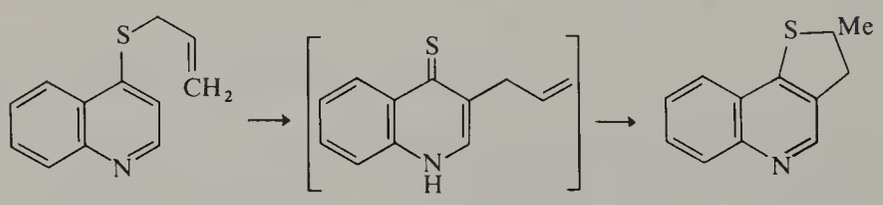
The Claisen rearrangement of allyloxy heterocycles is another reaction which has been studied in some detail. Yields can be variable and mixtures of *N*- and *C*-allyl products are sometimes obtained (*e.g.* equation 70). In other cases the reaction can be of considerable synthetic utility (*e.g.* equation 71). The thio-Claisen rearrangement has also been studied; in many cases the intermediate thiones react further (equation 72), although they can also be trapped, for example with ethyl chloroformate.



(70)



(71)

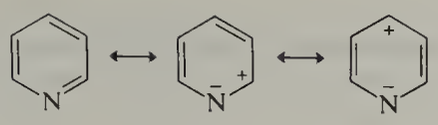


(72)

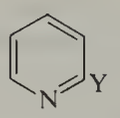
2.02.3 REACTIVITY OF SUBSTITUENTS: AROMATIC COMPOUNDS

2.02.3.1 General Survey

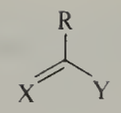
The influence of the heteroatoms on the reactivities of substituent groups in the six-membered π-deficient heterocyclic systems is very largely predictable as a consequence of the relative electron distribution within the ring (see, for example **43**). This in turn is dependent on both the number and nature of the heteroatoms, particularly whether or not they are charged. As a general rule, the effect of the heteroatom on substituent groups is greater in pyridinium, pyrylium and thiopyrylium systems than in uncharged systems. Another general rule is that the effect of the heteroatom is relatively small with respect to substituents β to it whereas the effect on α and γ substituents is pronounced. This follows because substituents β to the heteroatom cannot conjugate with it and consequently react very much as they would do if they were attached to a benzene ring. The reactivity of a 2- (and by vinylogy 4-) substituted pyridine (**44**) is frequently likened to that of the corresponding acyl (**45**) or imino (**46**) derivative and while this can be a useful rule of thumb it should be explained that acyl derivatives are almost invariably much the more reactive; the reactivity of α and γ substituent groups is thus intermediate between those of the same substituent groups attached to a benzene ring and to an acyl group.



(43)



(44)

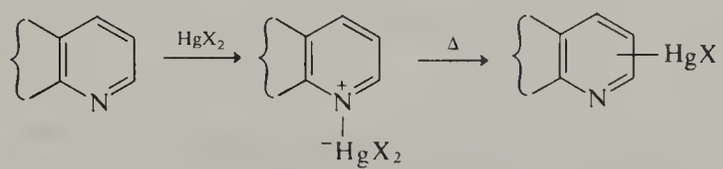


(45) X = O
(46) X = NH

Simple considerations such as these account adequately for many of the familiar reactions of substituted π-deficient heterocycles, such as nucleophilic displacement, tautomerism in hydroxy, mercapto and amino heterocycles, facile deprotonation of alkyl substituents, decarboxylation of carboxymethyl groups and electrophilic substitution of benzo-fused and aryl-substituted heterocycles. These individual effects are discussed separately in the following subsections.

2.02.3.2 Fused Benzene Rings

There is a substantial amount of evidence to indicate that fusion of a benzene ring to a six-membered π-deficient heterocyclic system results in a certain degree of bond fixation and, consequently, much of the chemistry of quinoline and isoquinoline, for example, can be rationalized in terms of the chemistry of naphthalene and pyridine. The most important effect of benzo fusion is in electrophilic aromatic substitution reactions where, as would be predicted, reaction almost invariably occurs in the benzo ring and not in the heterocyclic ring. The only common exception is mercuration; both quinoline and isoquinoline, for example, undergo mercuration in the heteroaromatic ring, although elevated temperatures are necessary to induce rearrangement of the initially formed N—HgX_2 adduct (equation 73).



(73)

In other common electrophilic aromatic substitution reactions such as halogenation, nitration and sulfonation, substitution takes place exclusively in the benzo-fused ring, and while quinoline and isoquinoline undergo substitution under mild to moderate conditions, rather forcing conditions may be necessary for substitution in the benzodiazines. Nitration of quinoline and isoquinoline, for example, proceeds in good yield and gives a mixture of the 5- and 8-nitro derivatives. The parallel between quinoline and naphthalene can be clearly seen in sulfonation. Thus treatment of quinoline with sulfuric acid at 220 °C gives a mixture of the 8- and the 5-isomer with the former predominating. At higher temperatures (300 °C) the main product is the thermodynamically favoured 6-isomer and, as expected, both the 5- and 8-isomers undergo rearrangement to the 6-isomer under the appropriate conditions. Isomer distributions in electrophilic halogenation of quinoline are very similar to those in nitration but at high temperatures the reactions become radical in nature and quinoline undergoes substitution either at the 3- or the 2-position depending on the reaction temperature. With isoquinoline, bromination in the presence of a Friedel–Crafts catalyst results in substitution at the 5-position. When isoquinolinium hydrobromide is heated with bromine, however, an addition–elimination reaction occurs with overall substitution at the 4-position. With the exception of nitration, electrophilic aromatic substitution of benzodiazines and triazines has not been studied in any great detail, partly because the products that would be expected from these reactions are often easier to obtain *via* ring synthesis of the heterocyclic system.

Electrophilic aromatic substitution of other benzo-fused π-deficient systems generally follows predictable pathways. Thus, benzopyrylium salts are in general resistant to electrophilic substitution even in the benzo-fused ring. Chromones behave somewhat similarly, although substitution can be effected under forcing conditions. Coumarins, on the other hand, undergo nitration readily in the 6-position while bromination results in substitution at the 3-position as a consequence of addition–elimination.

The effects of substituent groups in the benzo-fused ring on the ease of electrophilic aromatic substitution are essentially identical to those of the same substituent groups in benzene, so electron-donating groups facilitate reaction while electron-withdrawing groups

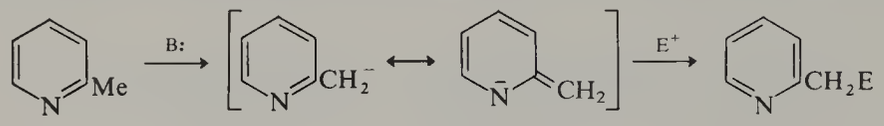
make further substitution more difficult. The orientation of substitution, however, can be influenced substantially by bond fixation. Thus, nitration of 5-methylquinoline gives both the 6- and 8-nitro isomers while nitration of 7-methylquinoline gives only the 8-nitro product. The effect of substituents in the heterorings is also largely predictable. Thus, introduction of a hydroxy substituent into the 4-position of coumarins greatly facilitates electrophilic substitution at the 3-position.

Oxidation of quinoline and isoquinoline under vigorous conditions with potassium permanganate results in oxidative degradation of the benzo-fused ring and formation of pyridine-2,3- and -3,4-dicarboxylic acid respectively. As expected, the presence of electron-donating substituents facilitates the reaction while electron-withdrawing substituents make oxidation much more difficult. Apart from *N*-oxide formation, little study has been devoted to the oxidation of other benzo-fused π–deficient systems.

2.02.3.3 *C*-Linked Substituents

2.02.3.3.1 Alkyl groups

Alkyl groups in the π-deficient six-membered heterocyclic systems are more reactive than alkyl groups attached to a benzene ring. Substituents in the 3-position are slightly more reactive as a consequence of the overall electron deficiency of the ring system while substituents α and γ to the ring nitrogen are significantly more reactive, especially in processes which proceed *via* base-catalyzed deprotonation from the alkyl substituent, as the resulting anions are resonance-stabilized (equation 74).



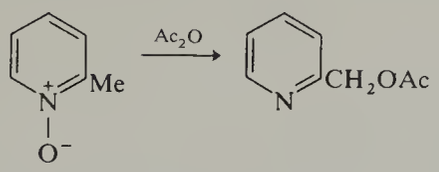
(74)

As expected, substituents in positively charged heterocyclic systems, *i.e.* the *N*-oxides and the pyridinium, pyrylium and thiopyrylium salts, are even more reactive than those in uncharged systems. The effects of other substituent groups on the reactivity of alkyl substituents is also generally predictable; for example, electron-withdrawing groups further facilitate the ease of proton removal from alkyl groups α and γ to the ring nitrogen atoms. Alkyl groups α and γ to the ring heteroatom in pyridones, pyrones and thiopyrones also readily undergo a range of base-catalyzed condensation reactions.

The increased reactivity of alkyl substituents α and γ to a ring heteroatom, compared with those in benzene, is of very considerable synthetic utility. Many 2- and/or 4-alkyl- (and in particular methyl-) substituted heterocycles are relatively readily available either from commercially exploitable natural sources (for example, coal tar distillation) or by ring synthesis (see the monograph chapters); by contrast, there are certain other functional groups, ranging from simple substituents such as acyl to more complicated functionalized side chains, which are not at all readily available from either of these routes. The ease with which alkyl substituents can be converted into a wide range of other substituents is thus the basis of the most important general process for the introduction of functionalized carbon substituents into the π-deficient heterocyclic systems. Direct oxidation of 2- and 4-methyl substituents with potassium permanganate, for instance, results in conversion into the corresponding carboxylic acids, while use of selenium dioxide gives the corresponding aldehydes. The latter are also available by controlled vapour phase oxidation and, of course, serve as precursors to the corresponding primary alcohols. Indirect oxidation of methyl groups is also possible. Thus, radical bromination with NBS gives the corresponding bromomethyl compound (not easily available by base-catalyzed halogenation), which can be converted into the corresponding aldehyde, cyanide, *etc.*, by standard transformations. Reaction of α- and γ-methyl substituents with chlorine, sodium hypochlorite, bromine, *etc.*, normally results in formation of the trihalomethyl derivative (*cf.* the haloform reaction) and these in turn can be hydrolyzed to the corresponding carboxylic acids.

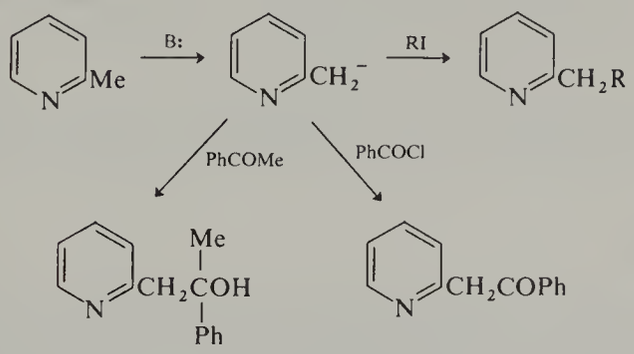
One very important method for the indirect oxidation of a 2-methyl substituent group in particular, in the azines, is the reaction of the corresponding *N*-oxide with acetic anhydride. This process, outlined in equation (75), gives initially the corresponding 2-acetoxymethyl derivative; yields are generally good to excellent with only minor amounts

of isomeric by-products being formed. Substituents of the type $PyCH_2R$ usually, but not invariably, behave in an analogous fashion. Direct oxidation gives the corresponding ketone PyCOR which may also be obtained indirectly *via* halogenation to give $PyCX_2R$ followed by hydrolysis.

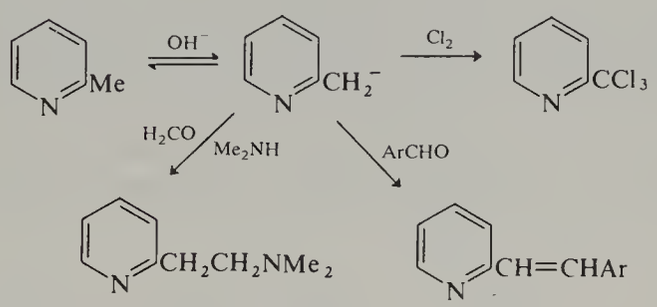


(75)

The most important reactions of alkyl substituents α and γ to the ring heteroatom are those which proceed *via* base-catalyzed deprotonation. Treatment of 2- and 4-alkyl heterocycles with strong bases such as sodamide and liquid ammonia, alkyllithiums, LDA, *etc.*, results in an essentially quantitative deprotonation and formation of the corresponding carbanions. These then react normally with a wide range of electrophiles such as alkyl halides and tosylates, acyl halides, carbon dioxide, aldehydes, ketones, formaldehyde/dimethylamine, *etc.*, to give the expected condensation products. Typical examples of these transformations are shown in Scheme 17. Deprotonation of alkyl groups by the use of either aqueous or alcoholic bases can also be readily demonstrated by NMR spectroscopy, and while the amount of deprotonation under these conditions is normally very small, under the appropriate conditions condensations with electrophiles proceed normally (Scheme 18).

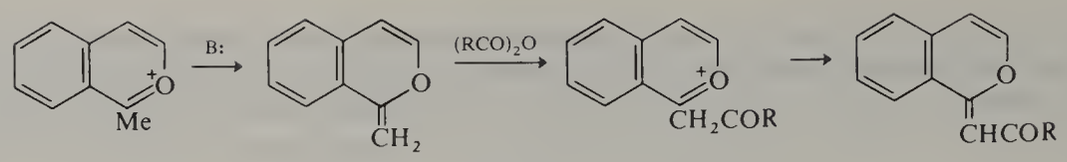


Scheme 17

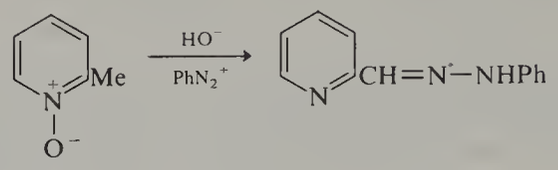


Scheme 18

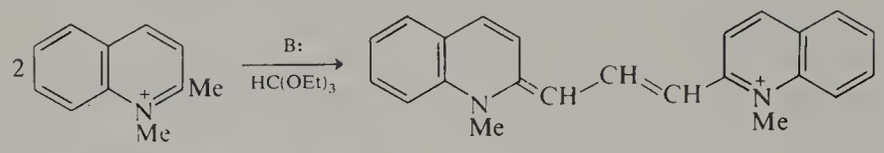
N-Oxides, pyridinium, pyrylium and thiopyrylium salts undergo essentially similar types of reaction, but, as expected, these take place somewhat more easily than with the corresponding uncharged heterocycles. 2-Methylpyridine, for example, does not undergo Claisen condensation with diethyl oxalate; the reaction can, however, be carried out successfully with 2-methylpyridine 1-oxide. Deprotonation of pyridinium, pyrylium and thiopyrylium alkyl substituents gives relatively stable neutral anhydro bases which can sometimes be isolated. These readily react with electrophilic reagents and under the reaction conditions the products frequently undergo further deprotonation to give substituted resonance-stabilized anhydro bases (Scheme 19). Moreover, because of the increased reactivity of alkyl substituents α and γ to a charged heteroatom it is possible to effect certain transformations with weak electrophiles which do not take place in uncharged π-deficient heterocyclic systems. The Claisen condensation of 2-methylpyridine 1-oxide described above is one such example, and other important instances are the formation of phenylhydrazones and oximes by reaction with diazonium salts and nitrosating agents, and the preparation of cyanine dyes (equations 76 and 77).



Scheme 19



(76)



(77)

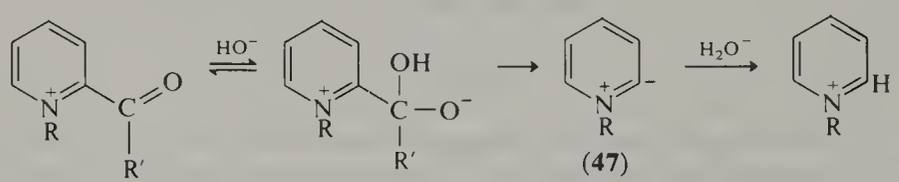
2.02.3.3.2 Aryl groups

Many aryl- and heteroaryl-substituted derivatives of the π-deficient heterocyclic compounds have been prepared and some of them are of considerable commercial importance, for example as pesticides (paraquat and diquat) and as pharmaceuticals.

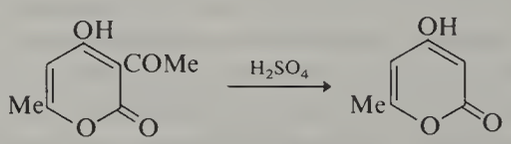
The chemistry of the aryl and heteroaryl substituents is very largely predictable and unremarkable; it is governed by the number and nature of other substituent groups in the ring, including the electron-withdrawing π-deficient heterocyclic system.

2.02.3.3.3 Acyl groups

The situation with respect to acyl substituents is similar to that of aryl substituents, *i.e.* the π-deficient heterocyclic system exerts a significant electron-withdrawing effect on the carbonyl group and consequently nucleophilic attack at that centre takes place readily. The acyl groups therefore form normal derivatives such as oximes and phenylhydrazones and undergo normal reactions of the functional group such as reduction, the Cannizzaro and Willgerodt reactions and the benzoin condensation. Acyl groups adjacent to a quaternized pyridinium nitrogen atom are susceptible to removal by nucleophilic attack (equation 78). A similar removal of 2-(α-hydroxyalkyl) groups by action of a base is known. These reactions are of the 'retro-aldol' or 'retro-Claisen' type, and the heterocycle is eliminated as the zwitterionic species, or 'nucleophilic carbene' (**47**). Acid-catalyzed deacylation can also occur, at an activated site (*e.g.* equation 79).



(78)

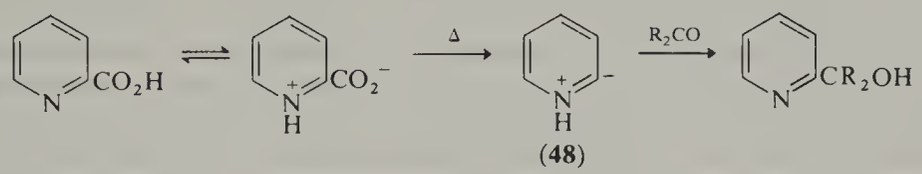


(79)

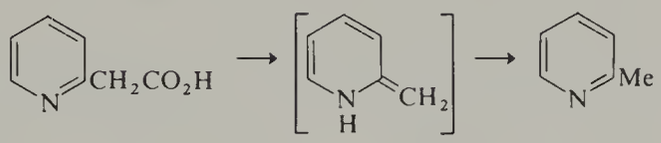
2.02.3.3.4 Carboxylic acids, acid halides and cyanides

Pyridine, pyrone and pyridone carboxylic acids undergo decarboxylation when heated, and the general order of reactivity is $\alpha \gg \gamma > \beta$. In pyridine, the carboxylic acids, as expected, exist mainly in the zwitterionic forms and decarboxylation of the α and γ isomers under fairly mild conditions is a consequence of the relative stability of the ions of the type (**48**).

The intermediacy of the ions (**48**) can readily be demonstrated by carrying out the decarboxylation in the presence of aldehydes or ketones, which results in the formation of secondary or tertiary alcohols (equation 80). Though yields are generally low to moderate in this, the Hammick reaction, it is still a useful method for the preparation of such alcohols. Pyridines which contain a carboxymethyl group α or γ to the ring nitrogen undergo very facile decarboxylation in a manner analogous to that of β-keto acids, as outlined in equation (81), and it is frequently impossible to isolate these compounds. Consequently, in transformations such as carboxylation of the anion of 2-methylpyridine outlined above, the product must be isolated as an ester or some other suitable derivative. As expected, 3-pyridineacetic acid does not undergo such facile decarboxylation. As with acyl groups, carboxy and alkoxycarbonyl groups in the 3- and 5-positions of 4-hydroxypyrones are readily removed on treatment with acid.

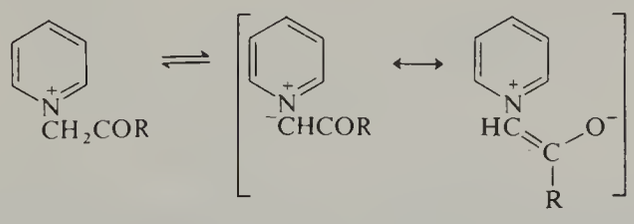


(80)

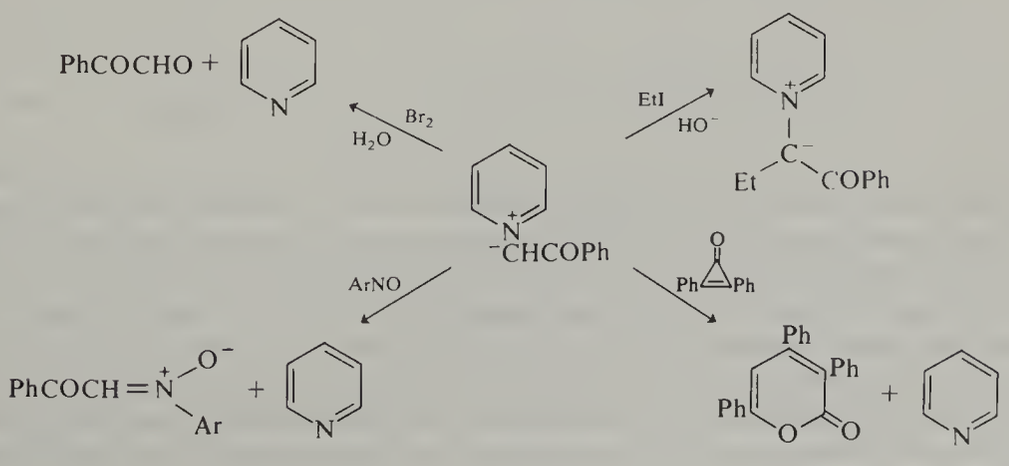


(81)

Pyridinecarboxylic acid chlorides can be prepared by a number of standard methods but they show a marked tendency to self-quaternize and, consequently, are usually best isolated as the corresponding hydrochloride salts. The carboxylic acid, carboxylic acid chloride and cyano derivatives of the π-deficient heterocycles show normal reactivity at the functional groups and they undergo a wide range of standard reactions. The effect of the heterocyclic ring on alkyl, aryl and acyl substituents in pyridinium salts is as expected, *i.e.* increased acidity of α-CH bonds and increased electrophilicity at the carbonyl group of acylpyridinium salts. The effect on CH bonds is the basis of the chemistry of the pyridine ylides, which is now thoroughly well developed. Generation of ylides is normally a straightforward process, particularly if an acylmethyl group is used to quaternize the ring nitrogen atom, and in many cases the ylides themselves can be isolated as stable products (equation 82). They undergo a wide range of reactions with electrophiles and illustrative examples are seen in Scheme 20.



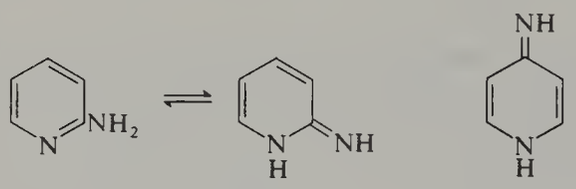
(82)



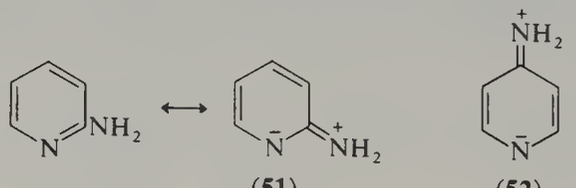
Scheme 20

2.02.3.4 *N*-Linked Substituents

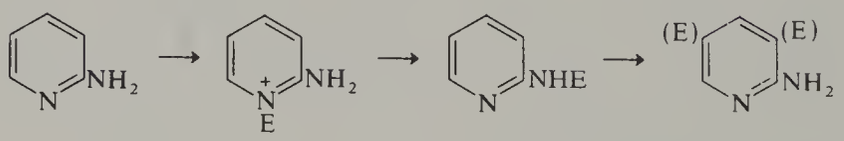
The amino group in 3-aminopyridine is very similar to that in aniline, and the diazonium salt derived from it is reasonably stable and undergoes a range of normal diazonium salt reactions. In principle, amino groups α and γ to a ring heteroatom can exist in tautomeric forms as shown in (**49**) and (**50**). In fact, the imine tautomers of 2- and 4-aminopyridines are present to only a very small extent, and the same applies fairly generally to amines of other six-membered heterocycles. Mesomeric forms such as (**51**) and (**52**) result in increased nucleophilicity at the ring nitrogen and decreased nucleophilicity at the exocyclic nitrogen atom; reaction with electrophiles, therefore, takes place initially at the ring heteroatom. In certain cases, such as alkylation and reaction with Lewis acids such as mercury(II) and thallium(III) salts, this results in the formation of stable and isolable pyridinium products which undergo rearrangement to exocyclic-*N*-substituted or *C*-ring-substituted products only under rather vigorous conditions. With other electrophiles, initial reaction at the ring nitrogen atom results in formation of unstable pyridinium salts or adducts which may rearrange to give the corresponding exocyclic-*N*-substituted products (equation 83). Thus, acylation and sulfonylation of 2-aminopyridine gives the corresponding 2-acylamino and 2-sulfonylamino derivatives. Migration to thermodynamically still more stable *C*-linked substituents can also occur. Treatment of 2-aminopyridine with nitric acid/sulfuric acid, for example, gives the corresponding 2-nitroaminopyridine which can readily be rearranged to give 2-amino-5-nitropyridine. Preferential reaction of α- and γ-amino-substituted azines with electrophiles at the ring nitrogen atom obviously presents problems when the desired reaction is at the exocyclic amino group. Clearly, to achieve this the electron density must be concentrated at the exocyclic nitrogen atom and this can be effected by conversion into a sulfilimine (**53**; equation 84) ⟨82JOC552⟩. Oxidation of (**53**) with MCPBA gives the corresponding nitroso compounds. Use of dimethyl sulfide ditriflate (rather than Me_2S/NCS) has been recommended for the preparation of sulfilimines from very poorly nucleophilic aminoazines such as methyl 2-aminopyrazine-3-carboxylate ⟨83TL1011⟩.



(**49**) (**50**)



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



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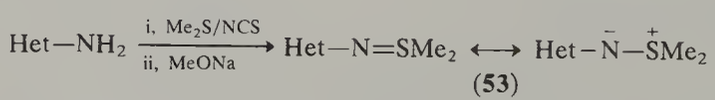
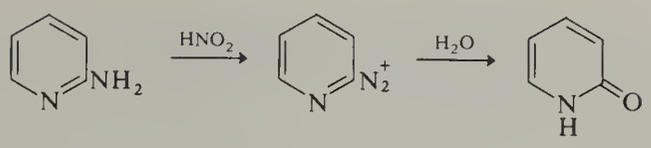


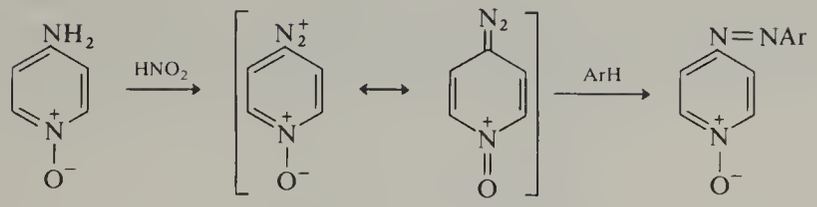
(84)

(**53**)

Diazotization of 2- and 4-aminopyridines leads to the corresponding diazonium salts which, as they cannot be stabilized by mesomeric donation of electrons from the heterocyclic ring, tend to be highly unstable. Under normal aqueous diazotization conditions, therefore, the major products tend to be 2-pyridones (equation 85). 2-Chloro- and 2-bromo-pyridines can be obtained in moderate to good yield if the diazotization is carried out in concentrated hydrochloric or hydrobromic acid. In contrast to this situation which pertains with simple aminopyridines, the diazonium salts obtained on diazotization of 2- and 4-aminopyridine *N*-oxides are stabilized by resonance and therefore undergo normal diazonium salt reactions (equation 86).

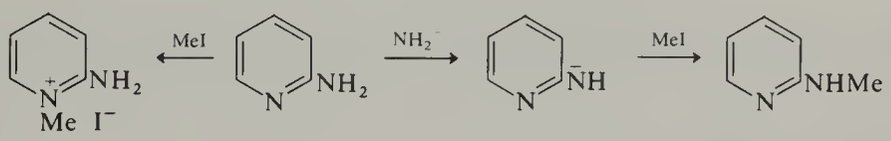


(85)

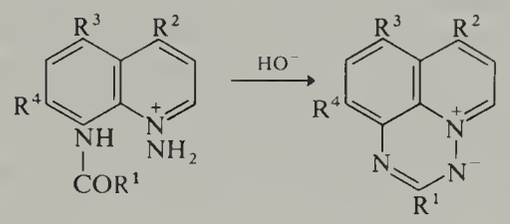


(86)

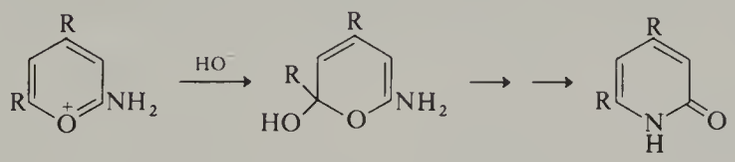
Treatment of 2- and 4-aminopyridines with strong bases such as sodamide and alkyllithiums results in deprotonation and formation of the powerfully nucleophilic anion which reacts with electrophiles preferentially at the exocyclic nitrogen atom. Thus, while treatment of 2-aminopyridine with methyl iodide gives 2-amino-*N*-methylpyridinium iodide, reaction with sodamide followed by methyl iodide gives the 2-methylamino derivative (Scheme 21). *N*-Aminopyridinium salts also undergo deprotonation to give the corresponding *N*-imides. The *N*-amino and *N*-imido compounds, and other types of *N*-amino derivative such as *N*-aminopyridones ⟨e.g. 83S49⟩, react normally with electrophiles, sometimes to produce interesting new heterocyclic systems (*e.g* equation 87) ⟨83JCS(P1)349⟩.



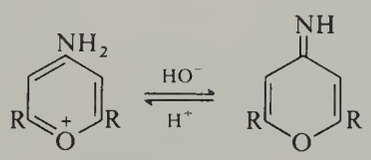
Scheme 21



(87)



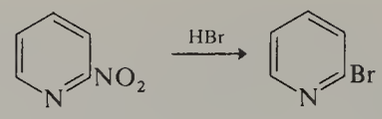
(88)



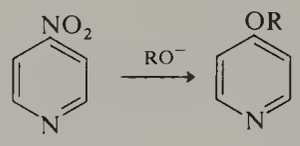
(89)

There is little or no well-defined chemistry of 2-amino-pyrones, -pyrylium salts, *etc.*, because of the ease with which these systems undergo ANRORC reactions to give substituted pyridones (equation 88). 4-Aminopyrylium salts are reversibly deprotonated to the imines (equation 89). Amino groups in the 3- and 5-positions of pyrones can be diazotized normally.

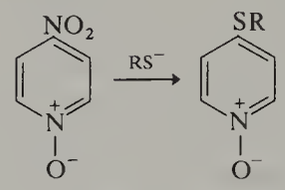
Nitro groups substituted β to a ring heteroatom are comparable to the nitro group in nitrobenzene and undergo all of the standard reactions of that functional group. Nitro groups substituted α or γ to a ring nitrogen atom, however, serve to increase the electron deficiency of the carbon atom to which they are attached and, consequently, nucleophilic attack with subsequent rearomatization and expulsion of the nitro group can be a dominant feature of these substituents. The nitro group is, in fact, an excellent leaving group, often superior to halogen, and this is an especially important feature of the chemistry of 2- and 4-nitro-substituted heterocyclic *N*-oxides. Typical transformations are outlined in equations (90)–(92). These nitro groups can also be catalytically reduced to the corresponding amino derivatives. Selective reduction of a nitro group in the presence of an *N*-oxide is possible (equation 93), while the *N*-oxide group can be removed under conditions which do not affect the nitro group. *N*-Nitropyridinium salts react readily with electron-rich aromatic



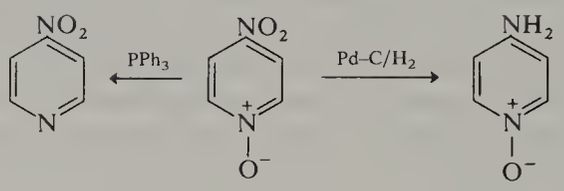
(90)



(91)



(92)

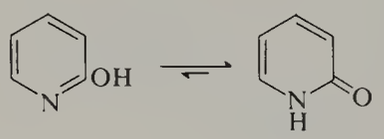


(93)

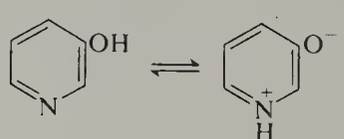
compounds to give the corresponding nitroarenes. Apart from reduction, and a little photochemistry, there has been little systematic study of the chemistry of nitropyrones.

2.02.3.5 *O*-Linked Substituents

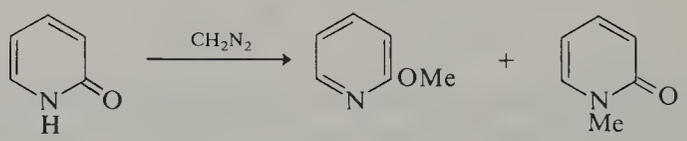
Tautomerism is a very important feature of the chemistry of heterocycles substituted with a potential hydroxy group. As described in detail in Chapter 2.01, where a potential hydroxy group is α or γ to a ring heteroatom, the -one tautomer is preferred, often to a very large extent (*e.g.* **54**), and this situation obtains rather generally. When the hydroxy group and a nitrogen in an azine are *meta* to one another, as in 3-hydroxypyridine (**55**), the NH/OH tautomerism is fairly evenly balanced in aqueous solution. Although there exist claims to the contrary, it is probable that 4-hydroxypyran-2-ones exist as such and not as the 2-hydroxy-4-ones, while 2-hydroxyazine *N*-oxides exist largely as the *N*-hydroxy-2-ones.



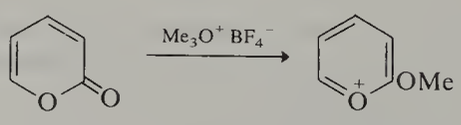
(**54**)



(**55**)



(94)



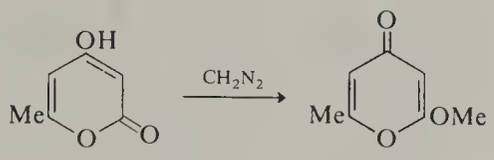
(95)

Pyridones and pyrones undergo protonation at the oxygen of the carbonyl group to give resonance-stabilized cations, and a number of other reactions with electrophiles also occur at the carbonyl oxygen atom. Treatment of 2-pyridone with diazomethane, for example, gives predominantly the 2-methoxypyridine (equation 94), while pyrones can be converted into alkoxypyrylium salts with powerful alkylating agents (equation 95).

Azinones are readily converted into the corresponding chloroazines on treatment with reagents such as phosphorus oxychloride or thionyl chloride (equation 96), *via* reaction of the carbonyl oxygen atom at the electrophilic phosphorus atom. This method can be used to introduce several chlorine atoms into polyaza heterocycles in a single operation, and the

bromo analogues are prepared similarly. 3-Hydroxypyridine does not react under these conditions, nor do the pyrones or thiopyrones. Alkylation of 3-hydroxypyridine with diazomethane gives the 3-methoxy derivative, as expected; 3- and 5-hydroxypyrones react similarly, but 4-hydroxypyran-2-ones give mainly or exclusively the 2-methoxypyran-4-ones with diazomethane (equation 97). 4-Hydroxypyran-2-ones react cleanly with phosphorus oxychloride to give the corresponding 4-chloro-2-pyranones (equation 98). Azinones are converted into the corresponding thiones on treatment with phosphorus pentasulfide, again almost certainly *via* initial attack at electrophilic phosphorus.

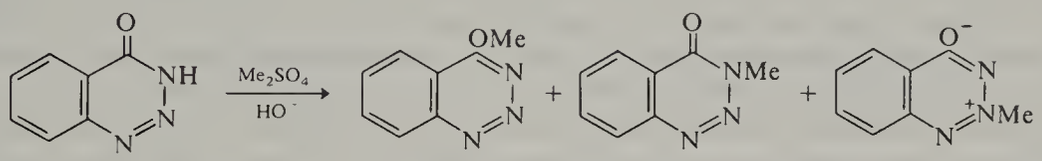
(96)



(97)

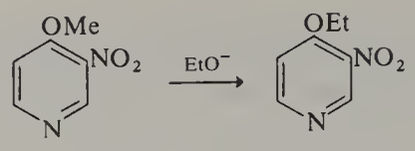
(98)

Alkylation of oxygenated heterocycles under neutral or basic conditions usually gives products isomeric with those obtained with diazomethane, although the reactions can be very sensitive to the conditions and the nature of the reagents employed. Treatment of the sodium or potassium salt of 2-pyridone with methyl iodide, for example, gives predominantly *N*-methyl-2-pyridone, while use of the silver salt gives predominantly the 2-methoxy isomer. Mixtures of the *N*- and *O*-alkylated (and sometimes *N*,*O*-dialkylated) products are commonly formed (*e.g.* equation 99), but in general this is a very important procedure for the preparation of *N*-alkyl heterocycles. 3-Hydroxypyridines are alkylated at nitrogen with alkyl halides, but hydroxypyrones are smoothly alkylated with alkyl halides or sulfates under basic conditions. Both *N*-oxides and *N*-hydroxy-2-pyridones are alkylated at the *N*-oxygen atom.

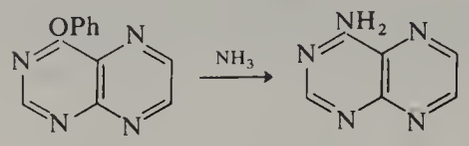


(99)

Alkoxy and aryloxy groups, when α or γ to a ring nitrogen, behave like amidic esters (iminoethers). The alkoxy group can be displaced by other nucleophiles, particularly when it is further activated by electron-withdrawing substituents (equation 100). Aryloxy groups are still better leaving groups, and are frequently used for this purpose (for instance, in the preparation of aminoheterocycles from the phenoxy compounds; equation 101). The alkyl portion of an alkoxy substituent is usually fairly readily removed, and 2- and 4-alkoxypyridines, for instance, rearrange on heating to the corresponding *N*-alkylpyridones. This reaction is catalyzed by the alkyl iodide, but it usually goes well enough without it. The aryloxy groups are fairly resistant to this rearrangement, unless nitro activation of the aryl group is present; however, under forcing conditions it too will proceed, and this reaction forms the basis for a synthetic technique for converting a phenol into an amine (equation 102). Reaction of the oxygenated heterocycles with carboxylic and sulfonic acid halides under standard conditions usually gives the *O*-derivatives, even with azinones. Using special procedures and/or conditions it is possible to obtain *N*-acyl derivatives from pyridones, but these rearrange very easily to the more stable *O*-isomers (equation 103). This contrasts with the situation in the open-chain aliphatic series, when imides (**58**) are favoured over isoimides (**57**). The reason for this difference is not certain, but it is likely that the amide resonance in the *N*-acyl from (**56**) cannot properly be developed for steric reasons. Acyloxy groups on electron-deficient heterocycles are usually very easily hydrolyzed to the corresponding acid and the hydroxy heterocycle or its tautomer; in many instances, in fact, they can be difficult to isolate.



(100)



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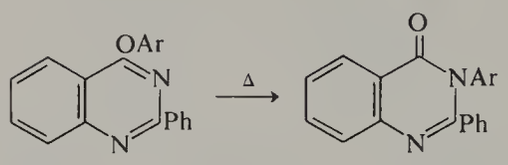
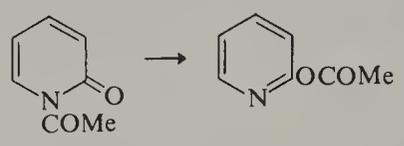
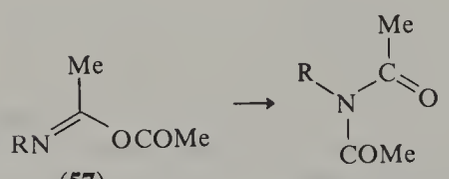


(102)



(103)

(56)

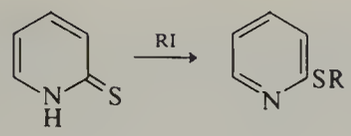


(57) (58)

2.02.3.6 *S*-Linked Substituents

Substituents attached to a heterocyclic ring through a sulfur atom exist in wider variety than those through oxygen. Besides the simple thio analogues—the thiols (mercaptans), thioethers, thioesters and the like—they include compounds of various higher oxidation states of sulfur, including sulfoxides, sulfones, sulfinic and sulfonic acids and their derivatives.

The tautomeric systems which exist where a mercapto group is *ortho* or *para* to a heterocyclic nitrogen atom are analogous to those which were discussed earlier in connection with the hydroxy compounds. A mercapto group is, in general, more acidic than a hydroxy group, but the thione grouping (C=S) has less strength in its π-bond compared with the carbonyl (C=O). These effects tend to cancel one another and, as a result, the SH/NH tautomerism is fairly similar to the OH/NH tautomerism of the hydroxyazines. Substituent and medium effects are also similar in the two series: ring halogenation near to the nitrogen weakens its basicity and favours SH forms, and thiols are frequently the favoured tautomers in the vapour phase. The reactivity of the *O*- and *S*-linked substituents of the π-deficient six-membered heterocycles is thus very similar in many instances. With the sulfur compounds, however, where most attention has been devoted to azinethiones and to thioethers derived from them by alkylation, the azinethiones behave very much as cyclic thioamides and, in contrast to the oxygen analogues, undergo smooth and essentially exclusive alkylation at sulfur (equation 104). All alkyl- and aryl-thio substituents α or γ to a ring nitrogen atom behave as reactive leaving groups in nucleophilic substitution reactions, and their oxidized forms, the sulfoxides and sulfones, are even more readily displaced. Sulfonic acids, which usually exist in zwitterionic forms in the simple aza heterocycles, also lose sulfite on attack by nucleophiles such as hydroxide or cyanide ion, though vigorous conditions are necessary. The sulfur derivatives also undergo a few reactions which are not observed with the oxygen analogues. Both thiols and thiones, for example, are oxidized to disulfides by iodine (*e.g.* equation 105), while thiones are oxidized to sulfonic acid groups under vigorous conditions (equation 106). Thioethers can be reductively removed with a variety of reagents. Cyclic thioamide or thioester reactivity has been observed in a number of reactions of thiones with typical 'ketonic' reagents (*e.g.* equation 107).



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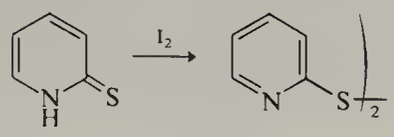
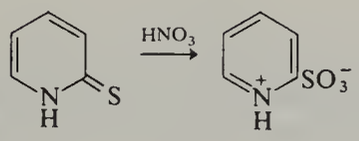
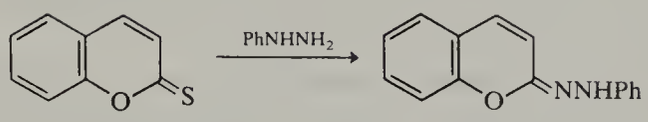


(105)



(106)

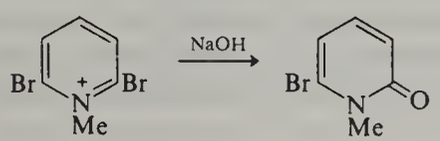


(107)

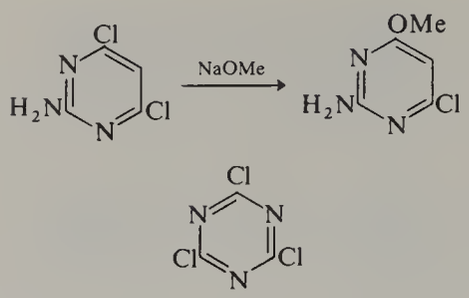
2.02.3.7 Halogen Substituents

Halogen substituents in all three positions of the pyridine ring are more reactive in nucleophilic substitution reactions than the corresponding halobenzenes as a consequence of the overall electron deficiency of the heterocyclic ring. The same general trends in substituent reactivity as are found with, for example, alkyl substituents apply to halogen substituents. Thus halogen substituents in the 2- and 4-positions are almost invariably more reactive than those in the 3-position while substituents α and γ to a positively charged ring heteroatom are even more reactive. In practice, only chloro and, to a lesser extent, bromo substituents have proved to be of any great significance in synthesis. Iodides are normally used only in special circumstances and, while there has been considerable study of polyfluoro heterocycles and of individual compounds such as 5-fluorouracil, the chemistry of simple fluoro derivatives of the π-deficient heterocycles has not been widely explored.

The relative reactivity of the halogens with respect to nucleophilic substitution is Cl < Br < I, but in practice most reactions of this type have been carried out with the chloro derivatives. Nucleophilic substitution of 2- and 4-halo derivatives generally occurs smoothly under relatively mild conditions but more forcing conditions are normally required with 3-halo derivatives. Nucleophilic substitution of 2- and 4- halo heterocycles is an extremely important method for the introduction of a wide range of oxygen (OH, OR, OAr), sulfur (SH, SR, SAr), nitrogen (NH_2, NR_2, $NHNH_2$, *etc.*) and carbon (CN, CR_3) substituents. Moreover, by appropriate control of the reaction conditions it is usually possible to effect selective halogen replacement in di-, tri- and poly-halo derivatives; typical examples are shown in equations (108) and (109). These reactions are of particular importance in the chemistry of the diazines and triazines. As mentioned previously, the overall effect of introducing additional nitrogen atoms into the pyridine ring system is greatly to facilitate nucleophilic attack across a polarized C=N bond and this trend can be clearly seen in the relative reactivities of the di, tri- and poly-halo derivatives of diazines and triazines. The reactivity of the chlorine atoms in cyanuric chloride (**59**) towards nucleophilic substitution, for example, approaches that of an acid chloride, while chloropyrazine, 3-chloropyridazine, and 2- and 4-halopyrimidines are all significantly more reactive in nucleophilic substitution reactions than 2-chloropyridine. 2- and 4-Halopyrimidines in turn are more reactive than 2-chloropyrazine or 3-chloropyridazine. These relative reactivities can be explained in terms of the resonance stabilization possible in the anionic intermediate formed by addition of the nucleophile to the halo heterocycle. Thus, in cyanuric chloride, 2- and 4-halopyrimidines, 2-chloropyrazine and 3-chloropyridazine, three, two, one and one nitrogen atoms, respectively, participate in stabilization of the negative charge. Similar arguments can be used to account for the fact that 3-haloisoquinolines undergo nucleophilic substitution much less readily than the isomeric 1-halo derivatives.



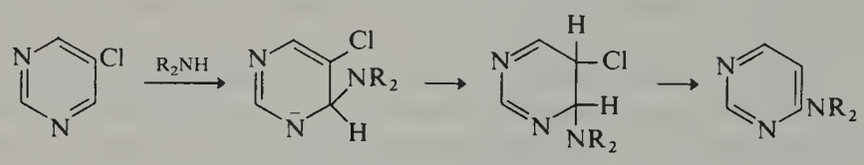
(108)



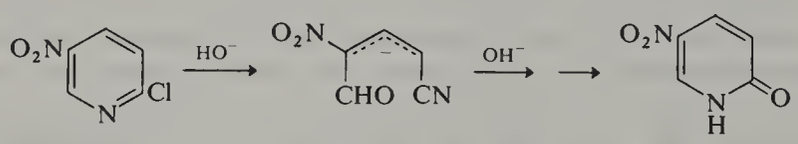
(**59**)

The effects of other substituent groups on the reactivity of ring halogen atoms are predictable. Electron-donating substituents make nucleophilic substitution more difficult while electron-withdrawing substituents facilitate the process. The effect of an electron-withdrawing substituent which is so positioned that it can participate in resonance stabilization of the intermediate adduct can be considerable.

The vast majority of the nucleophilic substitution reactions in halo derivatives of six-membered heterocycles proceed by a 'normal' addition–elimination mechanism (AE_n) but there are other well-established pathways for substitution. One involves aryne intermediates, as in the pyridynes, which, as in benzenoid chemistry, can be generated from either 2,3- or 3,4-dihalopyridines, or by dehydrohalogenation of halopyridines, usually the 3-halo derivatives. This involves the elimination–addition sequence (EA), and may proceed with partial or complete '*cine*-substitution', where the entering group occupies a site adjacent to that vacated by the leaving group. Another addition–elimination process, which involves complete *cine*-substitution, is the 'abnormal' (AE_a) mechanism ⟨65AG(E)543⟩. In this the nucleophile adds to the neighbouring site, and elimination proceeds with intervention of protonation, as shown in equation (110). A variant of this, in which the nucleophile attacks a more distant site, results in '*tele*-substitution'. A further category of substitution reaction is the S_N(ANRORC) type; an example is shown in equation (111) ⟨80JOC3097⟩.

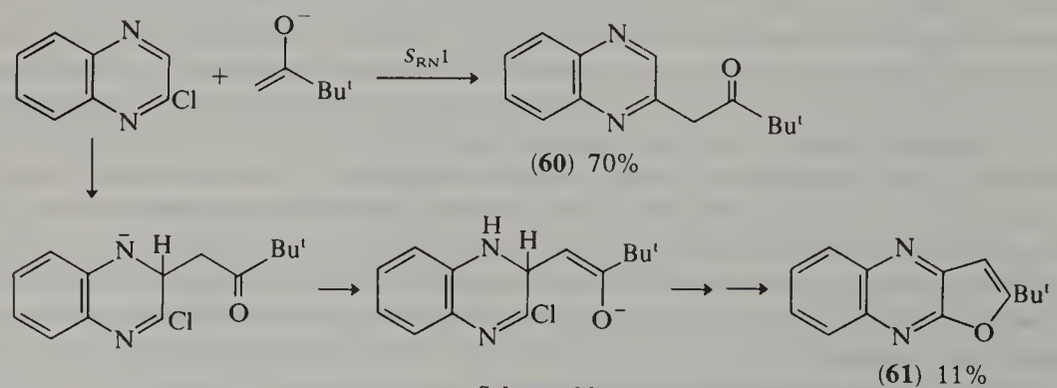


(110)



(111)

A mechanism for heteroaromatic nucleophilic substitution which is under considerable active study at the present time is the S_{RN} process, which often competes with the addition–elimination pathway. S_{RN} reactions are radical chain processes, and are usually photochemically promoted. An example is shown in Scheme 22, where (**60**) is formed by the $S_{RN}1$ pathway and (**61**) *via* an initial addition reaction ⟨82JOC1036⟩.



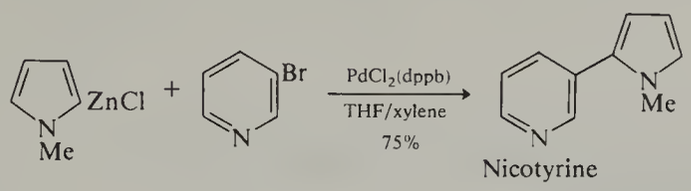
(**60**) 70%

(**61**) 11%

Scheme 22

Apart from nucleophilic substitution reactions, the chemistry of the halo derivatives of the π-deficient heterocycles is fairly similar to that of aromatic halides. Thus, heterobiaryls can be prepared by the Ullman reaction, and Grignard reagents and organolithium compounds can be prepared, although in many instances, and especially with Grignard reagents,

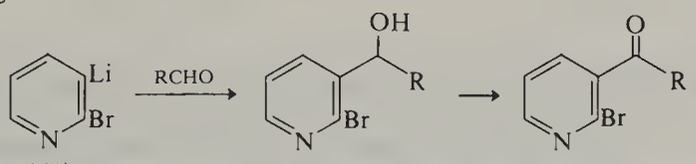
the reactions are sluggish and inefficient unless experimental variations of the standard methods are used. Halopyridines, like aromatic halides, also participate in transition metal cross-coupling reactions, and these processes are being investigated in increasing detail as methods for the rapid and efficient preparation of moderately complicated molecules (*e.g.* equation 112). Reductive dehalogenation of haloazines can be carried out either by catalytic hydrogenation or by chemical reduction. As expected, halogen atoms α and γ to ring nitrogen can be selectively reduced (*e.g.* with zinc and acid).



Nicotyrine (112)

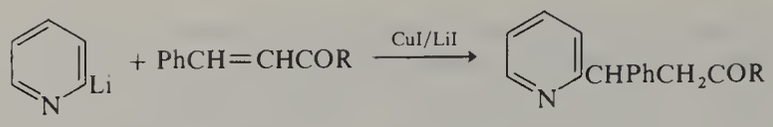
2.02.3.8 Metal Substituents

The organometallic chemistry of the π-deficient heterocycles is still relatively sparse, primarily because many of the classical methods for the synthesis of organometallic compounds are incompatible with the properties of the π-deficient heterocyclic ring. Thus, processes which involve the use of anionic reagents can be complicated by nucleophilic addition reactions to the ring, while those which involve the use of electrophilic metal salts, for example, give rise to Lewis acid–Lewis base complexes by reaction at a ring nitrogen position. Formation of Grignard reagents by direct reaction of halogenopyridines with magnesium normally proceeds poorly and these organometallics are best prepared by use of the entrainment method. Heteroaryllithium reagents can be prepared by halogen–lithium exchange using alkyllithiums, but careful control of the experimental conditions is usually necessary to minimize nucleophilic addition reactions. Organolithium derivatives may also be prepared by hydrogen–lithium exchange and there is increasing interest in this area, especially in 'directed' lithiation. Both the Grignard and organolithium reagents react normally with a wide range of electrophiles and these reactions can be of considerable synthetic utility. 2-Bromopyridine, for example, can be lithiated exclusively in the 3-position using LDA; reaction of the 3-lithio derivatives (**62**) with aldehydes followed by oxidation of the product secondary alcohols with chromium trioxide or manganese dioxide gives 2-bromo-3-pyridyl ketones not readily accessible by other routes ⟨82JCR(S)278⟩. As mentioned earlier, the pyrones can be lithiated in the 3(5)-position by treatment with LDA. These lithio derivatives react normally with electrophiles, but the field has not been extensively investigated.

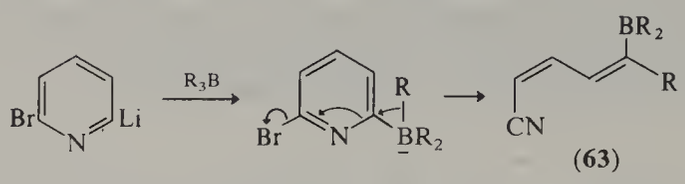


(**62**)

As expected, the heteroaryllithio derivatives undergo metal–metal exchange reactions with metal salts, and magnesium, boron, copper, mercury, tin and arsenic derivatives have been made in this way. Again, however, this whole area remains virtually unexplored, even though in some instances there are clear indications that useful and/or novel chemistry could be developed. The organocuprate derived from 2-pyridyllithium, for example, undergoes smooth conjugate addition to α,β-unsaturated ketones and esters (equation 113) ⟨82T1509⟩, while treatment of 2-bromo-6-lithiopyridine with a trialkylborane, for example, results in initial formation of the corresponding organoborate, which undergoes very facile opening of the heterocyclic ring to give the organoborane (**63**; equation 114). In other cases, however, the reactions are less exciting. Organomercury compounds, for example, which can be prepared as outlined above, can be converted into bromides, iodides, *etc.*, by standard procedures. In most cases the overall yields of substituted heteroaromatics are at best moderate and the overall process offers little advantage over alternative methods for the preparation of these derivatives. This general approach may, however, be of some value in the cases of oxygen and sulfur heterocycles. 1,4-Benzodithiin, for example, undergoes mercuration in good yield, and a more systematic study of related reactions could be profitable.



(113)

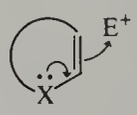


(114)

2.02.4 REACTIVITY OF PARTIALLY AND FULLY SATURATED COMPOUNDS

2.02.4.1 General Survey

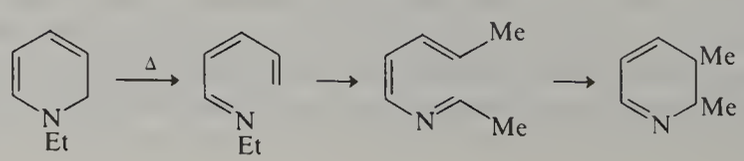
The very wide variety of saturated and partially saturated six-membered heterocyclic rings makes it very difficult to present a concise and unified picture of their reactivity. As with the aromatic compounds, however, the reactivity at the ring atoms of the partially and fully saturated six-membered heterocycles is largely predictable, but for these compounds the reactivity is based almost entirely on aliphatic/alicyclic/functional group chemistry. Thus, dihydro heterocycles, especially in the azine series, are often very labile and are easily oxidized to the corresponding aromatic compounds; dihydro compounds in which the heteroatom is directly attached to a carbon–carbon double bond react at carbon with electrophiles (see **64**); dihydropyranones react as typical lactones; and 1,2-dithianes undergo facile reductive cleavage of the S—S bond. Piperidine, tetrahydropyran and tetrahydrothiopyran behave as a typical secondary amine, ether and thioether respectively. The partially and fully reduced six-membered heterocycles thus show a very wide range of reactivity, though by no means all of it either involves a heteroatom or, indeed, is significantly influenced by the heteroatom. The main features of this reactivity are discussed briefly in the following sections, and more fully in the appropriate monograph chapters.



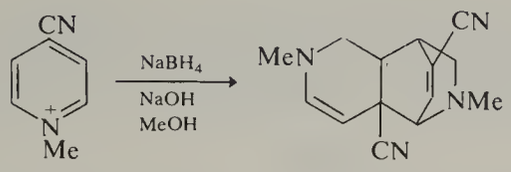
(**64**) X = NR, O, S

2.02.4.2 Thermal and Photochemical Reactions Involving No Other Species

There has been very little systematic study of thermal and photochemical processes involving no other species. Even so, some general trends are discernible with respect to *different* structural types. Thus, like cyclohexadienes, dihydropyridines undergo disproportionation on heating (*e.g.* distillation) to pyridines and tetrahydropyridines, and the benzo analogues behave similarly. In the classical Bischler-Napieralski synthesis of 1-phenylisoquinoline from *N*-phenethylbenzamide, this disproportionation went unnoticed for many years; what was originally believed to be the 3,4-dihydro compound was eventually found to be a mixture of the isoquinoline and the tetrahydro derivative. Alkenyl-substituted dihydropyridines undergo a related type of reaction, the heterocyclic ring being oxidized and the alkenyl substituent reduced. Rings with a 1,2-dihydro pattern of reduction (*i.e.* the 1,2-, 2,3- and 3,4-dihydro compounds) are capable of electrocyclic ring opening to form azahexatrienes. This kind of reaction is observed, *e.g.* in the thermal rearrangement shown in equation (115). They have also been observed to act as dienes, and dienophiles, as shown in equation (116).

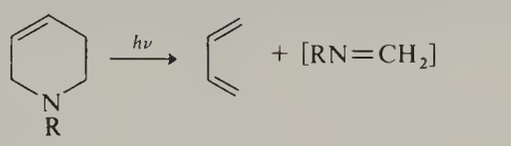


(115)

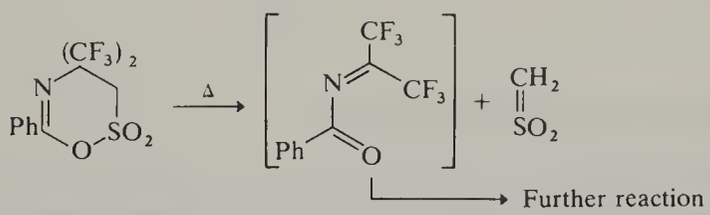


(116)

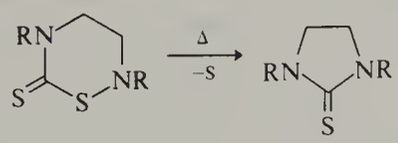
A number of thermal and/or photochemical reactions proceed either by fragmentation of the ring or by extrusion of part of the ring, for example as N_2, CO_2, SO_2, *etc.* Thus photolysis of 1,2,3,6-tetrahydropyridines results in retro-Diels–Alder reaction (equation 117) and similar reactions are observed with the sulfur and oxygen heterocycles (*e.g.* equation 118). Thermal and/or photochemical extrusion reactions are fairly common in heterocycles containing several heteroatoms. They frequently lead to ring contraction, usually to give four- or, especially, five-membered heterocyclic systems (*e.g.* equation 119), but a number of different types of ring transformation are known (*e.g.* equation 120). This last reaction presumably involves formation of a diradical species by loss of nitrogen, but the mechanisms (if any) suggested for most of these thermal and photochemical reactions are purely speculative.



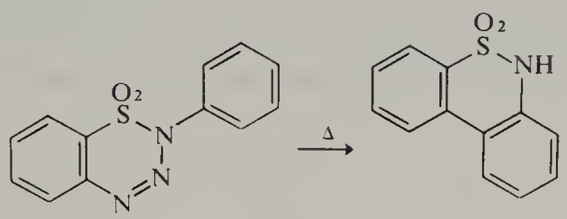
(117)



(118)



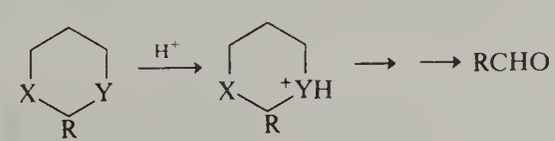
(119)



(120)

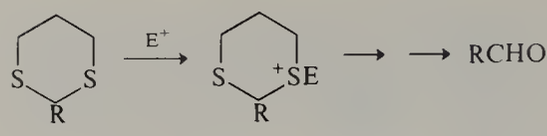
2.02.4.3 Reactivity Towards Electrophiles and Free Radicals

The reactivity of the fully saturated six-membered heterocycles towards electrophiles is predictable and, apart from stereochemical considerations, unexceptional. Ring carbon atoms do not react with electrophiles, while heteroatoms show reactivity characteristic of amines, ethers or thioethers. Thus, the nitrogen compounds are protonated, alkylated, acylated, quaternized and oxidized at nitrogen. Oxidation of sulfur heterocycles to sulfoxides or sulfones is also generally straightforward. Compounds with two heteroatoms in a 1,3-disposition are readily cleaved, either by acid hydrolysis, which involves protonation at a heteroatom (equation 121), or, in the case of the hydrolytically more stable 1,3-dithianes, by initial reaction with a more powerful electrophile, such as an alkyl halide, mercury(II) chloride, NBS, *etc.* (equation 122). This last reaction is of course of great importance in general organic synthesis.

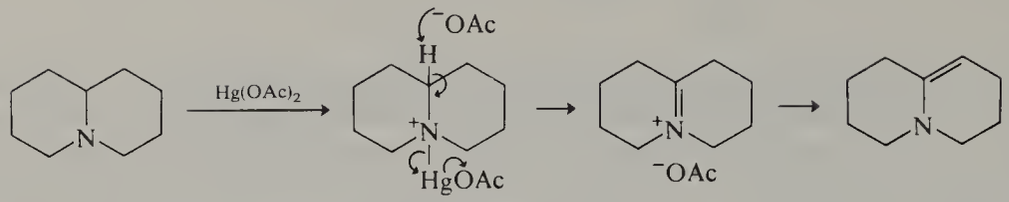


(121)

X = Y = O
X = Y = NR′
X = O, Y = NR′



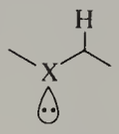
(122)



(123)

The mercury(II) acetate oxidation of tertiary amines is a reaction which can be used to introduce unsaturation β to the nitrogen atom (equation 123).

It is generally observed that a C—H bond which is antiperiplanar to a lone pair of electrons (**65**) is weakened and susceptible to removal by electrophilic or free-radical oxidizing agents. This provides an explanation for the ready hydroperoxidation of aliphatic ethers, both cyclic and acyclic, by atmospheric oxygen. These considerations, however, go beyond the special area of six-membered heterocyclic reactivity presently considered.

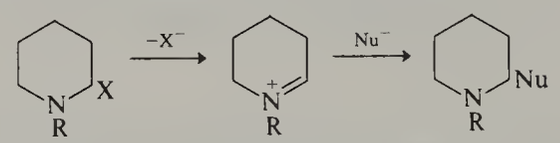


(**65**)

2.02.4.4 Reactivity Towards Nucleophiles

Nucleophilic substitution reactions, and others involving attack by nucleophilic species on fully and partially saturated systems, form a very heterogeneous set of reactions, from which we select only a few representative examples to illustrate special points. For the most part, the reactions involved are of the kind familiar from aliphatic chemistry.

Halogen displacement from 2-halo-tetrahydropyrans and -hexahydropyrimidines is extremely easy, being assisted, in the S_N1 process, by the electron pairs on the heteroatom (equation 124). 3-Halohexahydropyridines can also show accelerated halogen displacement (anchimeric assistance from nitrogen; equation 125). Apart from these and other (normal) substitutions, eliminations of H—Hal are also commonly found.



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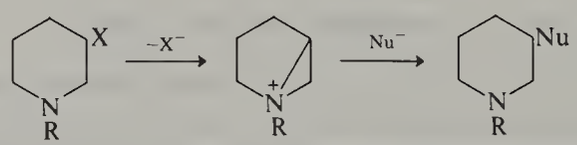

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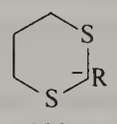
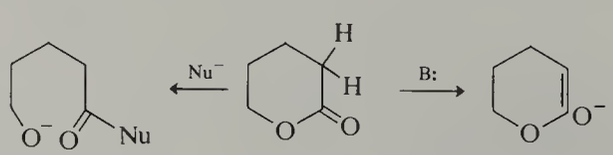


(**66**)

The ability of sulfur to stabilize an adjacent negative charge is shown in the reaction of a strong base (*e.g.* BuLi) with a 1,3-dithiane. The resulting carbanion (**66**) undergoes a range of reactions typical of such species, and the rest of the dithiane ring can be removed, by methods outlined in the preceding section, to leave the C-2 atom in the form of a substituted keto group.



(**67**)

Ring keto groups are attacked by the usual carbonyl reagents. Compounds such as tetrahydropyran-2-one (**67**), with the keto function adjacent to the heteroatom, behave as cyclic esters, and are ring-opened by hydroxide ion. Condensation reactions with (**67**) at C-3 can also be performed.

2.03

Synthesis of Six-membered Rings

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University of East Anglia

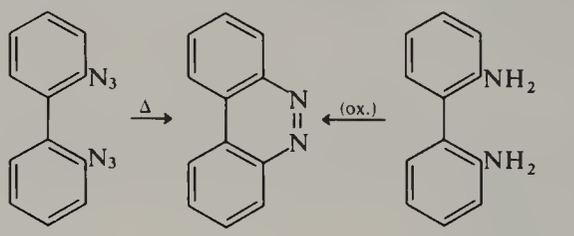
2.03.1 INTRODUCTION

Here we give a brief overview of the types of method available for the preparation of heterocyclic six-membered rings, both fully unsaturated and partially and fully saturated. The discussion is restricted to 'primary syntheses', that is those reactions and processes which result in formation of a heterocyclic ring, either by direct cyclization of an open-chain precursor or by ring transformation, for example by a ring opening/ring reclosure sequence or by cycloaddition followed by loss of a small, thermodynamically stable fragment. 'Secondary syntheses', that is introduction, modification and interconversion of existing functional groups, are discussed in general in Chapter 2.02 and in detail in the monograph chapters. Clearly, however, many reactions are used because they result in the formation of heterocycles with specific functional groups in a given orientation in the ring, and there is much continuing interest in the development of new and improved methods for carrying out such reactions.

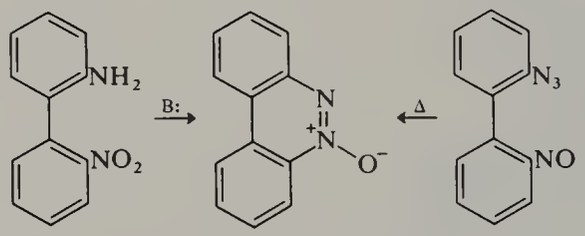
The methods are arranged first, according to the size and number of the fragments which together make the hexatomic ring, and second, according to the bond or bonds which are formed in the cyclization process and their orientation(s) relative to the heteroatom(s). Reactions which convert one type of ring system into another (ring interconversions or ring transformations) are treated in the same way, according to the size of the fragments which form the new ring, and the number of new bonds made in the process. Frequently, a reaction proceeds *via* a readily identifiable intermediate (*e.g.* [3+3]→[6+0]→ring), and so is assignable to more than one class. Our tendency here will be to treat the intermediate as

'starting material' if it can be readily isolated, or if a separate operation is required to cyclize it.

The above classification takes no account of the mechanism of cyclization, and the following sections will occasionally group together diverse reaction types. However, two generalizations can be made about heterocyclic ring-forming reactions. Firstly, the vast majority are of the heterolytic type, with bonds being formed between atoms of which one is clearly identifiable as an electrophilic and the other as a nucleophilic centre. Secondly, atoms of 'electrophilic' and 'nucleophilic' origin tend to alternate around the ring. Exceptions to this second generalization are not difficult to find, particularly in systems in which the heteroatoms are 1,2- or 1,4-oriented relative to each other; but our examples, culled rather at random from the broad area of six-membered-ring syntheses, will serve to show the wide applicability of this alternation principle.



(1)



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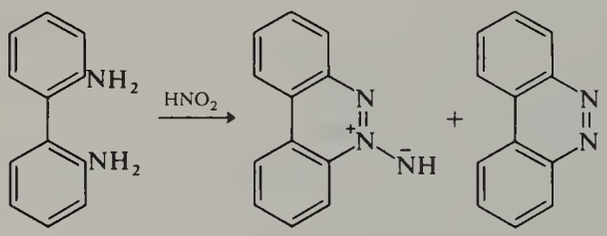
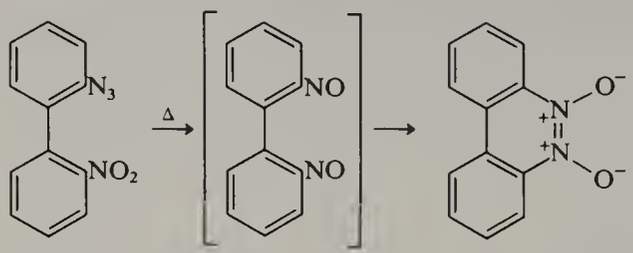


(3)



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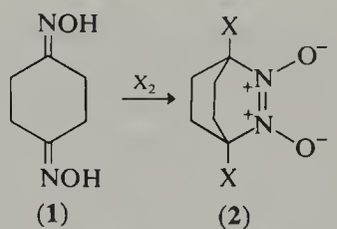
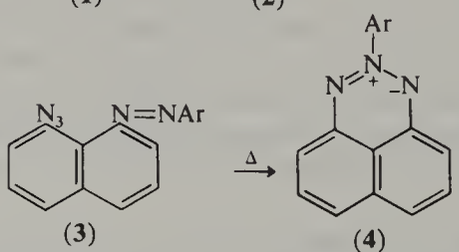


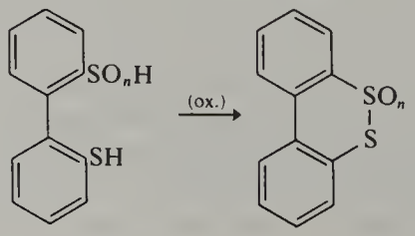
(1) (2)

(5)



(3) (4)

(6)



(7)

2.03.2 RING SYNTHESIS FROM NON-HETEROCYCLIC COMPOUNDS

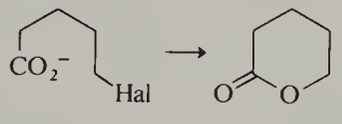
2.03.2.1 Formation of One Bond

2.03.2.1.1 Between two heteroatoms

There are few examples of the preparations of heterocyclic compounds containing two or more heteroatoms which involve cyclization with formation of a bond between two heteroatoms. The best known instances of this type of reaction, all of which are [6+0] reactions, are the preparations of benzocinnolines as outlined in equations (1)–(4). A similar type of approach to that outlined in equation (4) has been used for the direct preparation of the di-*N*-oxide (**2**) from the dioxime (**1**; equation 5). The naphthotriazine betaine (**4**) is obtained as one of the products of the thermal decomposition of the azidoazo compound (**3**; equation 6). 1,2-Dithiins and their dibenzo derivatives have been prepared by oxidation of appropriate dithiols and related starting materials as outlined in equation (7). All of these reactions are, however, somewhat specialized and there has been essentially no systematic study of the preparation of six-membered heterocycles *via* formation of a bond between two heteroatoms.

2.03.2.1.2 Adjacent to a heteroatom

Cyclization with formation of a bond between a carbon atom and a heteroatom occurs in the vast majority of heterocyclizations which result in the formation of six-membered ring systems. This is true for both aromatic and non-aromatic systems, and for the synthesis of heterocycles from a single component or from more than one component. There is a very wide range of [6+0] cyclizations which proceed *via* formation of a bond between a carbon atom and a heteroatom and every major mechanistic pathway has been exploited. Synthesis of saturated and partially saturated six-membered heterocycles by the general approaches illustrated in equations (8) and (9) is a well established and very important procedure. These are typical examples of the nucleophile → electrophile mechanism, and the method can readily be adapted to the synthesis of unsaturated heterocycles, as illustrated in equations (10)–(14) ⟨83JCS(P1)349⟩. Preparation of benzo-fused heterocycles by the general approach outlined in equations (8) and (9) is often not particularly satisfactory because of the lack of reactivity of the unactivated aryl halides. Given even moderate activation, however, aryl halides can be used in these reactions and a recently described example is outlined in equation (15) ⟨83S52⟩. In all of the above reactions the heteroatom functions as the nucleophile in the key bond-forming step. Numerous examples are known, however, where the heteroatom functions as the electrophile and another functional group as the nucleophile. A recent example leading to formation of the interesting 12 π-electron system (**5**) is shown in equation (16) ⟨83CC74⟩, 3-Substituted 1,2,4-benzotriazines can be prepared easily by a modified Bamberger reaction in which an aromatic ring again functions as the nucleophile (equation 17) ⟨82T1793⟩, while the C=C bond of the enamide functions as nucleophile in the synthesis of the 3,4-dihydrophenazin-1(2*H*)-ones (**6**) outlined in equation (18) ⟨82S852⟩.



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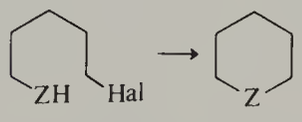

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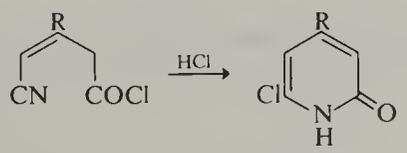

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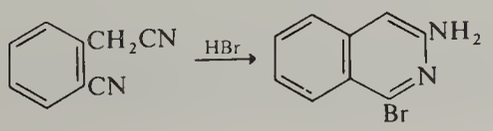

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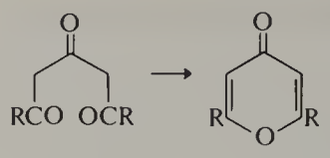

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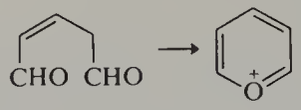

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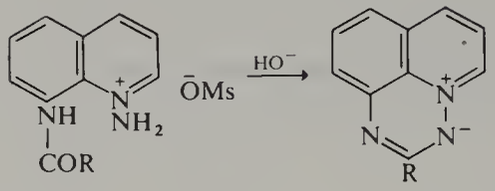

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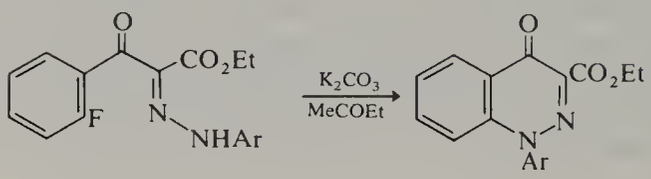

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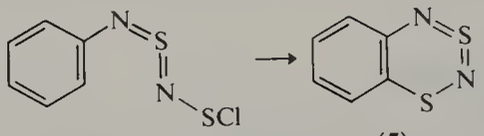

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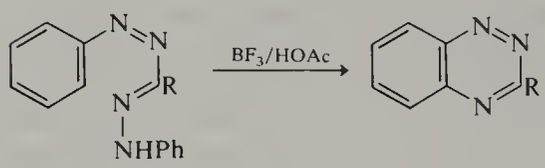

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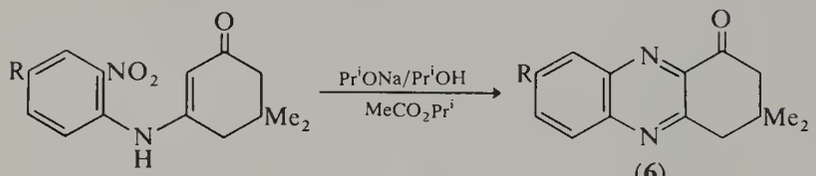
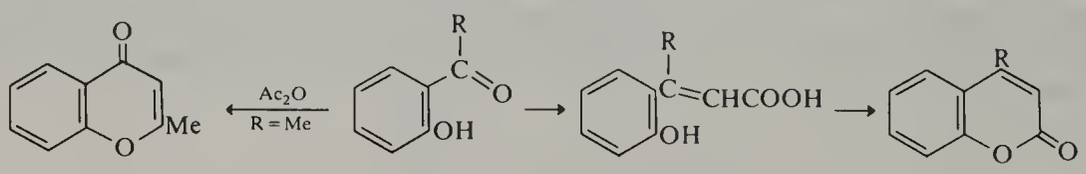


(18)

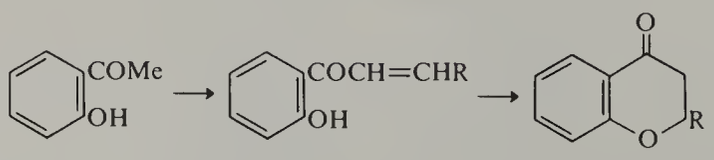
(6)

There are many other common reactions which are widely used for the synthesis of benzo-fused heterocycles, including such well-known 'named' reactions as the Kostanecki–Robinson synthesis of coumarins and chromones (equation 19) and the Pfitzinger modification of the Friedländer quinoline synthesis (equation 20), which can formally be regarded as [6+0] processes. These reactions are, however, better regarded as [4+2] fragment processes involving formation of two ring bonds, and are accordingly treated as such in Section 2.03.2.2.2. Likewise, the intramolecular conjugate addition reactions shown in equations (21) and (22) are treated as [5+1] and [3+3] two-bond formation processes

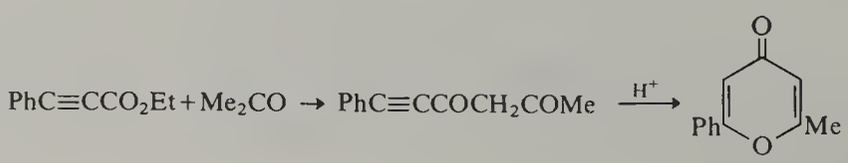


(19)

(20)



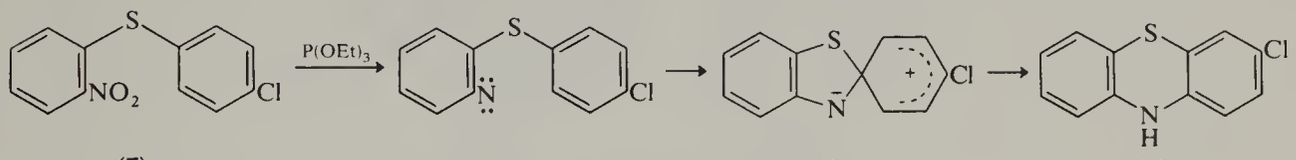
(21)



(22)

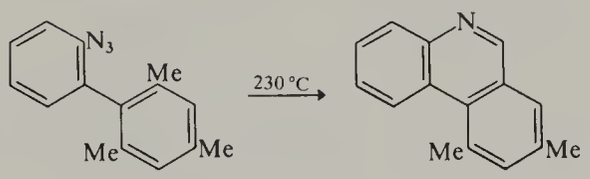
respectively rather than as simple [6+0] cyclization reactions (see Sections 2.03.2.2.1 and 2.03.2.2.3).

Other variations in the nucleophile → electrophile approach for [6+0] synthesis include the generation and trapping of nitrenes and benzynes and other electron-deficient species, and the use of transition metal reagents and complexes as catalysts for carbon–heteroatom bond formation. These types of reaction have been fairly widely studied and are especially useful when applied in an intramolecular sense for the synthesis of condensed systems. Reduction of the diaryl sulfide (**7**) with triethyl phosphite, for example, gives the phenothiazine (**9**) in good yield *via* formation and rearrangement of the spiro intermediate (**8**; Scheme 1), while thermolysis of the azide (**10**) in hexadecane at 230 °C gives the phenanthridine (**11**) by insertion of the nitrene into the methyl group (equation 23). Synthesis of condensed systems *via* benzyne intermediates can also be a useful method (*e.g.* equation 24) and this type of reaction has been used occasionally in alkaloid synthesis. The reader is referred to the monograph chapters for more detailed discussions of these reactions.

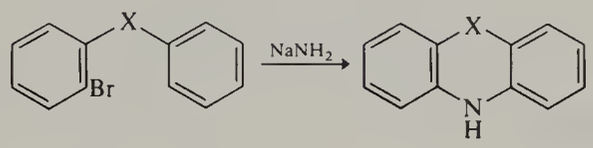


(**7**) (**8**) (**9**)

Scheme 1

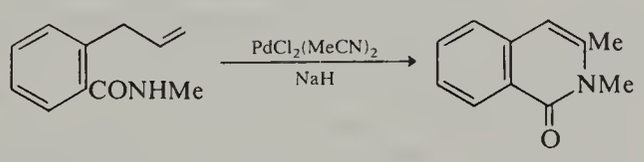


(**10**) (**11**) (23)



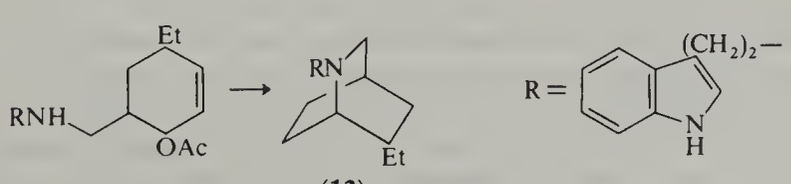
(24)

The use of transition metal reagents for heterocyclic synthesis is a rapidly expanding area of research. The mechanisms of most of these reactions are not yet known in detail, but they appear to be basically of the nucleophile → electrophile type, at least as far as carbon–heteroatom bond formation is concerned. Formation of the isoquinolone (**12**) for example, almost certainly involves initial aminopalladation of the allylic C=C bond (equation 25) ⟨77JOC1329⟩, whereas nucleophilic attack on a π-allylpalladium complex is involved in formation of the isoquinuclidine derivative (**13**; equation 26) ⟨78JA3930⟩. The interesting ruthenium-catalyzed cyclization shown in equation (27) has been rationalized in terms of oxidation of the alcohol to the corresponding aldehyde, cyclization to an iminium salt and reduction ⟨82TL229⟩. [6+0] Cyclizations *via* oxymetallation mechanisms are important in the synthesis of oxygen heterocycles, especially the use of thallium(III) salts for the preparation of isoflavones (see Chapter 2.24).

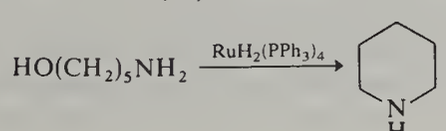


(25)

(**12**)



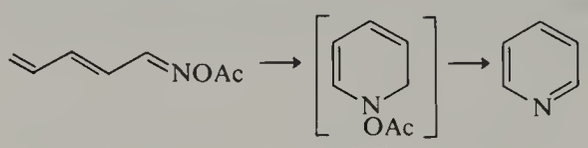
(**13**) (26)



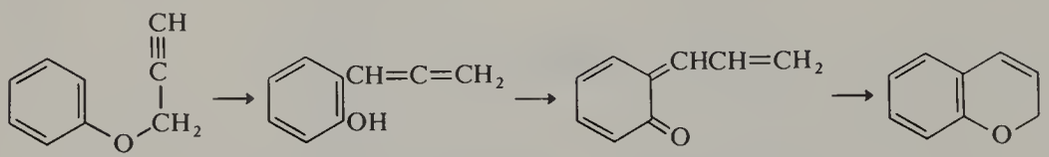
(27)

[6+0] Ring closure by radical pathways has been studied to some extent, but in general the methods are of little preparative importance, as the products are usually obtainable more easily and in better yield by other means. The reader is referred in particular to Chapter 2.08 for more details.

One final important type of reaction for heterocyclic synthesis by [6+0] ring closure is by electrocyclic cyclization. The oxime (**14**), for example, very readily undergoes electrocyclization to the dihydropyridine (**15**), from which pyridine is derived by loss of acetic acid. In other instances the mechanism is more complex. The propargyl ether (**16**), for example, is converted on heating into 2*H*-chromene (**17**) *via* a Claisen ([3+3]) rearrangement, a 1,5-hydrogen shift and electrocyclic ring closure (Scheme 2). This general type of reaction, and variations on it, is especially common in the chemistry of the benzopyrans (see Chapter 2.24). 2*H*-Thiopyran is formed similarly from the sulfide (equation 29).

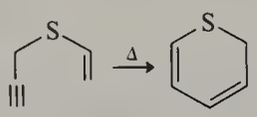


(14) (15) (28)



(16) (17)

Scheme 2

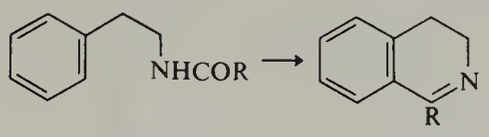


(29)

2.03.2.1.3 β to a heteroatom

With the two notable exceptions of the Bischler–Napieralski reaction and the Pictet–Gams reaction, [6+0] cyclization involving formation of a single bond β to a heteroatom has been little investigated as a synthetic route for the preparation of six-membered heterocycles. The Bischler–Napieralski reaction is the acid-catalyzed cyclodehydration of β-phenethylamides to 3,4-dihydroisoquinolines (equation 30). The reaction is normally carried out by refluxing a mixture of the amide and a dehydrating agent such as phosphorus oxychloride, phosphorus pentachloride or phosphorus pentoxide in a solvent such as chloroform, toluene or xylene. Mechanistically, the reaction involves intramolecular electrophilic substitution of the aromatic ring and is subject to normal substituent effects. Thus, electron-releasing substituents in the *meta* position generally facilitate reaction, but in the *para* position they can inhibit cyclization. Use of *m*-substituted phenethylamides can in principle result in formation of either a 6- or 8-substituted dihydroisoquinoline, but in practice the 6-substituted isomer is obtained. The 3,4-dihydroisoquinolines which are obtained can readily be converted into either tetrahydroisoquinolines by reduction (*e.g.* with sodium borohydride in acid solution, or hydrogen/palladium) or isoquinolines by dehydrogenation with, for example, palladium black. The Pictet–Gams reaction, which is an alternative direct route to isoquinolines, is a modification of the Bischler–Napieralski reaction in which the cyclodehydration is performed on a β-hydroxy-β-phenethylamide (equation 31). Both the Bischler–Napieralski and the Pictet–Gams reactions have, of course, been most widely used in the synthesis of isoquinoline and β-carboline alkaloids. Phenanthridines have been prepared in an analogous manner by cyclodehydration of acylated 2-aminobiphenyls (equation 32), and in principle this reaction is capable of extension to oxygen- and sulfur-containing heterocycles. Aromatic aldazines have recently been shown to undergo oxidative cyclization to 1-arylphthalazines (equation 33) on treatment with aluminum chloride/triethylamine at 170–200 °C; yields are in general moderate. If the triethylamine is omitted from the reaction mixture the 1-aryl substituent is lost during aromatization and phthalazines unsubstituted in the heterocyclic ring are obtained in low to moderate yields.

In a related type of reaction, the styryl isocyanates, readily available by Curtius rearrangement of cinnamoyl azides, undergo thermal cyclization to 1-isoquinolones in good yield (equation 34); the reaction can also be carrried out using Friedel–Crafts catalysts. 2,3-Dihydro-4(1*H*)-isoquinolones are obtained by Dieckmann cyclization of *N*-(*o*-carbalkoxybenzyl)glycine ester derivatives (equation 35). The same reaction has been used for the synthesis of a range of non-aromatic heterocycles (equations 36 and 37).



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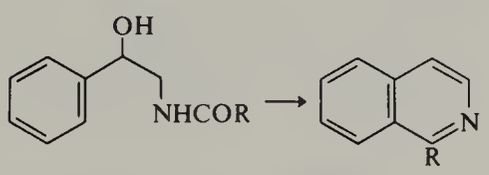

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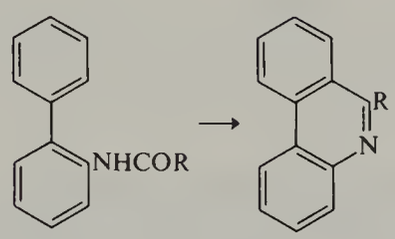

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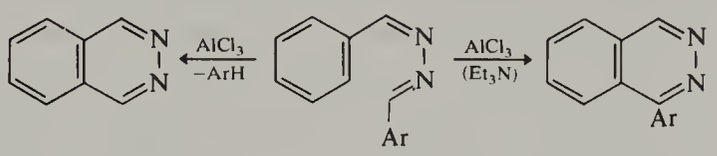

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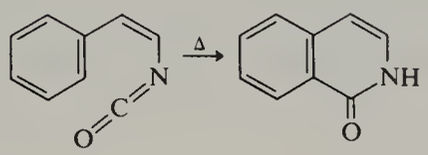

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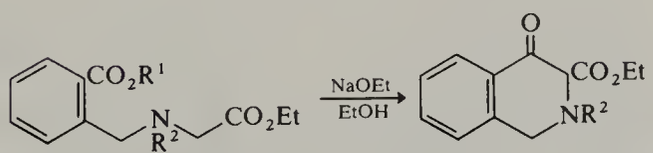

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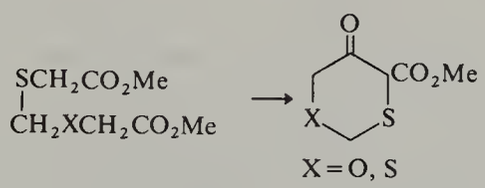

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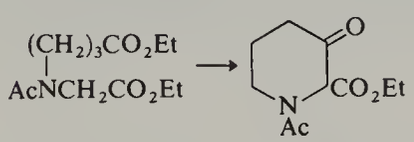
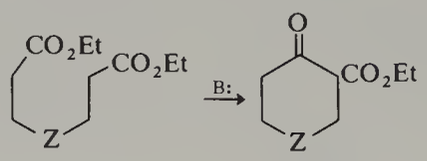


(37)

2.03.2.1.4 γ to a heteroatom

As with the other procedures for the preparation of six-membered heterocyclic systems which proceed *via* formation of only one ring bond there are relatively few methods which involve formation of a ring bond γ to the heteroatom and which can best be classified as [6+0] processes rather than [4+2], [3+3], *etc.*, processes. Of those which can be so represented, however, a number are important processes which are widely used for the synthesis of saturated, partially saturated and aromatic six-membered heterocyclic systems and their benzo derivatives. Mechanistically, the nucleophile → electrophile approach is by far the most common, but in contrast to the reactions discussed in the previous three sections, radical cyclizations are of considerable utility here.

The use of classical condensation reactions is important. Thus, the Dieckmann reaction (equation 38) and the Thorpe–Ziegler cyclization (equation 39) have been used for almost a century for the preparation of a wide range of monocyclic and benzo-fused heterocycles. The aldol condensation and related reactions have also been fairly widely exploited, especially for the synthesis of 4-quinolones (the Camps reaction, *e.g.* equation 40), and various extensions of this general approach are described in the monograph chapters.



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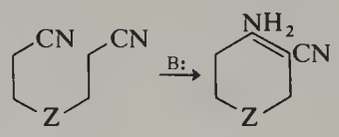

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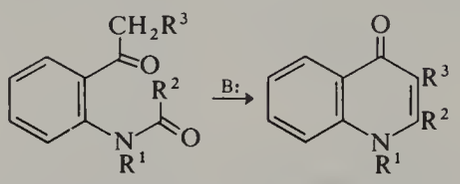
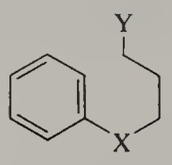
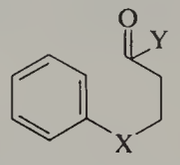


(40)

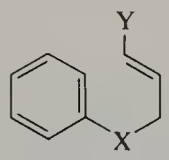
An equally important general type of synthesis which proceeds *via* heterocyclization with formation of a ring bond γ to the heteroatom involves acid-catalyzed intramolecular electrophilic aromatic substitution, especially those in which a carbonyl group functions as the electrophile. The most common structural requirements are summarized in (**18**)–(**21**);



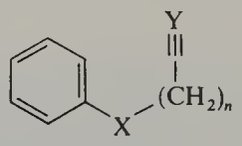
(**18**) Y = OH, OR, OTs, halogen, *etc.*



(**19**) Y = halogen, OH, OR, NR_2, alkyl, aryl, *etc.*

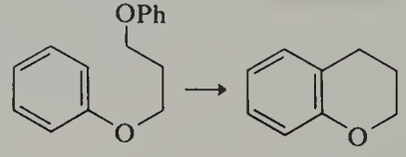


(**20**) Y = OR, NR_2, alkyl, aryl, *etc.*

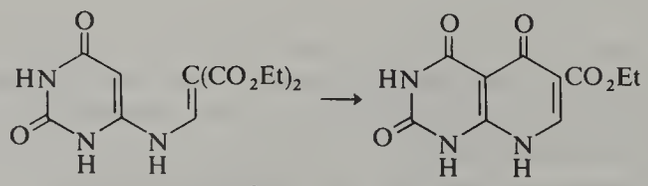


(**21**) Y = C—(alkyl, aryl, H, *etc.*), $n = 1$
Y = N, $n = 2$

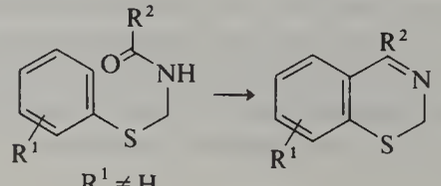
the use of other electrophiles such as imines and isocyanates is discussed in the monograph chapters. Representative examples of these various forms of ring closure are given in equations (41)–(45) and it can be seen that the level of oxidation of the heterocyclic ring in the product can be controlled by appropriate choice of the side chain attached to the heteroatom. It can often also be controlled either by the incorporation of leaving groups into the side chain (*e.g.* equation 46) or by suitable choice of acid catalyst (*e.g.* equation 47). This type of reaction is also widely used for the synthesis of polycyclic heterocycles, as outlined in equation (48).



(41)

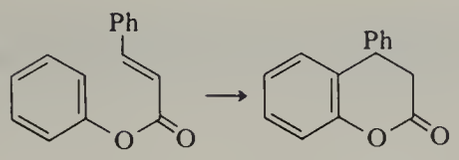


(42)

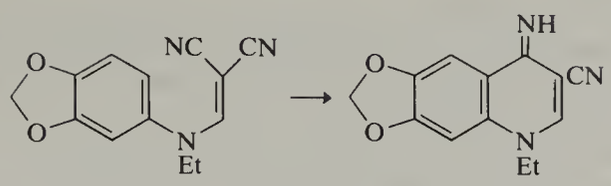


$R^1 \neq H$

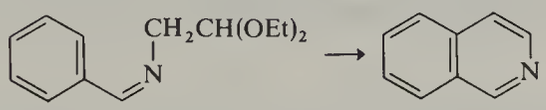
(43)



(44)



(45)



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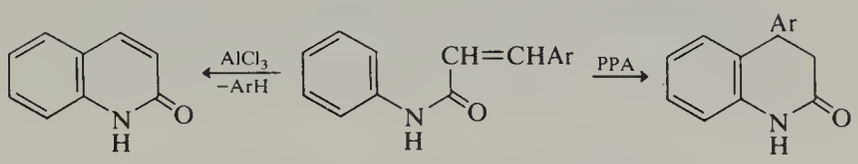
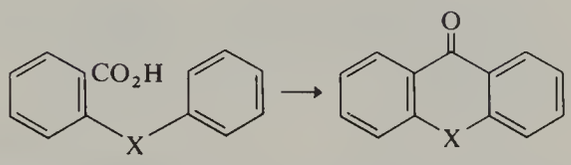
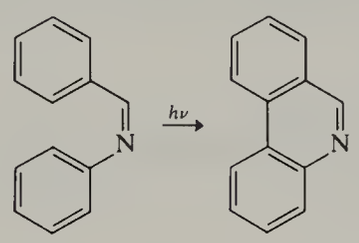


(47)

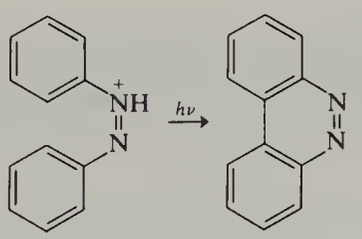


(48)

Radical [6+0] cyclization is of some importance for the preparation of polycyclic azines, but is of no significant synthetic utility for the preparation of mono- or bi-cyclic compounds. Photochemical oxidative cyclizations of aromatic Schiff bases (equation 49) and azo compounds (equation 50) constitute important procedures for the preparation of phenanthridines and benzocinnolines. These reactions proceed by initial formation of the dihydro compounds and aromatization is effected with either oxygen or, preferably, iodine (present in the reaction mixture).



(49)



(50)

2.03.2.2 Formation of Two Bonds

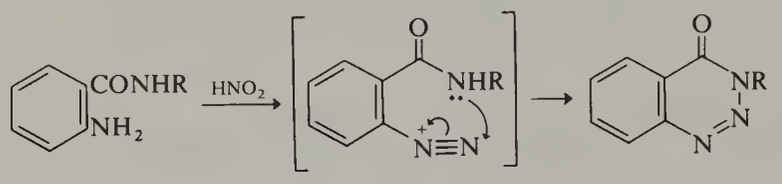
2.03.2.2.1 From [5+1] atom fragments

There are many important [5+1] two-bond formation heterocyclic syntheses and in certain instances this approach constitutes the method of choice for the preparation of particular classes of heterocycle. Where a carbon atom constitutes the one-atom fragment it is almost invariably present in the form of an electrophilic species such as an aldehyde, carboxylic acid, ketone, ester, acid chloride, urea, *etc.*, and fundamentally condensation consists of reaction of this electrophilic species with a 1,5-dinucleophilic reagent. Where the one-atom fragment is either nitrogen, oxygen or sulfur then the heteroatom may function either as a nucleophile or, in the case of nitrogen and sulfur, also as an electrophile. Almost

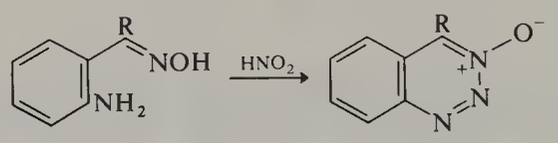
all of the generally useful [5 + 1] two-bond formation heterocyclizations proceed *via* formation of a bond between a heteroatom and carbon or between two heteroatoms in the cyclization step.

(*i*) *Between two heteroatoms*

There are a number of important reactions in this category and all of them involve at least one heteroatom functioning as a nucleophile and another as an electrophile. Diazotization of a variety of *ortho*-substituted anilines for instance, followed by intramolecular nucleophilic trapping of the corresponding diazonium salts by either nitrogen or carbon nucleophiles, is the basis of a series of very important syntheses of 1,2,3-benzotriazine and cinnoline derivatives, and this general approach has been widely exploited for the preparation of polycyclic systems. Representative examples are given in equations (51)–(54).



(51)



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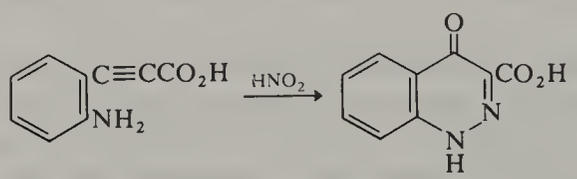
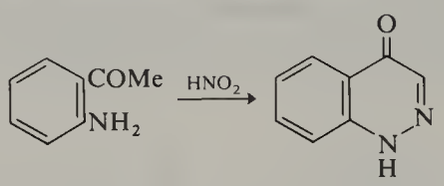
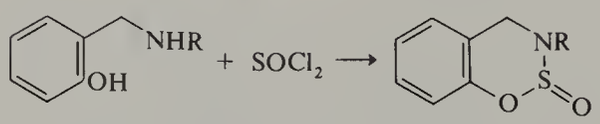


(53)



(54)

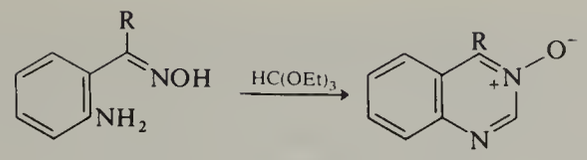


(55)

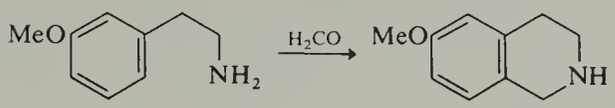
Formation of a bond between two heteroatoms is also of considerable utility in the synthesis of sulfur-containing polyheteroatom systems. Reaction of 1,5-dinucleophiles with electrophilic sulfur reagents such as thionyl chloride or sulfur dichloride leads directly to the heterocycles (*e.g.* equation 55). A fuller discussion of these types of reaction is given in Chapter 2.28.

(*ii*) *Adjacent to a heteroatom*

This is by far the most important and common type of [5 + 1] heterocyclization reaction. The concept of condensation of an electrophilic one-carbon atom fragment with a 1,5-dinucleophile is a very familiar one, as for example in the preparation of 1,3-dioxanes and 1,3-dithianes. Other examples which illustrate the general principle are summarized in equations (56)–(62) and include the important and widely used Pictet–Spengler reaction for the preparation of 1,2,3,4-tetrahydroisoquinoline derivatives and the Baker–Venkataraman and related syntheses of chromones. The use of transition metal-catalyzed reactions for heterocyclic synthesis is also becoming important for [5 + 1] heterocyclizations. Some reactions are mechanistically quite complex (*e.g.* equation 63), but the most useful reactions, those involving insertion of carbon monoxide into the C—Pd bond, are relatively straightforward. The intermediate organopalladium compounds can be conveniently prepared either by direct reaction of an aryl halide with a palladium salt (*e.g* equation 64) or by a metal–metal exchange reaction (*e.g.* equation 65).



(56)



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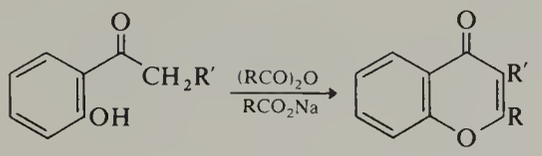

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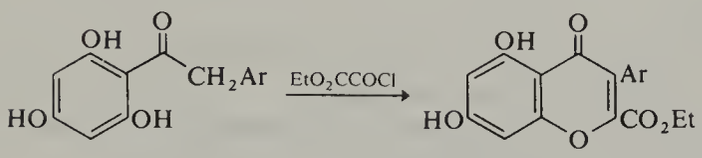
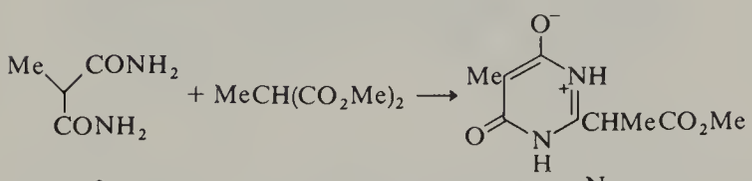
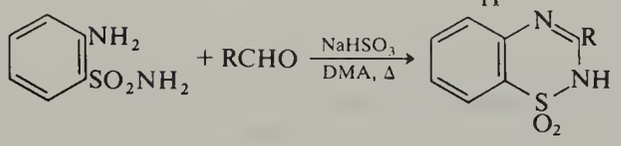


(59)

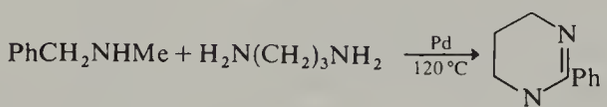
(60)



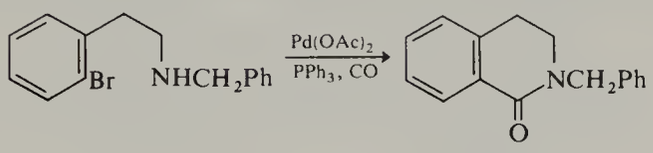
(61)



(62)



(63)



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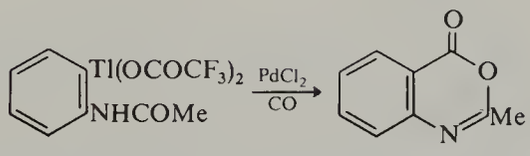
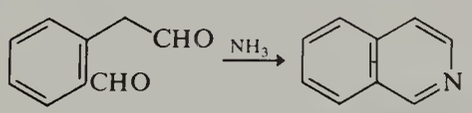


(65)

Syntheses based on the condensation of a 1,5-dielectrophile with a heteroatom nucleophile are also very important [5+1] heterocyclization processes, especially for the synthesis of azine derivatives. Representative examples are summarized in equations (66)–(71).



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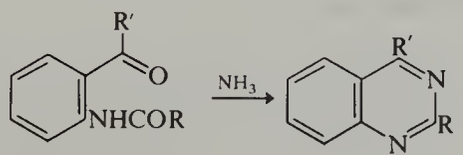

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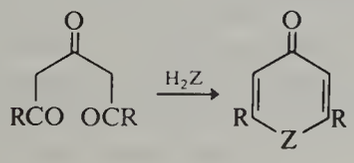

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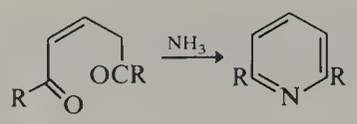

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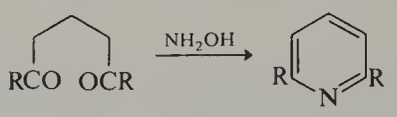

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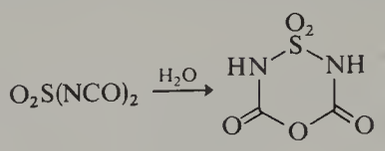
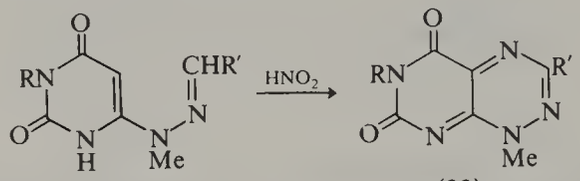


(71)

(iii) β to a heteroatom

There are very few examples of [5+1] two-bond formation processes which proceed *via* formation of a ring bond *β* to the heteroatom. An example is the formation of the pyrimido-1,2,4-triazinediones (**22**) outlined in equation (72), in which a heteroelectrophile undergoes condensation with a 1,5-dinucleophile, but this particular mode of ring closure is, in general, of little preparative significance.

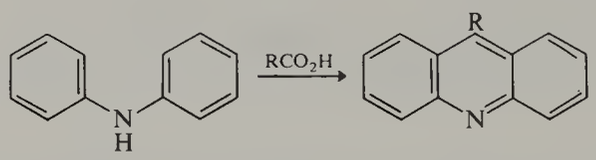


(72)

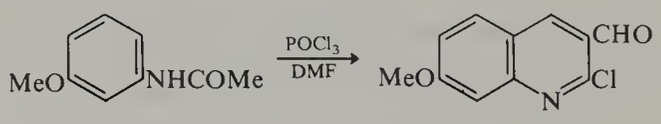
(**22**)

(iv) γ to a heteroatom

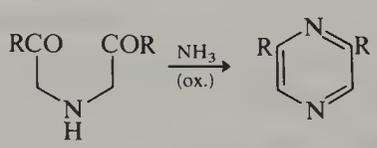
Ring closure *γ* to a heteroatom is also a rather uncommon [5+1] procedure although there are some important exceptions. The most widely investigated is the Bernthsen acridine synthesis in which a diarylamine is condensed with a carboxylic acid in the presence of a Lewis acid (equation 73). More recently, it has been shown that acylanilines react with the Vilsmeier–Haack reagent to give quinolines in good yield (*e.g.* equation 74) and the mechanism of the reaction has been elucidated. A final example of [5+1] ring closure *γ* to a heteroatom which is of occasional use is the pyrazine synthesis outlined in equation (75).



(73)



(74)



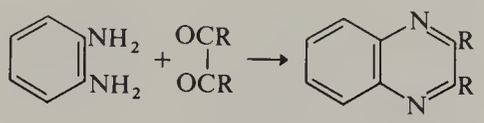
(75)

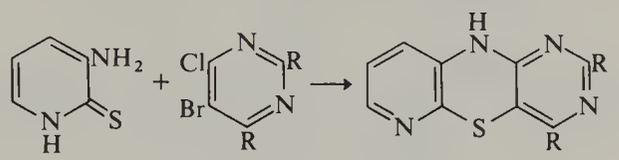
2.03.2.2.2 From [4+2] atom fragments

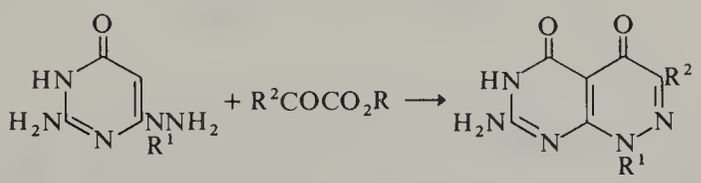
Condensation reactions involving [4+2] atom fragments are extremely important processes for the preparation of six-membered heterocyclic systems and, in some cases, are among the most important general methods for the preparation of specific six-membered heterocyclic systems. Almost all [4+2] atom fragment condensations can be conveniently classified in one or other of the following ways: (i) condensation of a 1,4-dinucleophile with a 1,2-dielectrophile; (ii) condensation of a 1,4-dielectrophile with a 1,2-dinucleophile; (iii) condensation of a 1,4-nucleophile–electrophile with a 1,2-electrophile–nucleophile; (iv) Diels–Alder-type and other [4+2] cycloaddition reactions.

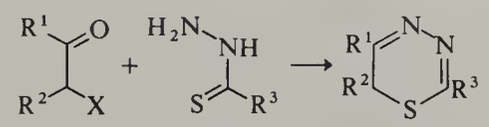
It should be noted that in certain of these condensations the initial reaction leads to a di- or even tetra-hydro derivative of the aromatic heterocyclic system. In principle, these partially saturated intermediates can be further reduced to give the fully saturated heterocyclic systems; more commonly in practice, however, either the reaction conditions are adjusted such that aromatization takes place or an additional oxidizing reagent is deliberately added to the reaction mixture to ensure aromatization.

In the 1,4-dinucleophile → 1,2-dielectrophile approach the most common situation is where heteroatoms function as nucleophiles and 1,2-dicarbonyl compounds, 1,2-dihalides or sulfonate esters, α-halocarbonyl compounds, *etc.*, as the dielectrophile component. Representative examples are given in equations (76)–(79). Condensation of hydrazine and its derivatives with 1,4-dicarbonyl compounds is the common situation in the 1,2-dinucleophile → 1,4-dielectrophile approach, and the vast majority of pyridazine derivatives are prepared in this way (*e.g* equations 80 and 81). Sulfur 1,4-dielectrophiles have been used in related processes, but the method is not readily adaptable to the synthesis of oxygen heterocycles.

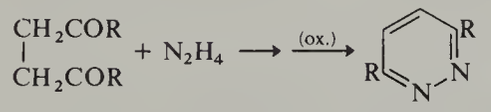

(76)

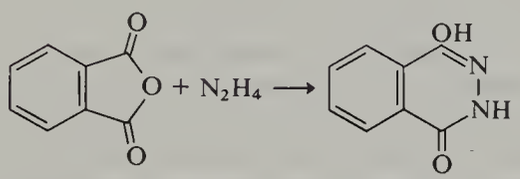

(77)


(78)

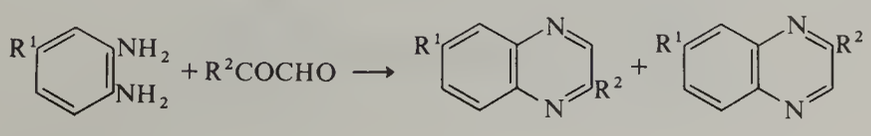

X = halogen

(79)


(80)


(81)

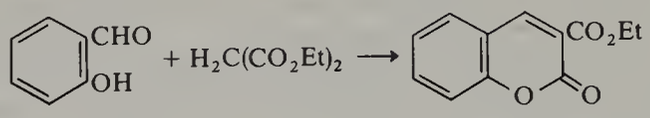
There is one important aspect of these types of reaction which must always be borne in mind, namely that the relative reactivities at the termini of the individual components may be sufficiently different that reaction results in formation of a single product, or they may be so similar that a mixture of isomers is produced. This situation is illustrated in the unsymmetrically substituted 1,2-phenylenediamine (**23**; equation 82). If $R^1 = NO_2$, the 2-amino group is considerably more nucleophilic than the 1-amino group and condensation with an α-keto aldehyde will occur initially between the 2-amino group and the more electrophilic aldehyde carbonyl group to give the 2,6-disubstituted quinoxaline (**24**). If $R^1 = OMe$, on the other hand, the situation is reversed and the 2,7-isomer (**25**) is formed, while if $R^1 = Me$ the two amino groups are of almost identical nucleophilicity and a 1 : 1 mixture of (**24**) and (**25**) is obtained. This type of problem has long been recognized in the classical Isay synthesis of pteridines, and various experimental procedures and alternative


(82)

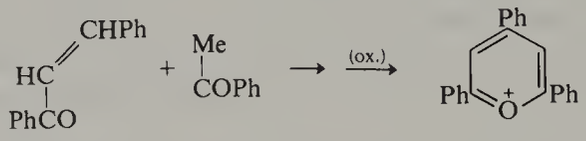
(**23**) (**24**) (**25**)

syntheses have been devised in efforts to avoid formation of difficultly separable mixtures of isomer products (see Chapter 2.13).

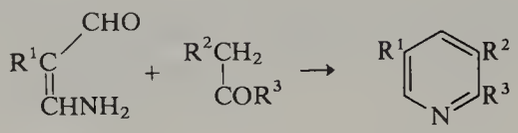
Condensation of a 1,4-nucleophile–electrophile with a 1,2-electrophile–nucleophile is the most versatile and widely exploited of these nucleophile → electrophile reactions for [4+2] heterocyclization and a number of classical methods for the preparation of six-membered heterocycles are based on this principle. Representative examples are given in equations (83)–(88).



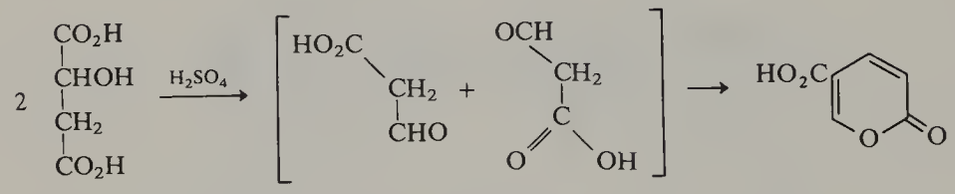
(83)



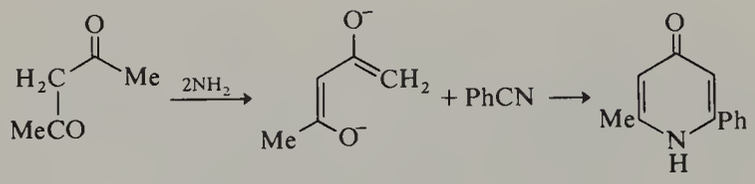
(84)



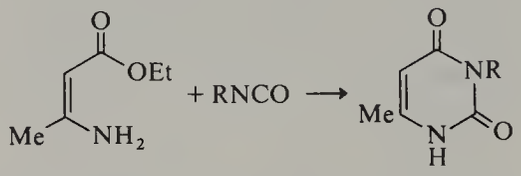
(85)



(86)



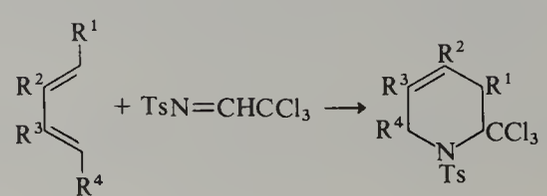
(87)



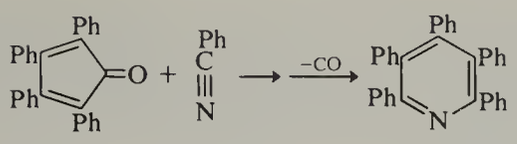
(88)

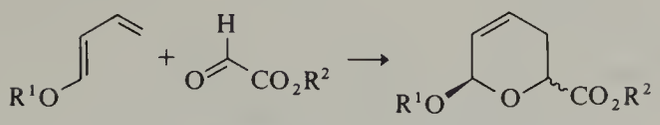
The final important category of [4+2] cyclization is the Diels–Alder and other [4+2] cycloaddition reactions. This topic has been the subject of intense study for many years and continues to attract the attention of many researchers, as in a great many instances the reactions involved constitute excellent procedures for the synthesis of both heterocyclic and non-heterocyclic compounds. The discussion in this section is restricted to processes which result in the formation of heterocyclic compounds from non-heterocyclic precursors, although of course a heterocycle may be present as a substituent in either the diene or ene component but have no significant or controlling effect in the cycloaddition reaction.

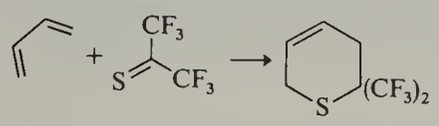
The versatility of these [4+2] heterocyclization reactions is a consequence of the wide range of ene and diene components which can be used. In addition to alkenes and alkynes functioning as ene components, a variety of heterodienophiles is available such as electron-deficient imines (*e.g.* equation 89), nitriles (*e.g.* equation 90), electrophilic carbonyl compounds (*e.g.* equation 91), thiocarbonyl compounds (*e.g.* equation 92), singlet oxygen (*e.g.* equation 93), nitroso compounds (*e.g.* equation 94), sulfenylsulfonamides (*e.g.* equation 95) and azo compounds (*e.g.* equation 96). Many of these reactions proceed with excellent regioselectivity and stereoselectivity, probably because in many instances they involve

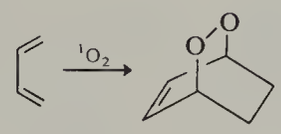


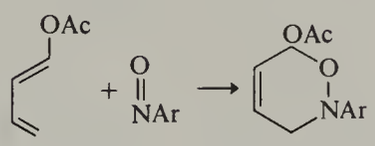
(89)


(90)


(91)


(92)


(93)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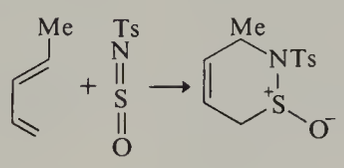
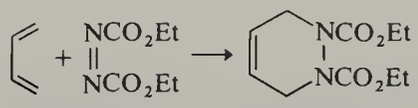
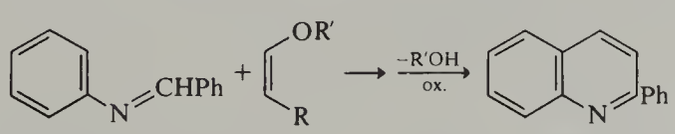

(95)


(96)

dipolar transition states. In most cases, however, there has been little systematic mechanistic investigation. An excellent review of the synthetic aspects of Diels–Alder cycloadditions with heterodienophiles has appeared recently ⟨82T3087⟩.

In contrast to the rich variety of reactions and reagents possible with heterodienophiles, relatively few dienophiles incorporating heteroatoms in the conjugated system have been widely exploited in synthesis so far, although interest in this topic is currently increasing. Among the best known examples are those in which the 'heterodiene system' is part of a polyazine; these reactions are discussed in Section 2.03.3.4.2. In principle, one or more carbon atoms in a butadiene can be replaced by nitrogen atoms and examples of aza- and diaza-diene cycloadditions are known. α,β-Unsaturated Schiff bases and isocyanates condense with electron-rich alkenes and alkynes (equations 97 and 98), while a number of cycloaddition reactions are known which involve 1,4-diazadienes such as *o*-benzoquinone dibenzimide derivatives (equation 99) and bis-Schiff bases derived from α-dicarbonyl compounds (equation 100) ⟨57CB2460⟩. More recent studies with functionalized azadienes have illustrated the potential of these types of reaction for the synthesis of pyridone and piperidone derivatives (equation 101) ⟨82JA1428⟩. Nitrosoalkenes are interesting substrates for cycloaddition studies, as they can participate either as 2π components (the NO group) or as 4π systems (the heterodiene). Both types of reactivity are known and a typical example illustrating heterodiene activity is shown in equation (102) (for a recent review of nitrosoalkenes see ⟨83CSR53⟩). 1,4-Benzoxazines are available by reaction of the copper complexes derived from *o*-nitrosophenols with alkynic dienophiles (equation 103).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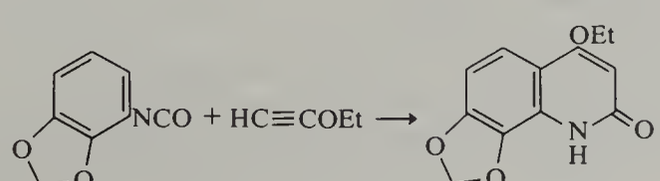
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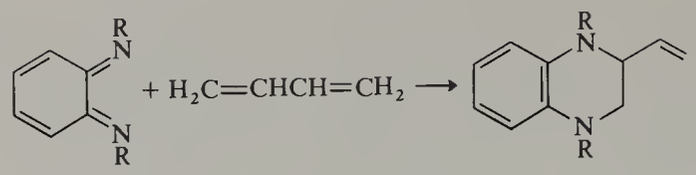
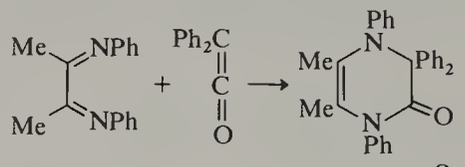
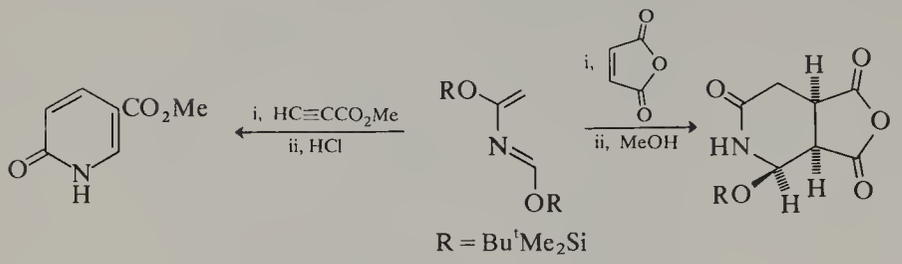


(99)

R = COAr, SO_2Ar

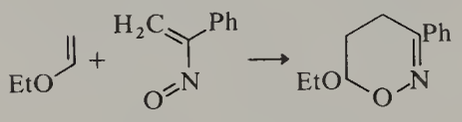


(100)

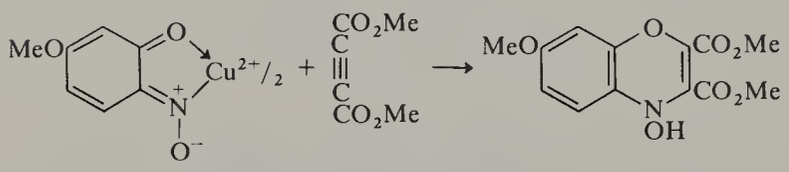


(101)

R = Bu^tMe_2Si

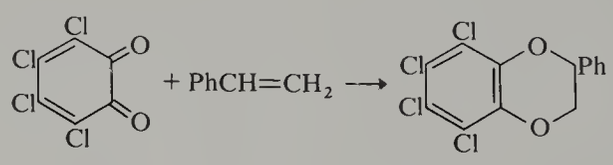


(102)

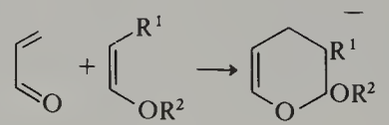


(103)

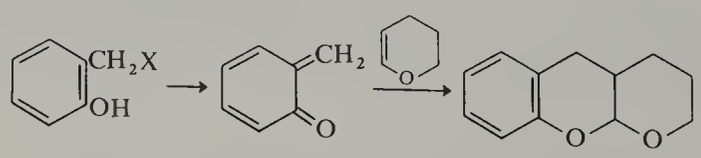
[4+2] Heterocyclizations in which oxygen is part of a heterodiene system are quite well known. In addition to the reactions shown in equations (102) and (103), in which the oxygen is present as a nitroso group, cycloaddition reactions involving carbonyl compounds have been investigated in some detail. *o*-Benzoquinones, for example, often condense with alkenes to give dioxins (*e.g.* equation 104) but the reactions can be complicated by the fact that both diene systems of the benzoquinone can function in 1,4-addition reactions, and the benzoquinone can also act as a dienophile. Rather more useful are the reactions of α,β-unsaturated carbonyl compounds with electron-rich alkenes and alkynes (*e.g.* equation 105), and an important and widely used extension of this approach is the generation and trapping of *o*-quinone methides (*e.g.* equation 106) (for a full discussion of these reactions see Chapter 2.24). Moreover, suitable substitution in the heterodiene can alter the overall mode of reactivity. Thus, in contrast to the above reactions of α,β-unsaturated carbonyl compounds, which undergo cycloaddition most efficiently with electron-rich dienophiles, the enaminothiones (**26**) react readily at room temperature with electron-deficient alkenes and alkynes to give dihydro-2*H*-thiopyrans (**27**) in quantitative yield (*e.g.* equation 107) ⟨82T1705⟩.



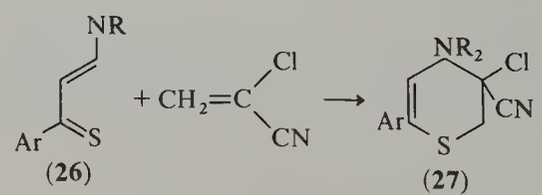
(104)



(105)



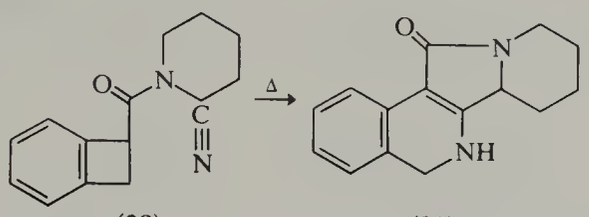
(106)



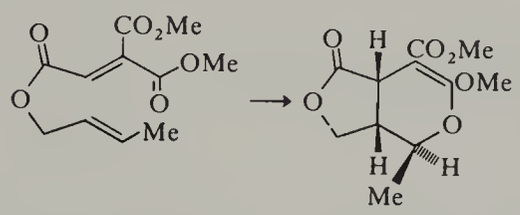
(107)

(**26**) (**27**)

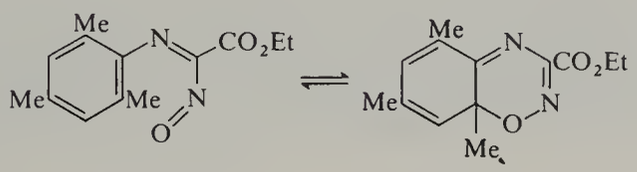
Intramolecular [4+2] cycloaddition reactions have been investigated in some detail in recent years, and this approach is being increasingly used for the preparation of polycyclic heterocyclic systems. These reactions can often give excellent yields of products: thermolysis of the benzocyclobutene (**28**), for example, gives the tetracyclic system (**29**) in 87% yield, presumably *via* trapping of quinone methide by the nitrile group (equation 108). An example of trapping of a heterodiene by an alkene is shown in equation (109), and the reaction outlined in equation (110) is particularly interesting. Here the heterodienophilic nitroso group undergoes reversible cycloaddition to the heterodiene system. It should also be noted that the intramolecular Diels–Alder reaction can be used for the preparation of heterocyclic compounds from precursors which do *not* contain a heteroatom in either the 4π or the 2π component (*e.g.* equation 111).



(28) (29) (108)



(109)



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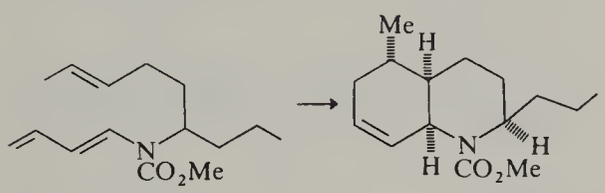
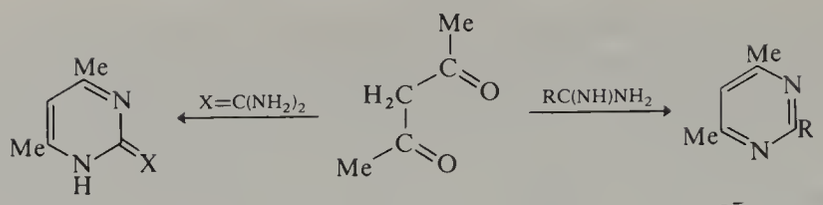


(111)

2.03.2.2.3 From [3+3] atom fragments

[3+3] Two-bond formation condensation reactions are of very considerable importance and utility in the synthesis of six-membered heterocyclic systems, and a large number of classical heterocyclic syntheses are included in this category. In mechanistic terms the vast majority of these reactions involve the simple concept of condensation of a 1,3-dinucleophile with a 1,3-dielectrophile, and in general these reactions are of most use for the synthesis of aromatic heterocycles. The most common 1,3-dinucleophiles are amidines, guanidines, ureas and thioureas, and sulfamide, where in each case the nucleophilic centres are heteroatoms, and enamines, enolates, anilines, phenols and thiophenols, where one of the nucleophilic centres is a carbon atom. There are only two major classes of 1,3-dielectrophile, namely 1,3-dicarbonyl compounds and related species such as cyanoacetic esters and malononitriles, and α,β-unsaturated aldehydes, ketones, esters and nitriles. Particularly useful examples of the latter category are ethoxymethylenemalonic esters and ethoxymethylenemalononitrile.

Many of the most versatile and widely used syntheses of pyrimidines are straightforward examples of [3+3] condensations of amidines, guanidines, ureas and thioureas with 1,3-dielectrophiles, and clearly a considerable measure of control over the degree and nature of the substitution pattern in the final product is possible by appropriate choice of the two three-component units. Representative examples are given in equations (112)–(115), and the use of sulfamide in place of amidines, *etc.*, allows the method to be extended to the synthesis of polyheteroatom systems (*e.g.* equation 116).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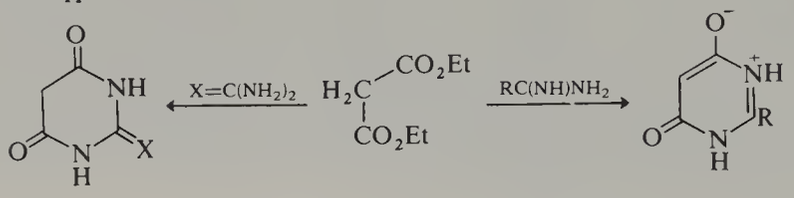
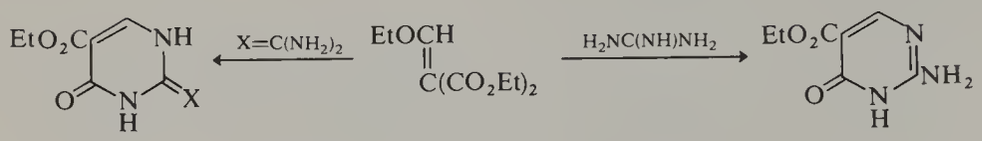
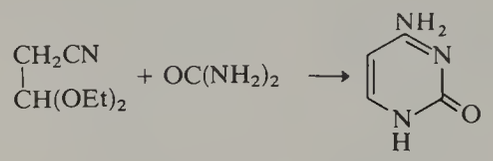
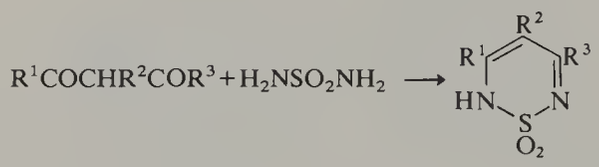
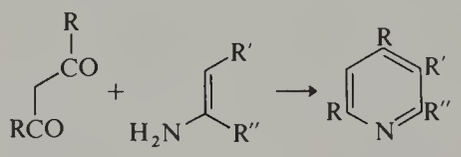

(113)

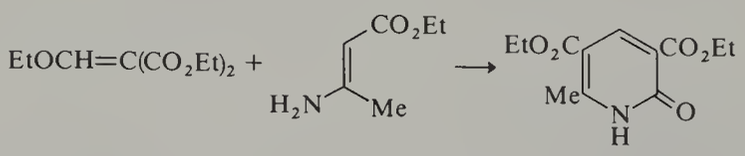

(114)


(115)


(116)

The formation of azine derivatives by condensation of enamines and enamides with 1,3-dielectrophiles has been known for almost a century, and there are a number of reactions (*e.g.* the Hantzsch pyridine synthesis) which proceed by intermediate formation of such compounds. Examples are shown in equations (117)–(119). The transformations outlined in equations (120) and (121) are mechanistically related processes.


(117)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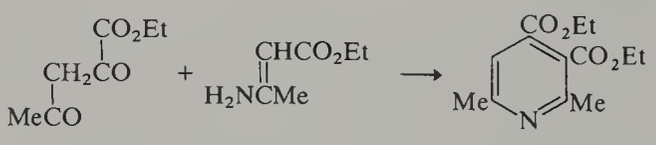
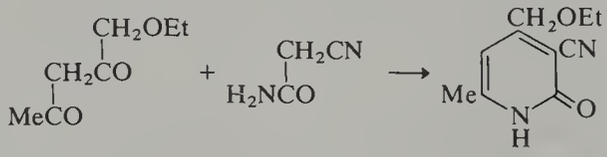
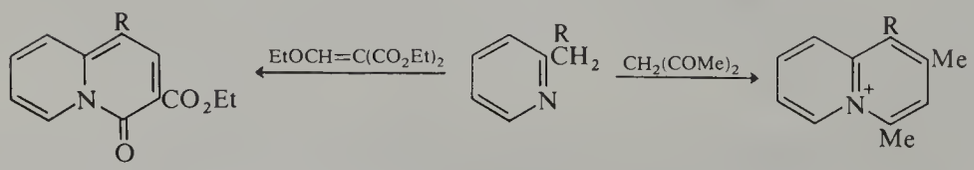
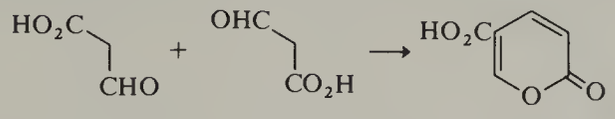

(119)


(120)

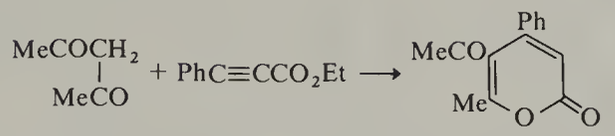

(121)

The use of enolates and enols has not been investigated in such great detail systematically, but 2-pyrones can be made by processes which, formally at least, are related to the above reactions of enamines and enamides (equations 122 and 123). In many 2-pyrone-producing reactions ambiguity exists as to the origin of the ring oxygen atom; equation (122) appears

earlier (*cf.* equation 86) as an example of a [4+2] cyclization process. Without isotopic labelling experiments it is not possible to decide in which category the reaction belongs.

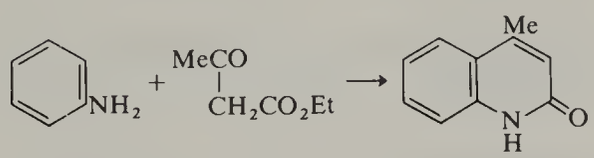


(122)

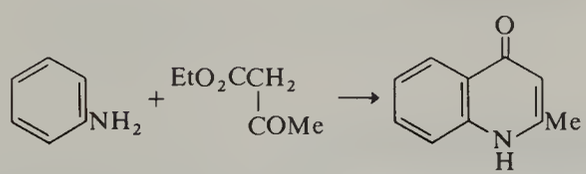


(123)

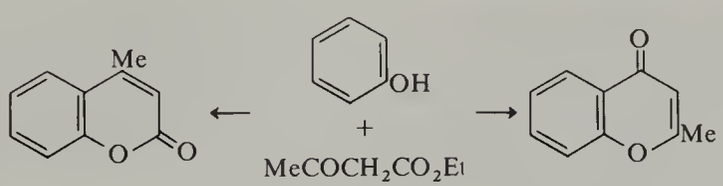
There are a significant number of important reactions which illustrate the same general principle for the synthesis of benzo-fused heterocyclic systems, in which a ring carbon atom *ortho* to a heteroatom functions as one of the nucleophilic centres in the 1,3-dinucleophile. Illustrative examples are given in equations (124)–(130). Many of these methods, which include many classical named reactions, have been investigated in considerable detail for many years, particularly with respect to the experimental conditions, mechanism and control of product formation. Condensation of phenols with β-keto esters, for example, can give either coumarins (the Pechmann reaction) or chromones (the Simonis reaction) or both (equation 126), and careful study of the experimental conditions, substituent effects, *etc.*, has resulted in the development of procedures whereby one or other product can be obtained predominantly or exclusively. Similar considerations apply to the condensation of anilines with β-keto esters, which can give either 2-quinolones (the Knorr reaction, equation 124) or 4-quinolones (the Conrad–Limpach reaction, equation 125), and the reader is referred to the monograph chapters for full details of these and related reactions. One final important point is that some of these reactions are also of great importance for the preparation of hetero-fused heterocycles. This is especially true for the preparation of naphthyridines from aminopyridines by the Skraup reaction (see Chapter 2.11), while a recently described variation on the general theme, in which an *o*-halogenobenzaldehyde functions as the 1,3-dielectrophile, provides a simple and very high yield method for the preparation of 5-deazaflavins (equation 131) ⟨82CC1085⟩.

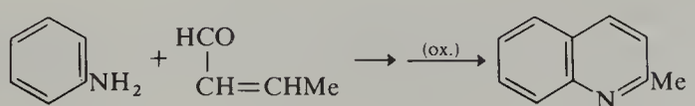


(124)

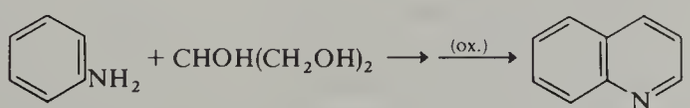


(125)

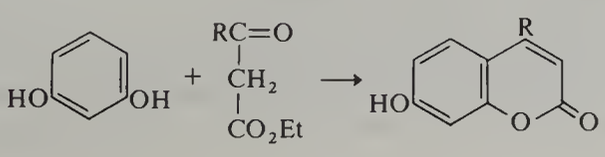




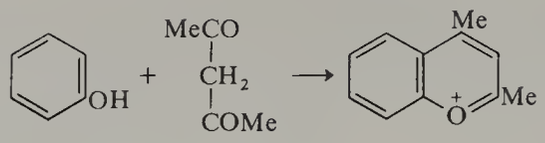
(127)



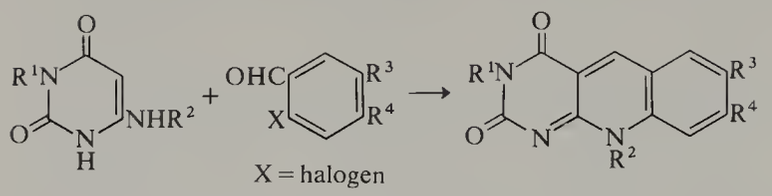
(128)



(129)

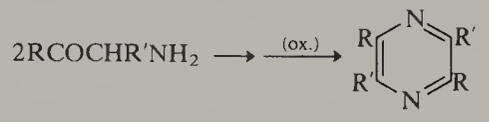


(130)

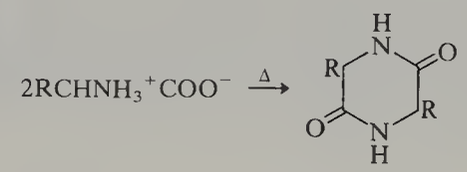


(131)

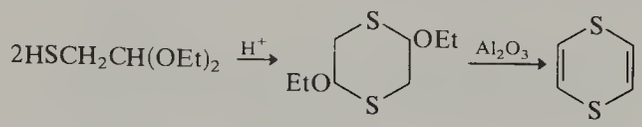
There are very few reactions of real synthetic significance which proceed *via* condensation of two 1,3-electrophile–nucleophile species. Probably the most important of this latter type of reaction is the synthesis of pyrazines by self-condensation of an α-acylamino compound to the dihydropyrazine followed by aromatization (equation 132). The α-acylamino compounds, which dimerize spontaneously, are normally generated *in situ*, for example by treatment of α-hydroxycarbonyl compounds with ammonium acetate or by reduction of α-azido, -nitro or -oximino carbonyl compounds. Cyclodimerization of α-amino acids gives 2,5-dioxopiperazines (equation 133), many derivatives of which occur as natural products. Two further reactions which illustrate the 1,3-electrophile–nucleophile approach are outlined in equations (134) and (135), but such processes are of little general utility.



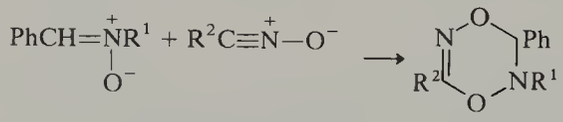
(132)



(133)



(134)



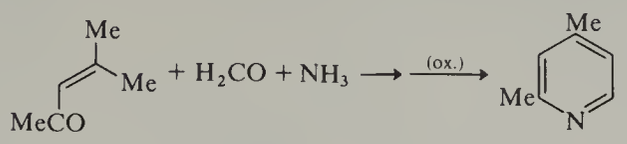
(135)

2.03.2.3 Formation of Three or Four Bonds

Synthetic methods for the preparation of six-membered heterocyclic systems which proceed *via* the formation of three or four bonds are virtually restricted in application to the monocyclic heterocycles and have been most widely applied to pyridine and pyrimidine derivatives. In principle, reactions which proceed with the formation of three ring bonds can be sub-classified into three groups, namely, those involving [4+1+1] atom fragments, [3+2+1] atom fragments and [2+2+2] atom fragments.

Reactions involving the [4+1+1] principle, an example of which is shown in equation (136), are rather uncommon and of strictly limited utility; [3+2+1] and [2+2+2] processes, on the other hand, are well known. Representative [3+2+1] three-bond formation processes are given in equations (137)–(141), from which it can be seen that the common situation is where ammonia, a substituted amine or formamide constitutes the one-atom fragment. Many [2+2+2] atom fragment syntheses are known and some are familiar reactions. Thus, the cobalt(I)-catalyzed condensation of nitriles and isocyanates with alkynes gives pyridines and 2-pyridones, often in excellent yield (*e.g.* equation 142), while the cyclotrimerizations of nitriles, imidates, isocyanates, *etc.*, are well established procedures for the synthesis of 1,3,5-triazine derivatives (*e.g.* equation 143). Further representative examples are given in equations (144)–(147), and the reader is referred to the monograph chapters for full discussion of these and other [2+2+2] processes. Examination of the

above reactions reveals that in mechanistic terms the underlying concepts are generally very simple, although in some instances the precise sequence of bond-forming reactions may be complex, or uncertain.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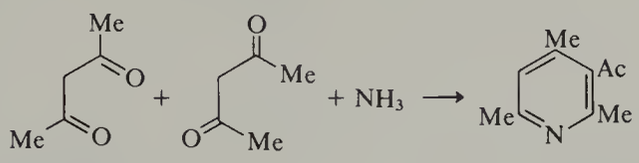
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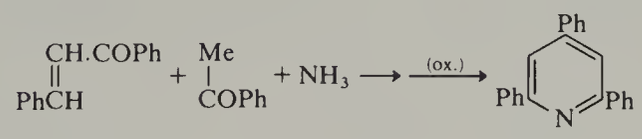
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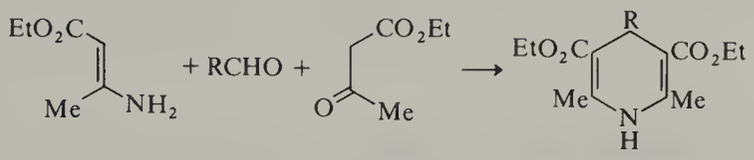
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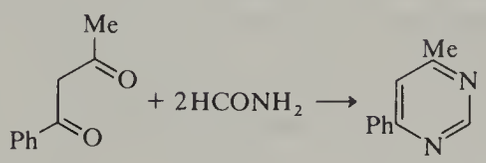
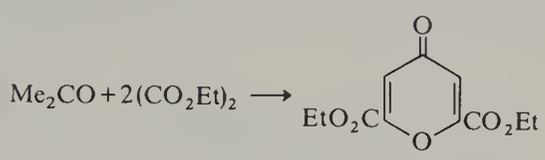

(140)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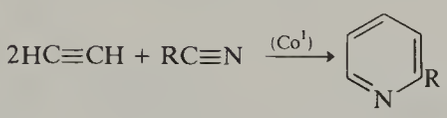
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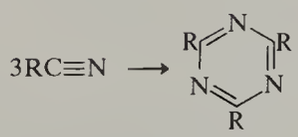
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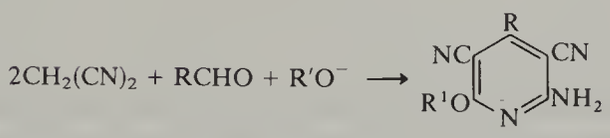
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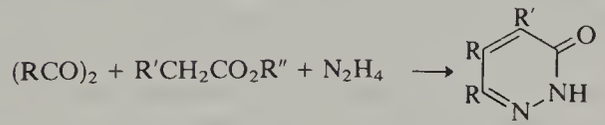
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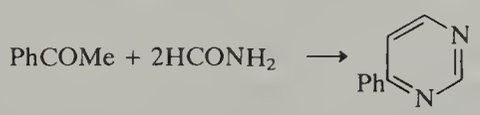
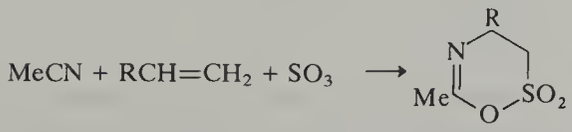
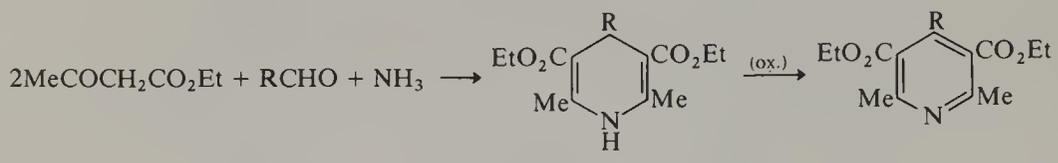

(146)


(147)

As might be expected, there are relatively few reactions for the preparation of heterocyclic systems which are useful on a laboratory scale and which involve the formation of four ring bonds. The Hantzsch pyridine synthesis (equation 148) (and a number of variations of the original procedure) is perhaps the classic example of this type of reaction, which is

necessarily limited in the type of heterocycle which can be prepared and in the substitution pattern around the ring. There are, of course, only two possible combinations of atom fragments for this type of ring synthesis, namely [3+1+1+1] and [2+2+1+1]. Only examples of the latter type of combination are well known (*e.g.* equations 149 and 150).



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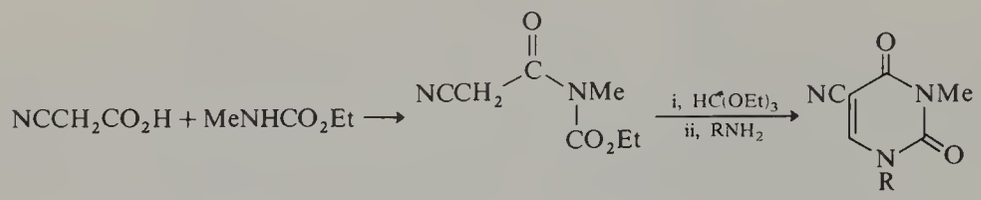

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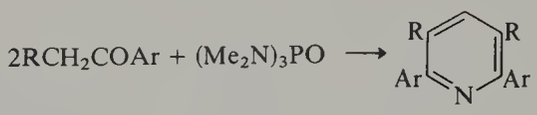
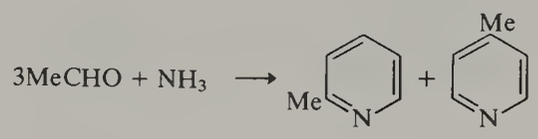
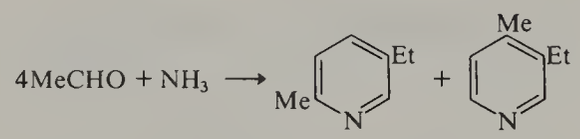


(150)

In contrast to laboratory scale operations, four-bond formation processes are of considerable importance as industrial routes to pyridine derivatives and have been investigated in considerable detail. Vapour phase condensation of aldehydes and ketones with ammonia and amines in the presence of a variety of silica/alumina catalysts containing different promoters (*e.g.* cobalt(II) chloride) can give excellent yields of substituted pyridines (*e.g.* equation 151), and the nature of the products formed can be largely controlled by change in the stoichiometry of the reactants and variation of experimental conditions (equation 152).



(151)



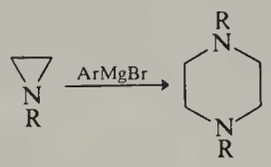
(152)

2.03.3 RING SYNTHESIS BY TRANSFORMATION OF OTHER HETEROCYCLES

An important and fascinating aspect of heterocyclic chemistry is the ease with which a wide variety of heterocyclic systems can be transformed into other heterocyclic systems, often in excellent yield and under mild conditions. These ring interconversion processes, most of which involve treatment of a given heterocyclic system with a specific reagent or reagents, and result in incorporation of at least part of the reagent into the final product, can be of various general types, *e.g.* ring expansion, ring contraction or with no overall change in ring size. There is no single mechanistic theme: some transformations proceed *via* an ANRORC mechanism, some by a Diels–Alder/retro-Diels–Adler-type sequence and others by diverse pathways. It must also be stressed that while many of these ring interconversion processes are of considerable synthetic utility, in many other instances the reactions are of mainly academic and mechanistic interest, as either the necessary starting materials are difficultly accessible and/or the products are more easily and efficiently prepared in other ways. In the following discussion, the synthesis of six-membered heterocyclic systems from other heterocyclic systems is presented in order of the ring size of the starting heterocycle, *i.e.* from three-membered heterocycles, four-membered heterocycles, *etc.* The literature on ring transformations of heterocycles has been covered to the end of 1970 in an excellent two-volume work ⟨B-73MI20300⟩.

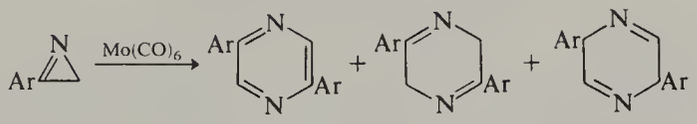
2.03.3.1 From Three-membered Heterocyclic Systems

Aziridines, and to a lesser extent azirines, can be usefully employed for the synthesis of six-membered heterocycles in two main types of [3+3] heterocyclization process. The first involves formal 'dimerization' of the three-membered heterocycle, as for example in the formation of piperazine by treatment of aziridine with ammonia. 1,4-Disubstituted piperazines are obtained similarly from 1-substituted aziridines by treatment with Grignard reagents (equation 153), while treatment of azirines with Group VI metal carbonyls gives mixtures of pyrazines and dihydropyrazines, often in high yield, and this general approach could be of some importance (equation 154). The second general type of [3+3] heterocyclization involves initial nucleophilic attack of the electrophilic three-membered heterocycle by a 1,3-electrophile–nucleophile to give, in the case of aziridines, a ring-opened intermediate, cyclization of which gives a six-membered heterocycle. Treatment of aziridines with either α-mercapto ketones or with a mixture of a ketone and sulfur, for example, gives 5,6-dihydro-1,4-thiazines (equation 155). Reaction of azirines with 1,3-electrophile–nucleophiles also occurs readily *via* initial nucleophilic attack at the heterocyclic ring, and can be used for the preparation of both pyrazinones (equation 156) and 1,4-oxazinones ⟨83TL1153⟩. In the latter case, *i.e.* reaction of α-hydroxy esters with azirines, an intermediate alkoxyaziridine has been isolated in low yield.

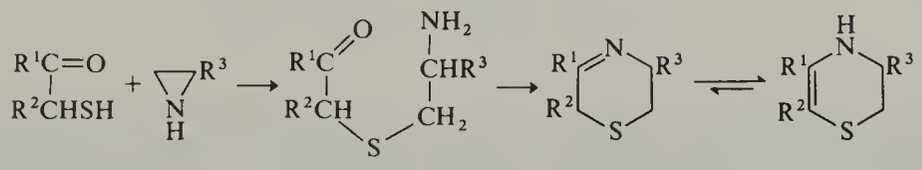


(153)

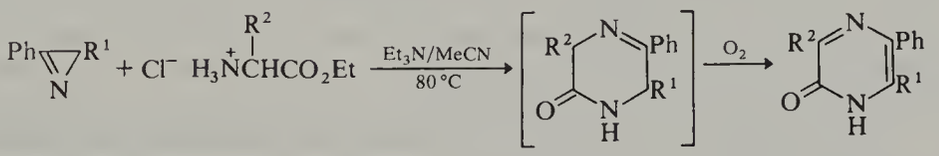
R = alkyl, aryl



(154)

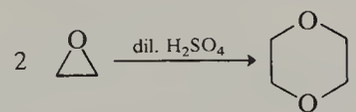


(155)

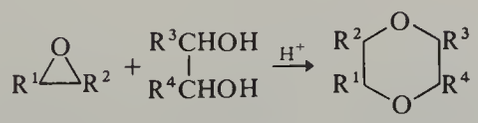


(156)

The most important use of oxiranes for the preparation of six-membered heterocycles is in 1,4-dioxane formation. 1,4-Dioxane, for example, is obtained in excellent yield by treatment of oxirane with dilute sulfuric acid (equation 157), and substituted dioxanes can be prepared in a similar manner. 1,4-Dioxanes can also be conveniently obtained by acid-catalyzed condensation of oxiranes with glycols (equation 158), while use of

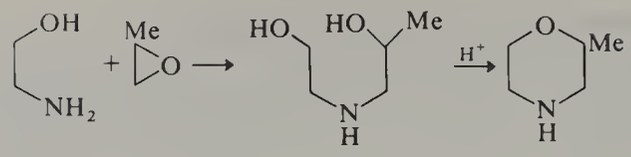


(157)

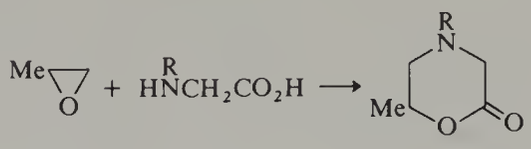


(158)

ethanolamines gives morpholines (equation 159). An important reaction for the preparation of tetrahydro-1,4-oxazin-2-ones is the base-catalyzed reaction of oxiranes with α-amino acids and esters (equation 160). 1,4-Dithianes have been prepared by the formal dimerization of thiiranes either in the vapour phase or in the presence of acid catalysts, but these reactions have not been explored in detail.



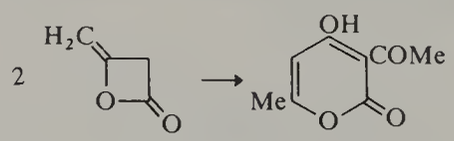
(159)



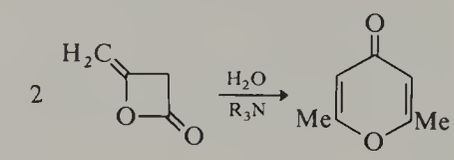
(160)

2.03.3.2 From Four-membered Heterocyclic Systems

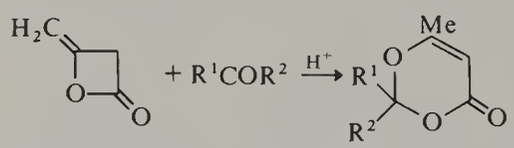
The only four- → six-membered ring interconversions of any real synthetic significance are those involving diketene. Base-catalyzed dimerization of diketene is a long-established and efficient method for the preparation of dehydroacetic acid (equation 161), while mild treatment with water in the presence of tertiary amine bases gives 2,6-dimethyl-4-pyrone (equation 162). 1,3-Dioxins are obtained from the acid-catalyzed condensation of diketene with ketones (equation 163).



(161)

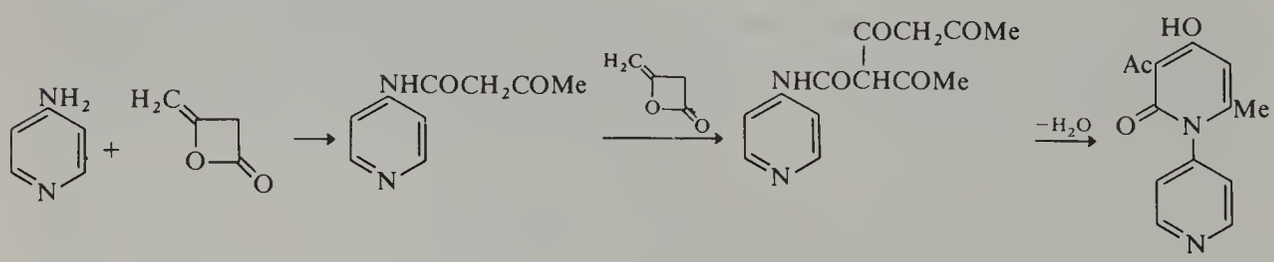


(162)



(163)

Diketene is of course a masked form of acetoacetic ester, and as such reacts in much the expected manner with a variety of mono- and di-nucleophiles. Aromatic and heteroaromatic amines, and phenols, for example, give acetoacetanilides and aryl acetoacetates; the latter can be cyclized in excellent yield to coumarins while reaction of the former with excess of diketene followed by cyclization gives dioxopyridines (*e.g.* equation 164). Amidines, ureas, thioureas, *S*-alkylthioureas and carbodiimides also react with diketene to give pyrimidines (*e.g.* equation 165), although in the case of amidines, *S*-alkylthioureas and carbodiimides the initially formed products are 1,3-oxazines which are converted into pyrimidines on subsequent treatment with acid or base.



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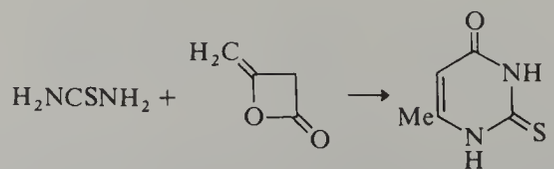


(165)

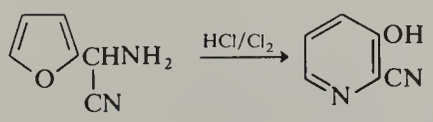
2.03.3.3 From Five-membered Heterocyclic Systems

There is a very wide variety of reactions in which five-membered heterocycles are transformed into six-membered heterocyclic systems and some of these processes are of

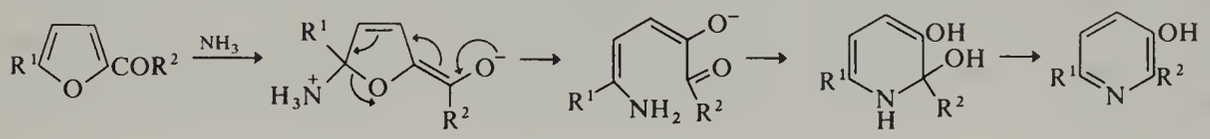
considerable synthetic utility. All of the possible atom fragment combinations are known: [6+0], [5+1], [4+2] and [3+3], and numerous different mechanistic pathways have been identified.

2.03.3.3.1 From five-membered heterocycles containing one heteroatom

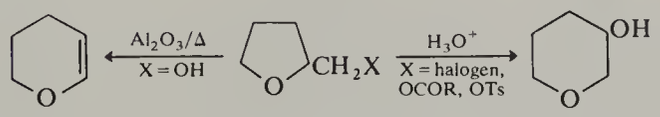
Ring interconversion reactions involving furans and fully and partially reduced furans, especially those leading to six-membered heterocycles, have been extensively studied. Aminomethylfurans, for example, are converted into 3-hydroxypyridines by reaction with acid in the presence of an oxidizing agent (equation 166), while treatment of 2-hydroxymethylfurans with chlorine in aqueous methanol gives 3-hydroxy-4-pyrones in good yield. 3-Hydroxpyridines can also be conveniently prepared by reaction of 2-acylfurans with ammonia, probably by the sequence of reactions outlined in Scheme 3. The use of tetrahydrofuran derivatives is illustrated by the conversion of 2-hydroxymethyltetrahydrofuran into 5,6-dihydro-4*H*-pyran and the acid-catalyzed rearrangement of other 2-substituted tetrahydrofurans into 3-hydroxypyrans (equation 167). The use of 2,5-dialkoxy-2,5-dihydrofurans as masked 1,4-dicarbonyl compounds is well established and, with suitably substituted furans as starting materials, has been exploited for the [6+0] synthesis of pyridines (equation 168) and pyridazines (equation 169). Alternatively, pyrazines can be prepared by eventual [4+2] heterocyclization as outlined in equation (170), or by the familiar [4+2] reaction of anhydrides with hydrazines (equation 171).



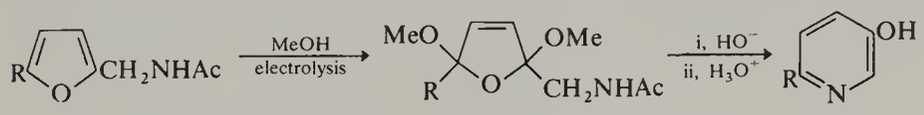
(166)



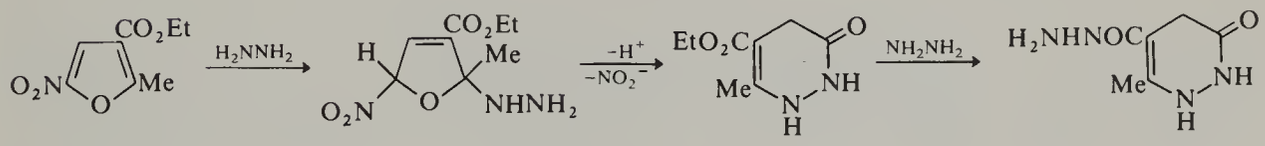
Scheme 3



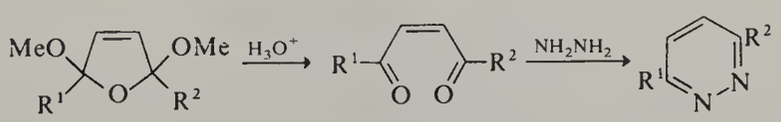
(167)



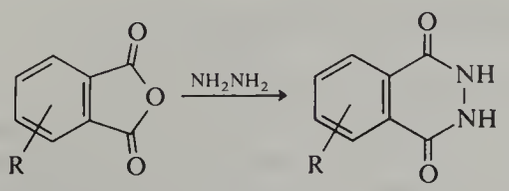
(168)



(169)



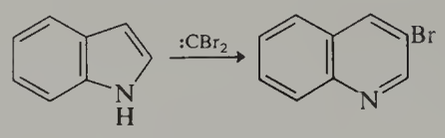
(170)



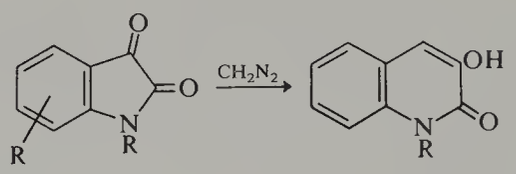
(171)

In contrast to the situation with furans, there has been little study of ring expansion reactions of thiophenes and reduced thiophenes and no procedures of significant synthetic utility are known. There are, however, numerous examples of useful ring transformations

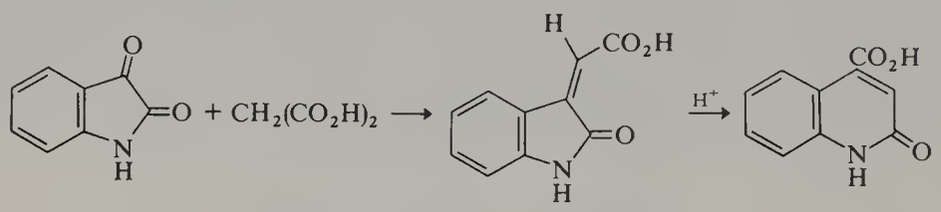
of pyrrole derivatives. Perhaps the classic example here is the [5+1] reaction of pyrroles and indoles with dihalocarbenes (equation 172), although the yields in these reactions are only low to moderate. Rather more useful are the transformations of oxindoles, isatogens and, especially, isatins into quinolines, cinnolines and quinazolines. Treatment of isatins with diazomethane, for example, gives 3-hydroxy-2(1*H*)-quinolones (equation 173); reaction with active methylene compounds also gives 2-quinolones *via* acid-catalyzed rearrangement of the initially formed alkylidene intermediates (equation 174). Treatment of isatogens



(172)

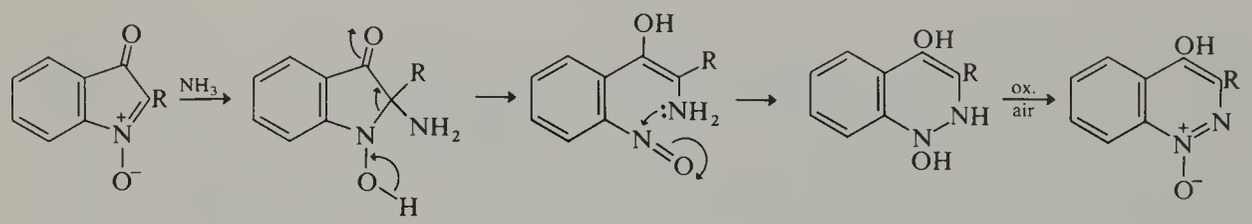


(173)

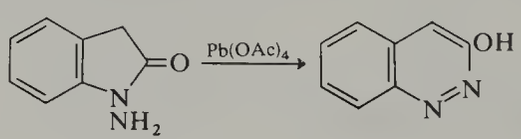


(174)

with ammonia gives cinnoline 1-oxides, probably by the mechanism outlined in Scheme 4, while oxidative ring expansion of *N*-aminooxindoles gives 3-hydroxycinnolines in excellent yield (equation 175). This latter type of reaction, which may proceed *via* a nitrene-like intermediate, has been widely investigated as a ring expansion procedure and is of considerable synthetic utility. A further useful ring expansion procedure is the Meisenheimer-type rearrangement of 1-substituted pyrrolidine 1-oxides to tetrahydro-2*H*-1,2-oxazines (equation 176).



Scheme 4



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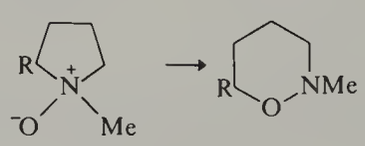


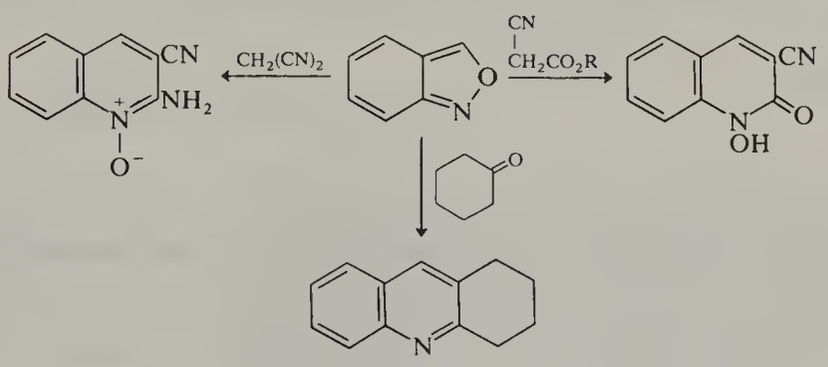
(176)

2.03.3.3.2 From five-membered heterocycles containing two or more heteroatoms

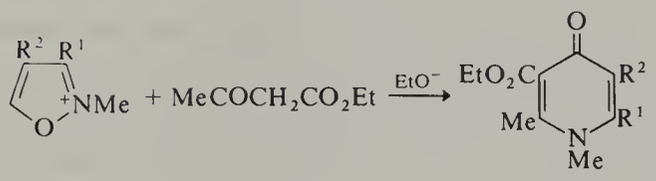
Some of the ring expansion reactions discussed in Section 2.03.3.3.1 can be extended to five-membered heterocycles containing two or more heteroatoms. Reaction of imidazoles and pyrazoles with dichlorocarbene, for example, gives chloropyrimidines together with small amounts of chloro-pyrazines or -pyridazines, and oxidative ring expansion of 1-aminopyrazole with nickel peroxide gives 1,2,3-triazine (this, in fact, constitutes the only known synthesis of the unsubstituted triazine). There are, however, a number of interesting and useful transformations which are unique to five-membered polyheteroatom systems.

In mechanistic terms, the most important of these processes involve either a ring opening/ring closure sequence, most commonly of the ANRORC type, or a cycloaddition reaction followed by decomposition/rearrangement of the cycloadduct.

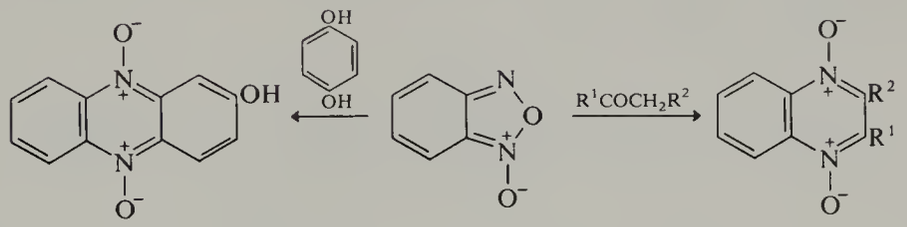
The ANRORC mechanism is well illustrated in the facile ring opening of anthranils by nucleophiles, followed by ring closure to give quinoline derivatives (Scheme 5). As expected, positively charged five-membered heterocycles are also very susceptible to nucleophilic attack, and a number of important transformations are based on this approach. Reaction of isoxazolium salts with active methylene compounds, for example, can be used for the preparation of pyridines, pyridinium salts and pyrimidines (*e.g.* equation 177), and initial nucleophilic attack and ring opening is probably involved in the important conversion of benzofuroxans into quinoxaline di-*N*-oxides by treatment with imines, enamines, carbonyl compounds, active methylene compounds and phenols (equation 178). The initial nucleophilic attack on the heterocyclic ring can also take place intramolecularly. Base-catalyzed reaction of the ethoxymethyleneoxazolones (**30**) with compounds containing active methylene groups, for example, results in ring expansion to 2-pyrones (Scheme 6).



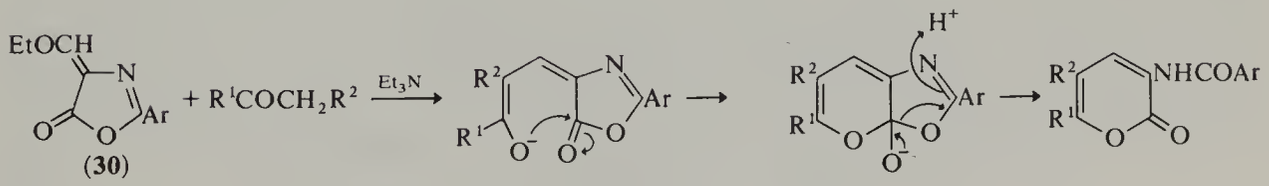
Scheme 5



(177)

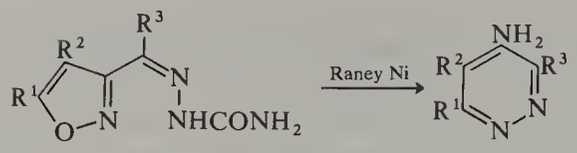


(178)

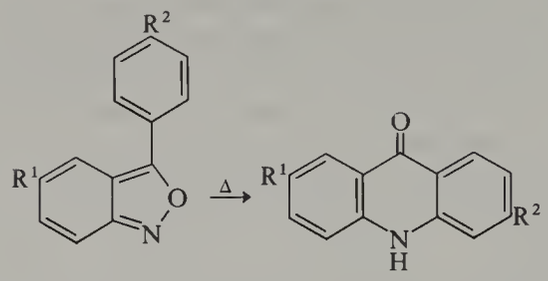


Scheme 6

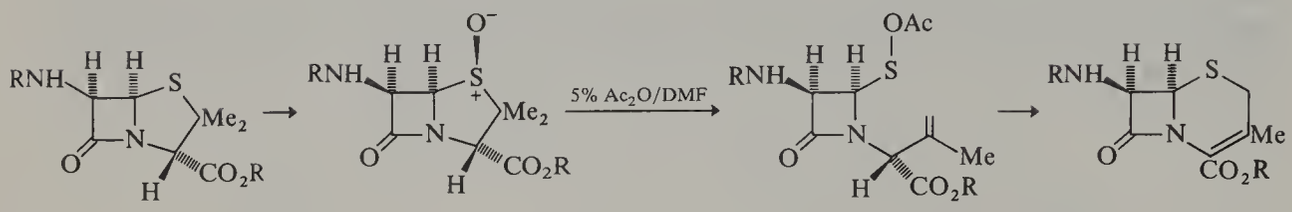
Ring opening/ring closure reactions by mechanisms other than the ANRORC pathway are also of considerable utility. Raney nickel hydrogenation of the semicarbazone derivatives of 3-acylisoxazoles, for example, gives pyrazines, presumably *via* hydrogenolysis of the N—O bond and cyclization of the keto-imine thus formed (equation 179). Thermolysis of 3-arylanthranils gives acridones, often in high yield (equation 180), and this transformation has been postulated to proceed *via* a nitrene intermediate. Finally, in this context, the conversion of the penicillin into the cephalosporin ring system has attracted a great deal of attention and various methods have been developed for the thiazolidine → dihydrothiazine transformation. Probably the most direct of these involves treatment of the sulfoxide with 5% Ac_2O/DMF at 130 °C, which gives the deacetoxycephalosporin in 60% yield (equation 181).



(179)

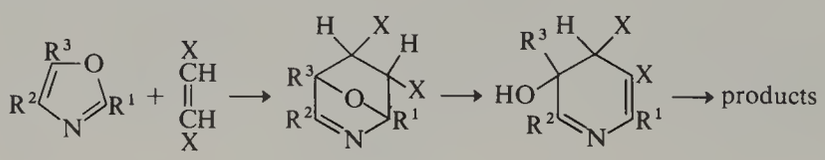


(180)

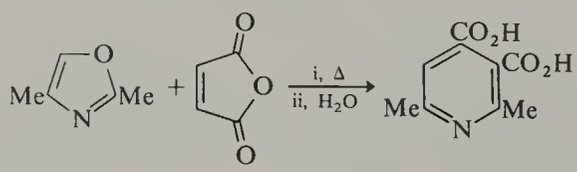


(181)

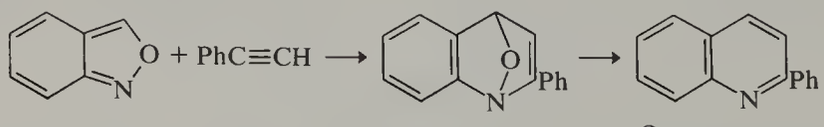
The most extensively studied five- to six-membered heterocyclic ring transformation involving a cycloaddition process is the reaction of oxazoles with dienophiles. Ring opening of the cycloadduct gives a dihydropyridine (equation 182) and the nature of the final product depends on which substituents (H_2O, XR^3, HR^3 or XOH) are lost from the 3- and 4-positions in the final aromatization step. In some instances mixtures of products are obtained, but normally, by appropriate choice of oxazole and dienophile, a single pyridine derivative can be obtained in good yield (*e.g.* equation 183). Thiazoles react in a similar manner, but have not been used as often as oxazoles. Cycloaddition reactions with anthranils have been studied to some extent and can be used for the synthesis of substituted quinolines (equation 184). A more unusual but nevertheless very useful cycloaddition reaction occurs when thiazoline-4,5-diones are decomposed thermally in the presence of alkenes, imines and nitriles. Carbon monoxide is evolved and a thioacyl isocyanate is probably formed; 1,4-dipolar cycloaddition to C=C, C=N and C≡N bonds gives the corresponding six-membered heterocycles (equation 185).



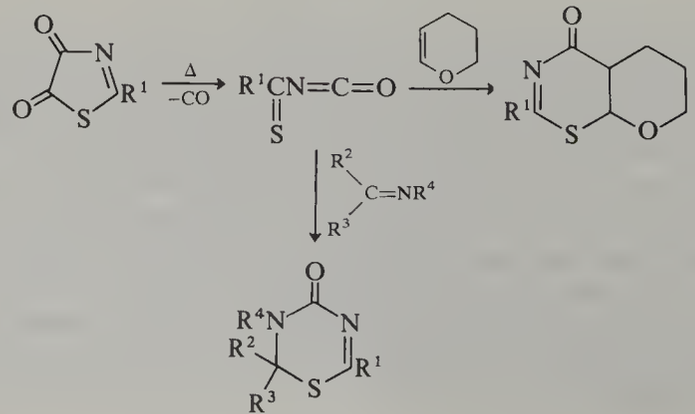
(182)



(183)

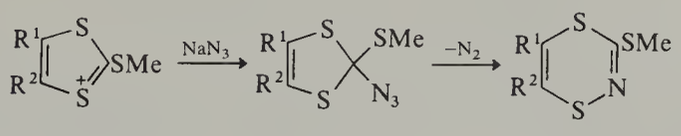


(184)

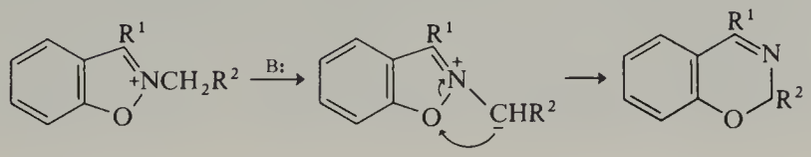


(185)

Finally, a number of useful ring expansion reactions are known which probably do not involve ring opening of a five-membered heterocycle, although the mcechanisms of these reactions are not known in detail. One important method for the preparation of 1,4,2-dithiazines, for example, is by reaction of dithiolylium salts with azide ion. The initially formed addition product is unstable and loses nitrogen to give the 1,4,2-dithiazines, possibly by a 1,2-shift (equation 186). A concerted ring expansion may well also be involved in the base-catalyzed conversion of *N*-alkylisoxazolium salts into 1,3-oxazines (equation 187).



(186)



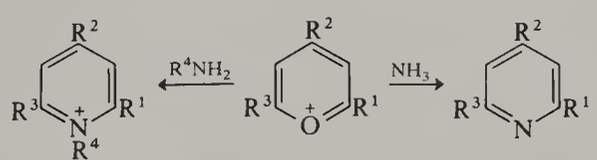
(187)

2.03.3.4 From Six-membered Heterocyclic Systems

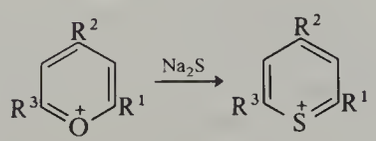
A number of very important synthetic methods are based on ring interconversions of six-membered heterocyclic systems. As with the transformations of five- into six-membered rings, examples are known of all of the possible atom fragments, but [5+1] and [4+2] processes are by far the most important. As described in Chapter 2.02, a number of [6+0] photoisomerizations of diazines have been discovered, but while these are of considerable mechanistic and theoretical importance they are of little preparative significance.

2.03.3.4.1 From six-membered heterocycles containing one heteroatom

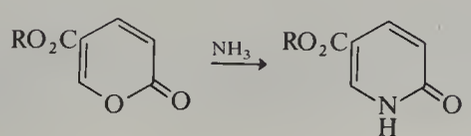
The most important type of reaction in this category is the conversion of pyrylium salts into pyridines and pyridinium salts. Nucleophilic addition at the 2-position of pyrylium salts occurs readily under mild conditions and when ammonia or primary amines are used the subsequent ring opening/ring closure sequences give pyridines and pyridinium salts respectively (equation 188). The process is most useful for the synthesis of 2,4,6-trisubstituted pyridine derivatives and has been investigated in great detail for many years. Thiopyrylium salts, which can be conveniently prepared from pyrylium salts by treatment with sodium sulfide (equation 189), react similarly with ammonia and amines, but there is no practical advantage in using thiopyrylium rather than pyrylium starting materials. Aminolysis of α- and γ-pyrones also proceeds by an ANRORC mechanism and is an important and widely used method for the preparation of 2- and 4-pyridone derivatives (*e.g.* equations 190 and 191). Use of hydrazine instead of ammonia can give good yields of pyridazines, but pyrazoles are often formed as by-products in low to moderate yield. Tetrahydropyran-4-ones are also converted into the corresponding piperidones and thiopyrones on treatment with amines and hydrogen sulfide respectively, but prolonged reaction times are necessary and these reactions are not of any great synthetic utility.



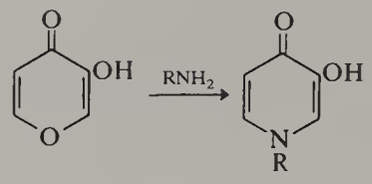
(188)



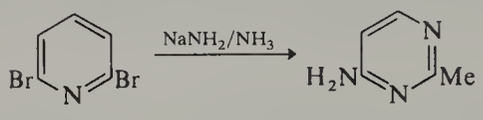
(189)



(190)



(191)

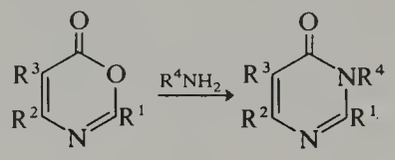


(192)

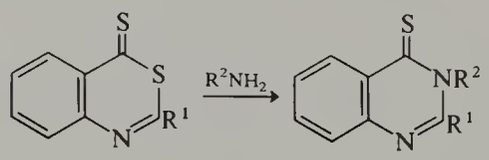
One final reaction of the ANRORC type which is of some limited synthetic utility is the conversion of certain 6-substituted 2-bromopyridines into pyrimidines by treatment with sodamide in liquid ammonia (*e.g.* equation 192). Here, the postulated mechanism involves addition of amide ion at the 4-position, ring opening by cleavage of the C(3)—C(4) bond and loss of the 2-bromo substituent, and ring closure of the acyclic intermediate thus obtained.

2.03.3.4.2 From six-membered heterocycles containing two or more heteroatoms

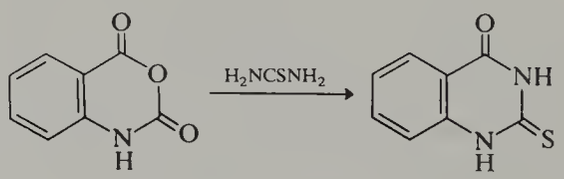
There are two important general types of reaction by which six-membered heterocycles containing two or more heteroatoms can be transformed into other six-membered heterocyclic systems, namely reactions which involve an ANRORC mechanism, and reactions which proceed by a Diels–Alder/retro-Diels–Alder type of mechanism. Transformation of 1,3-oxazinones and -thiazinones into pyrimidones (equations 193 and 194) has been extensively used, especially in the conversion of isatoic anhydride into quinazolinones (*e.g.* equation 195). 2,4-Diaryl-1,2,3,5-oxathiadiazines, which are readily accessible by reaction of sulfur trioxide with aryl isocyanates, are useful precursors to pyrimidines and 1,3,5-triazines (equation 196).



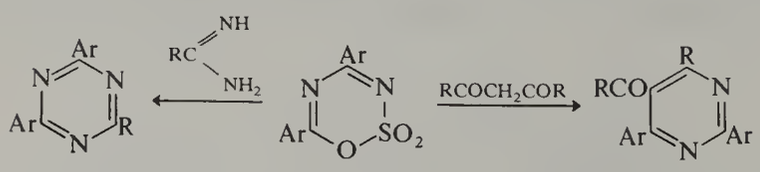
(193)



(194)



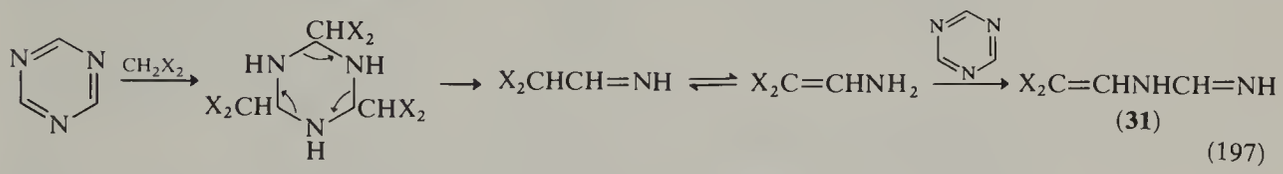
(195)



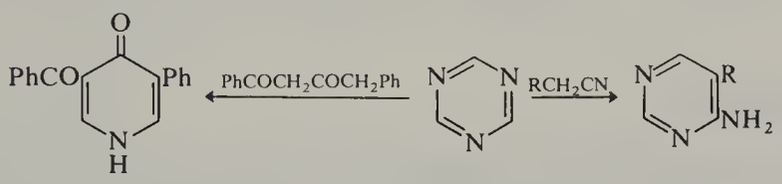
(196)

The above reactions are relatively straightforward in terms of mechanism. There are, however, a number of important transformations based on 1,3,5-triazine as starting material, and which result in formation of either pyridine or pyrimidine derivatives. 1,3,5-Triazine reacts very readily with nucleophiles, probably as outlined in equation (197); if X in (**31**) is a suitable electrophile, cyclization can take place. Thus, when X = CN, 4-amino-5-cyanopyrimidine is obtained, and other illustrative examples are shown in equation (198). This procedure is particularly useful for the preparation of 2-unsubstituted pyrimidines, a class of compound which is not readily accessible by other types of ring formation. The reverse type of transformation, *i.e.* of pyrimidines to 1,3,5-triazines, is also an important synthetic method, and one which has been studied in detail. Two types of substituted

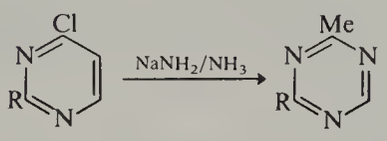
pyrimidine are suitable substrates, namely 6-unsubstituted 4- or 5-halopyrimidines and 4-amino-5-nitrosopyrimidines. Reaction of 2-substituted 4- or 5-halopyrimidines with sodamide in liquid ammonia gives 2-substituted 4-methyl-1,3,5-triazines (*e.g.* equation 199); the reaction is very general in nature and yields vary from moderate to excellent. The mechanism has been investigated in detail and is broadly similar to that of the related conversion of 6-substituted 2-bromopyridines into pyrimidines mentioned in Section 2.03.3.4.1, *i.e.* initial addition of amide ion at the 6-position of the pyrimidine, ring opening by cleavage of the C(5)—C(6) bond and loss of the halogen substituent, and ring closure of the acyclic product thus formed. Conversion of 4-amino-5-nitrosopyrimidines into 1,3,5-triazines proceeds by a rather different mechanism. This type of reaction is effected by acetic anhydride, phosphorus oxychloride or sulfonyl halides, and the mechanism outlined in Scheme 7 has been suggested.



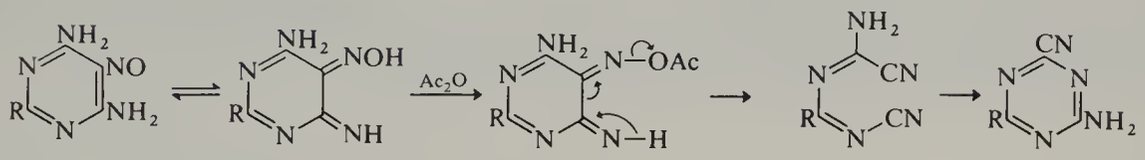
(197)



(198)

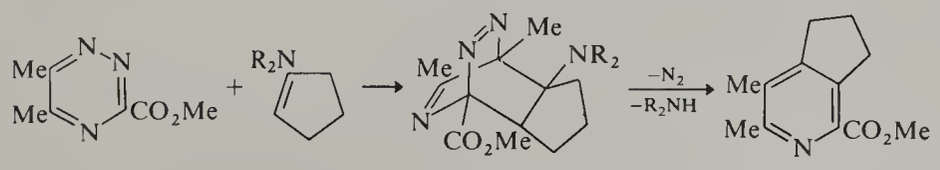


(199)

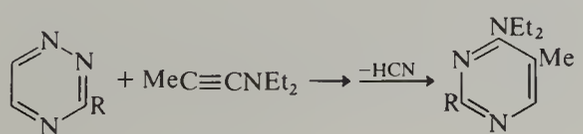


Scheme 7

Reactions of the Diels–Alder/retro-Diels–Alder type with diazines, and especially polyazines, are important methods for interconversion of six-membered ring systems. These are cases of 'inverse electron demand' Diels–Alder reactions, *i.e.* electron-rich dienophiles are required. Examples of such reactions are known with all of the diazines, but mixtures of products are common with these substrates and the most useful reactions are with triazines and 1,2,4,5-tetrazine. 1,2,4-Triazine, for example, readily reacts with enamines and enol ethers to give pyridines; a typical example is shown in equation (200). With ynamines, however, the initial cycloaddition takes place across the 2- and 5- rather than the 3- and 6-positions, and aromatization by loss of hydrogen cyanide gives pyrimidines rather than pyridines (*e.g.* equation 201). 1,3,5-Triazines also react readily with electron-rich alkenes and alkynes to give pyrimidines in good to excellent yield (*e.g.* equation 202), while the use of 1,2,4,5-tetrazine in such reactions has been extensively investigated. In the latter case, use of alkynes gives pyridazines directly, while alkenes initially yield dihydro derivatives. In most cases, however, the dienophile is selected such that aromatization can take

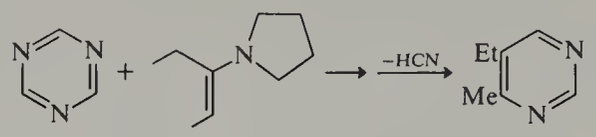


(200)

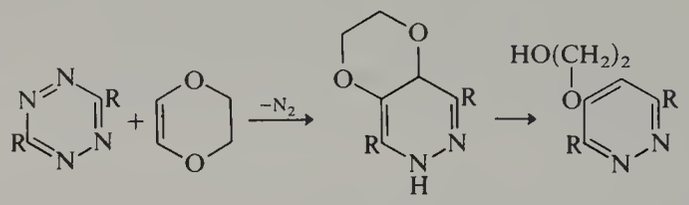


(201)

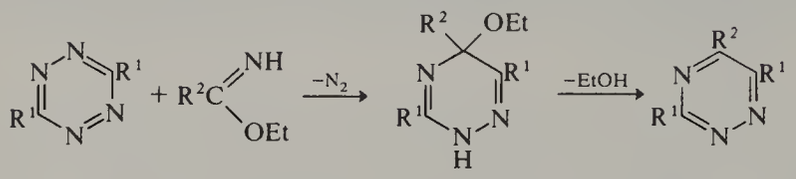
place easily (*e.g.* equation 203). Condensation of 1,2,4,5-tetrazine with imidates gives 1,2,4-triazines (equation 204), and this general approach to the synthesis of azines continues to attract much attention.



(202)



(203)



(204)

2.03.4 CONCLUSION

The reactions by which we have exemplified this brief survey of heterocyclic six-membered ring syntheses were in the main selected for their appropriateness to a discussion of general principles. Many important, interesting and unusual methods have been omitted, either because the point is already adequately illustrated, or because the examples are isolated and lacking in general applicability.

We have made no attempt to supply full referencing to the examples quoted: the references which are given here are usually recent ones, and if further information is needed the appropriate monograph chapter should provide the source.

2.04

Pyridines and their Benzo Derivatives: (i) Structure

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2.04.1 APOLOGIA: MOLECULAR ORBITAL CALCULATIONS

This section is concerned with the structure of pyridines: within this context we consider pyridine itself, pyridines substituted on carbon and nitrogen, including in the latter category ylide, betaine and zwitterion structures, and in the former benzo substituents. Thus quinolines and isoquinolines will receive attention as well as bipyridyls, but not, for example, cinnoline or quinoxaline. Completely saturated derivatives, such as piperidine, and partially saturated derivatives, such as dihydropyridines, will also be treated.

The various forms of experimental methodology, particularly predominant being that of spectroscopy, are discussed next. Accounts of the phenomena of tautomerism and conformation, both vital topics in this area, will then be given. Clearly such divisions will overlap, as in the first case we deal with methodology and in the second phenomenology, which is bound to involve some duplication of material. For example, the section on molecular spectroscopy (2.04.3) contains spectral data on potentially tautomeric molecules, although a later section (2.04.4) deals specifically with the topic of tautomerism. In such cases the experimental methods employed and the data obtained are dealt with in the first section, while the subsequent one attempts to draw conclusions on the general structural influences involved and the overall patterns of behaviour with the minimum of emphasis on the

Table 1 Diffraction and Spectroscopic Methods for Elucidation of Pyridine Structures

	Diffraction methods	*Radiation* *Energy* (kJ mol^{-1})	*Wavelength* (cm)		*Spectroscopic methods*
Electronic change	Electron diffraction Molecular dimensions in vapor phase	1.26×10^{6} — 10^{-10}	Cosmic rays 10^{-12}–10^{-10}		
	Neutron diffraction (as for X-rays)				
	X-ray diffraction. Molecular dimensions of crystalline pyridine compounds	1.26×10^{4} — 10^{-8}	X-rays, γ-rays 10^{-10}–10^{-8}		Mössbauer spectroscopy features relating to pyridine and derivatives complexed with Fe or certain other metallic ions in crystalline state[b]
				Mass spectrometry. Electron beam inducing fragmentation of pyridine molecules in the vapor phase[a]	
		1.26×10^{2} — 10^{-6}	Far UV (10^{-6}–2×10^{-5}) UV (2×10^{-5}–3.8×10^{-5})		Photoelectron spectroscopy (far UV) Molecular energy levels in aromatic heterocycles. $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ electronic transitions in pyridine. Phosphorescence and fluorescence
Vibration change		1.26 — 10^{-4}	Visible (3.8×10^{-5}–7.8×10^{-5}) Near IR (7.8×10^{-5}–3×10^{-4}) Middle IR (3×10^{-4}–3×10^{-3})		Raman spectroscopy IR spectroscopy. Stretching frequencies of bonds in pyridine derivatives
		1.26×10^{-2} — 10^{-2}	Far IR (3×10^{-3}–3×10^{-2})		
Rotation change		1.26×10^{-4} — 1	Microwave (3×10^{-2}–10^{2})		Microwave spectra. Rotational energy levels for pyridine using isotopic species. Definition of bond lengths and angles, dipole moment
Spin change					Electron spin resonance. Structure of pyridine derivatives with unpaired electrons
		1.26×10^{-6} — 10^{2}			NMR proton signals in pyridine
					Nuclear quadrupole resonance. Crystalline pyridine compounds at 77 K

[a] Not really a spectroscopic technique in that the line spectrum produced does not arise from quantization of electromagnetic radiation.
[b] Of specialized interest only; not further discussed here.

experimental evaluation. Where repetition is absolutely essential, it has been kept to a minimum and cross references constantly employed.

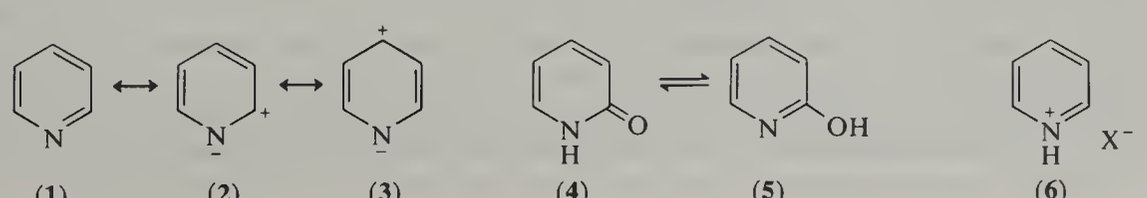
In spotlighting the role that physical methods play in elucidating the structure of pyridine and its derivatives, space is available to give only the briefest account of the theory and method of the physical techniques employed. This is dangerous, because frequently the significance to be placed on a result depends on an intimate knowledge of the assumptions made and the type of error implicit in the technique employed in its determination. It is hoped therefore to give at least some indication of the limitations involved in individual cases. For more detailed information on these underlying techniques, the interested reader should proceed *via* Katritzky's series 'Physical Methods in Heterocyclic Chemistry' to Specialist Periodical Reports of the Royal Society of Chemistry on 'Mass Spectrometry', 'Molecular Spectroscopy', 'Molecular Structure by Diffraction Methods' and 'Nuclear Magnetic Resonance', and thence to specialist accounts in the literature of physical chemistry.

We must note that we are dealing here not with static molecules, as no molecule is stationary even at the absolute zero of temperature, but rather with non-reacting molecules. This will be extended, however, to include mass spectrometry and the reactions which proceed within the mass spectrometry tube, as these are used to define the structure of the parent molecule. Obviously, though, such reactions have an importance of their own which is not neglected. Details of species involved as reactive intermediates, which may exist long enough for definition by physical techniques, will also be considered. For example, the section on ESR (Section 2.04.3.7) necessarily looks at unpaired electron species such as neutral or charged radicals, while that on UV spectroscopy (Section 2.04.3.3) considers the structure of electronically excited heterocyclic molecules.

Table 1 shows diagrammatically the diffraction and spectroscopic methods considered in this section, giving the types of beams used for the diffraction experiments, the wavelength of the electromagnetic radiation absorbed or emitted in the spectroscopy experiments, the character of the interactions thus involved, using pyridine or simple derivatives as examples, and the sort of information consequently derived.

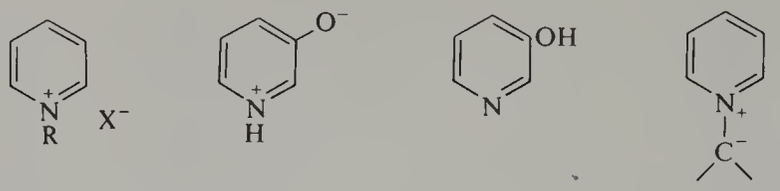
No separate section is devoted to dipole moments. A table of such quantities will be given in the microwave spectroscopy section (2.04.3.5); this describes a technique which leads apparently fairly readily both to group and overall dipole moment values. Generally, the measurement of dipole moments in solution from determination of dielectric constant has declined from being a much investigated area over the last decade or so. The theoretical information formerly thus obtained can now be garnered from alternative sources more readily available. This is not to deny, however, the key role that such measurements have played in the development of chemical theory, particularly, for example, in the determination of conformational equilibria, or of electronic effects producing polarization of molecules, nor to suggest that the technique may not yet still be of some utility in the appraisal of certain specific problems.

Pyridine (**1**) represents, ostensibly at least, a straightforward modification of the benzene system. One of the CH units in benzene is replaced with an sp^2 hybridized nitrogen. This leads to a distortion of the regular hexagon of benzene with a strengthening and subsequent shortening of the C—N bond, and contributes to the large dipole moment of about 2.2 D of the molecule. This may be defined as arising from both the inductive and resonance effect of the nitrogen, which is more electronegative than the sp^2 hybridized carbon that it has replaced, and which *via* the resonance effect gives rise to canonical forms (**2**) and (**3**). Substituents may be attached to the ring carbon atoms; if these contain ionizable hydrogen, equilibria involving the alternative structures with a proton on N are possible, for example 2-pyridinone (**4**) and 2-hydroxypyridine (**5**). This general area of tautomerism has been the subject of much interest and controversy, and it will receive close attention in this chapter. The basicity of the nitrogen centre leading to proton uptake also leads to protonated structures of form (**6**). The position of equilibria between free base and conjugate acid is defined by pK_a values; as such they are the subject of the reactivity section (Chapter 2.02), but nevertheless structural features of such pyridinium structures will concern us.



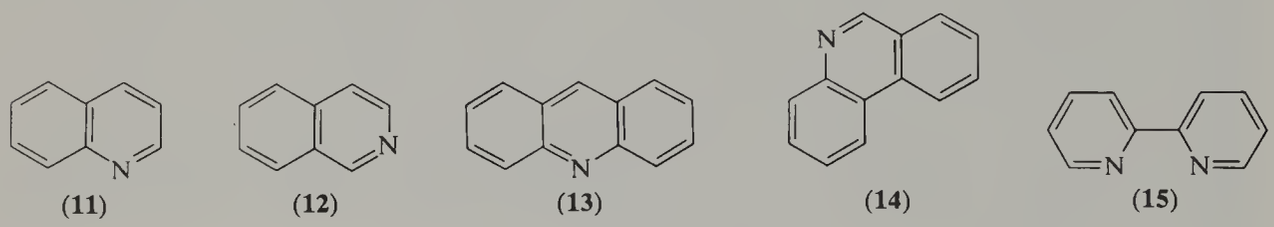
(1) (2) (3) (4) (5) (6)

The structures of other charged pyridines such as quaternary salts (**7**), zwitterions (**8**) arising from β-hydroxypyridines (**9**), another aspect of tautomerism, and ylides (**10**) will also be considered.

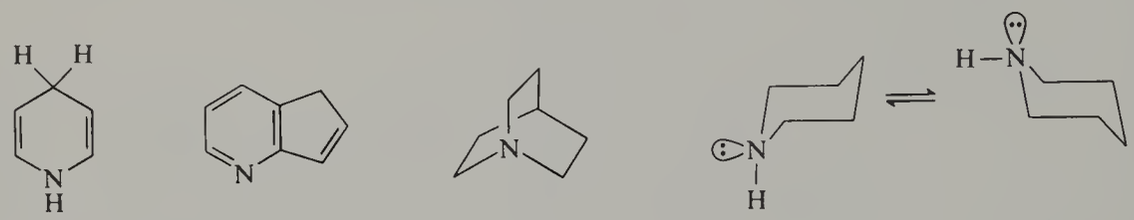


(**7**) R = alkyl (**8**) (**9**) (**10**)

Of relevance within this section are structures containing fused benzo substituents, such as quinoline (**11**), isoquinoline (**12**), acridine (**13**) and phenanthridine (**14**), but not those structures containing nitrogen at a bridgehead, which are in a separate section (2.10). Structures of bipyridyl form, for example (**15**), will also be considered, as will reduced derivatives of pyridine such as dihydropyridines, for example 1,4-dihydropyridine (**16**), as well as 1-pyrindine (**17**), and quinuclidine (**18**) and its derivatives. The saturated analogue of pyridine, piperidine (**19**)⇌(**20**), gives rise to interesting structural chemistry, with the possibility of conformational equilibria involving not only axial or equatorial substituents as in the homocyclic cases, but also the question of axial or equatorial lone pair disposition.



(**11**) (**12**) (**13**) (**14**) (**15**)



(**16**) (**17**) (**18**) (**19**) (**20**)

Undoubtedly, the two main areas of interest and controversy in this general area are (i) tautomerism, particularly in the vinylogous amides 2- and 4-pyridinone and related compounds, and (ii) the question of conformation in piperidine structures.

Is it possible to account theoretically for the structural phenomena observed? A wide range of molecular orbital (MO) methods of varying degrees of complexity can be used to calculate molecular dimensions and energy levels, in particular for pyridine type molecules. A number of general accounts are available ⟨B-61MI20400, B-68MI20400, B-69MI20400, B-70MI20400, 70ACR217, 75MI20401, B-78MI20401⟩ and a rather good summary is also available ⟨78MI20408⟩. Table 2 is based on this summary, and gives a brief description of each method in increasing degrees of sophistication.

Such methods, particularly if taken beyond the simple Hückel linear combination of atomic orbitals (LCAO) approach, but even at the ω-technique level, can give accurate estimates of bond orders and thus bond lengths, energy levels, electronic distribution and dipole moments. Such calculations may be checked against experimental data, and therefore, rather than giving a separate section to theoretical methods, these are discussed within the experimental section to which they refer. This is made more pertinent by the fact that very frequently the relevant calculations are made by the authors of the experimental work, in the same paper or series of papers, and also because the results of such calculations, apparently independent of experimental evidence, do seem to change as the thrust and emphasis of experiment is modified. It will be seen in particular that the experimental results in photoelectron spectroscopy have a direct relevance to electronic energy levels calculated by MO methods (Section 2.04.3.6): here a particularly instructive summary of MO calculations of varying complexity on pyridine *N*-oxide has been presented ⟨81JPR571⟩, allowing comparison of one with another and with experimental MO energy levels from photoelectron spectroscopy.

Table 2 Hierarchy of MO Methods[a]

(i) Treating π-electrons only

Hückel (electrons treated independently)

↓

ω-Technique, degree of electron correlation (self-consistent field SCF)

↓

Pople–Pariser–Parr PPP (CNDO) method. MO's from LCAO SCF, *i.e.* electron correlation taken into account. Equations to derive the LCAO coefficients by the variational procedure were proposed by Roothaan

(ii) Treating all valence electrons

Extended Hückel (fails to allow for the dependence of the electron attracting power of an atomic orbital on the electron on the same and surrounding atoms)

↓

Complete neglect of differential overlap, treats only valence electrons explicitly CNDO → CNDO/1 → CNDO/2

↓

Intermediate neglect of differential overlap INDO
(allowance for contribution of one-centre exchange integrals)

↓

Modified INDO → MINDO/1 → MINDO/2 → MINDO/3

↓

Partial neglect of differential overlap PNDO

↓

Neglect of diatomic differential overlap NDDO → NDDO/2

↓

Modified NDDO → MNDDO/1

↓

Ab initio calculations using direct evaluation of Roothaan equations. Financially restrictive, and thus little used for comparatively complex heterocyclic molecules

[a] Modified with permission from ⟨78MI20408⟩.

2.04.2 MOLECULAR DIMENSIONS

2.04.2.1 Microwave Spectroscopy

This form of spectroscopy, of which an earlier general account for heterocyclic molecules has been given by Sheridan ⟨74PMH(6)53⟩, is concerned with the study of rotating molecules. If such molecules have a permanent dipole, rotational transitions lead to emission or absorption of electromagnetic radiation. The spectra thus produced provide a very versatile method for determining overall molecular dimensions and dipole moments of molecules in the vapour phase. As only very low pressures are required ($\sim 10^{-2}$ Torr), and elevated temperatures may be used, a large proportion of compounds of moderate complexity are sufficiently volatile to be examined in this way. Generally only simple molecules have been measured, in contrast to the technique of X-ray diffraction, discussed next (Section 2.04.2.2), as in this latter technique crystalline samples are required. Microwave spectroscopy thus yields the molecular dimensions of, for example, pyridine itself free from intermolecular interactions, and for this reason is discussed first. Studies are usually carried out at room temperature or frequently much lower. The measurements give the three molecular moments of inertia, I_A, I_B and I_C, the rotational components obtained by resolution of the rotation perpendicularly through the centre of gravity. From these data certain conclusions may be drawn, *e.g.* if one of the moments is the sum of the other two, $I_A + I_B = I_C$, the molecule is planar. If, for a molecule which is planar at equilibrium, $(I_A + I_B)$ is slightly greater than the effective I_C, the difference is called the inertial defect. When vibrations cause a rotating body to change its size and shape, the speed of rotation will in consequence alter. This alteration in speed is said to be due to Coriolis forces. Different vibrations may thus be coupled together by virtue of these forces, for example, the NH axial conformer of piperidine has two vibrations at 240 cm^{-1} which differ by only 0.15 cm^{-1} and show strong Coriolis interaction ⟨74PMH(6)53, 68CC668⟩.

To obtain molecular dimensions the moments of inertia of isotopic species must be determined. These (most conveniently) are sufficient in their natural abundance. Of particular importance here is ^{13}C, but other atoms such as ^{2}H, ^{18}O and ^{15}N require isotopic enrichment. Application of Kraitchman's equations ⟨53MI20400⟩ then yields atomic coordinates to a few thousandths of an ångstrom and bond angles to an accuracy of better than

±0.2°, although if atoms are near to rotational axes they may not be accurately located. In a further valuable experimental innovation, Stiefvater has shown that double resonance modulated (DRM) spectroscopy ⟨75ZN(A)1742, 75ZN(A)1756⟩ leads to much easier analysis of spectra and also enables observation of rare isotopic species in their natural abundance. However, it must be stressed that generally analyses are less than complete and involve assumptions. For example, pyridine derivatives may be assumed to have ring dimensions the same as in pyridine itself.

Measurement of the Stark effect, *i.e.* the influence of an applied electrostatic field on the molecular transitions, permits the calculation of the magnitude and direction of the dipole moment. Dipole moments measured in this way are gathered together in Table 3. Observation of line splitting for molecules containing nuclei of spin quantum number greater than $\frac{1}{2}$, ^{14}N being of particular importance here, leads to values for nuclear quadrupole coupling constants, from which the electronic environments of the constituent atomic nuclei may be determined employing the Townes and Dailey theory ⟨49JCP(17)782, 55JCP(23)118, 74PMH(6)53⟩. Finally, the influence of applied magnetic fields on the rotational fine structure, the Zeeman effect, gives further precise information on electronic distribution and magnetic susceptibility anisotropies ($\Delta\chi$) which may be used as a criterion of 'aromatic character' ⟨74AHC(17)255⟩ (but tempered with the usual amount of criticism and doubt accorded to all criteria of this nebulous quantity!).

Table 3 Dipole Moments from Microwave Spectra[a]

Compound	*Dipole moment* (D)	*Components*	*Dipole moment* (D) (*calc.*)	*Ref.*
Pyridine	2.22	—	2.24 (CNDO MO)	74JST(20)119 75ZC401
3-Fluoropyridine	2.09	$\mu_a = 0.39$ $\mu_b = 2.05$	2.15 (INDO MO) —	76JSP(59)216
2,6-Difluoropyridine	3.17	—	—	76MI20403
	3.82	—	—	76ZN(A)53
Pyridine *N*-oxide	4.13	—	3.80–6.9 (various MO methods)	70MI20401
2-Fluoropyridine	3.33	$\mu_a = 2.78$ $\mu_b = 1.84$	3.22, $\mu_a = 2.65$ $\mu_b = -1.83$ (INDO MO)	71ZN(A)1342
Pentafluoropyridine	0.98	—	0.62 (INDO MO) 0.77 (CNDO MO)	74MI20402
4-Chloropyridine	0.76	—	—	76MI20401
2-Cyanopyridine	5.78	$\mu_a = 5.47$ $\mu_b = 1.87$	— —	75JSP(58)178
3-Cyanopyridine	3.66	$\mu_a = 3.13$ $\mu_b = 1.90$	— —	—
4-Cyanopyridine	1.96	—	—	—
2-Methylpyridine	—	$\mu_a = 0.72$ $\mu_b = 1.71$	—	70ZN(A)25
4-Methylpyridine	2.70	—	—	67ZN(A)1738
2-Formylpyridine	3.56	$\mu_a = 3.48$ $\mu_b = 0.76$	— —	75BCJ2009
3-Formylpyridine	1.44	$\mu_a = 1.35$ $\mu_b = 0.5$	— —	77MI20401
4-Formylpyridine	1.66	$\mu_a = 0.37$ $\mu_b = 1.62$	— —	80JSP(82)176
2-Aminopyridine	0.88[b]	$\mu_a = 0.17$ $\mu_b = 0.86$	0.98 (SCF MO[d]) —	72JSP(42)320 70SA(A)307
	0.96[c]	$\mu_a = 0.07$ $\mu_b = 0.96$	— —	—

[a] For other collections of dipole moments of pyridine derivatives, usually derived from dielectric constants in benzene or dioxane, see ⟨57JCS1769, 59BSF1947, 61BSF492, 63PMH(1)189, 66JCS(B)420, 67BSF4707, B-67MI20400, 67JCS(B)1096, 67JCS(B)1100⟩.

[b] For O^+ vibrational state.

[c] For O^- vibrational state.

[d] ⟨70SA(A)307⟩ gives a summary of MO calculations applied to mono- and di-aminopyridines.

Determinations in this area seem mainly confined to the simple aromatic molecules, pyridines and substituted derivatives, particularly the halogenopyridines. Figure 1 shows the results of determinations for pyridine ⟨74JST(20)119, 77JST(42)1⟩. Features to note are the

shortened C—N bond compared with those in benzene (1.397 Å), exemplifying the electron withdrawing effect of N, although the other C—C and C—H bond lengths are all closely similar to those in benzene (C—H benzene 1.084 Å). This possibly exemplifies the very short range of the pure inductive effect. The shortening of the C—N bond is associated with a closing of the bond angle from the 120° of benzene, with an accompanying increase in the angle at C-2. The dipole moment was calculated to be 2.215 ± 0.01 D from the Stark components of the ^{15}N pyridine transitions. The magnetic susceptibility anisotropy of pyridine is -57.4×10^{-13} J G^{-2} mol^{-1} ⟨70JCP(52)5636⟩ which is taken to mean that it has high aromatic character, the corresponding value for benzene being -59.7×10^{-13} J G^{-2} mol^{-1}.

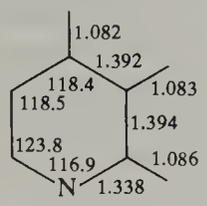
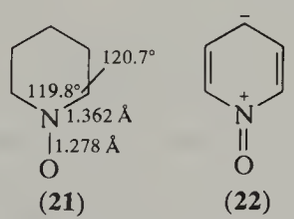


Figure 1 Molecular geometry of pyridine from microwave spectroscopy. (In Figures 1–12 all bond lengths are in ångstroms. Double bonds and designation of H and C are omitted for clarity)

It is of interest to compare the dimensions of the pyridine *N*-oxide molecule (**21**) with those of pyridine, the former also calculated from microwave data ⟨75JST(27)205⟩. The main differences come in the CNC portion of the ring, the molecule being planar overall ⟨70MI20401⟩. In fact, perhaps surprisingly, the structure is less distorted from benzene than pyridine itself; in particular, bond angles are nearer to 120°, and the C—N bond length is greater than in pyridine. This possibly points to back donation by the negative oxygen system so that canonical forms such as (**22**) become important contributors to the resonance hybrid. This conclusion is confirmed by estimates of the N—O bond length, which reveal it to be shorter than for simple *N*-oxides such as trimethylamine oxide ⟨70MI20401⟩. This leads in turn to a 'fattening' or 'dilation' of the pyridine *N*-oxide ring, which experimentally results in a smaller rotational constant *A* (589 974 GHz) than found for pyridine (603 913 GHz). Halogeno substituents on carbon also produce this effect as we shall see later. The conclusions are confirmed by electron diffraction (see Section 2.04.2.4).



Many halogenopyridines have been carefully examined by the microwave technique, most particularly the fluoropyridines. From these the complete analysis of 2,6-difluoropyridine by Stiefvater using the DRM technique ⟨75ZN(A)1765, 76ZN(A)53⟩ must be singled out, as this provided the first quantitative data for the geometry of a *C*-substituted pyridine ring, previous assignments involving the assumption that the ring structure was the same as in pyridine. Figure 2 shows the results of this study. The fluorine atoms have the effect expected from that observed in going from benzene to fluorobenzene ⟨68JST(2)209⟩, where the two C—C bonds nearest to F show a decrease in length while the rest of the molecule is little perturbed. It is postulated, in the case of 2,6-difluoropyridine ⟨76ZN(A)53⟩, that this arises from an increase in π-electron density in the C—N and C—C bonds adjacent to F, this outweighing by a factor of two the withdrawal of σ-electrons from the carbon atoms carrying the substituents. We should note, however, that this explanation contrasts with that given for the similar bond shortening found for the pair benzene/fluorobenzene

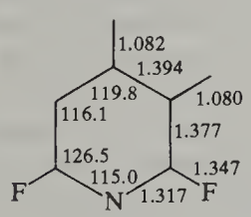
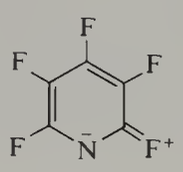


Figure 2 Molecular geometry of 2,6-difluoropyridine by microwave spectroscopy

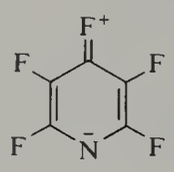
⟨68JST(2)209⟩. The C—F bond length in 2,6-difluoropyridine may be compared with that in fluorobenzene (1.354 Å) and in vinyl fluoride (1.347 Å). The dipole moment was found to be 3.82 D ⟨76ZN(A)53⟩. This may be broken down into a component of 1.35 D in the direction of each C—F bond, a π-electron moment of 2.40 D, and a σ-electron moment assumed to be the same as in pyridine, 0.86 D.

These definitive studies complement and corroborate earlier studies on fluoropyridines. These include evaluation ⟨71ZN(A)1644⟩ of the magnetic susceptibility anisotropy of 2-fluoropyridine as $-52.1\times10^{-13}\,\mathrm{J\,G^{-2}\,mol^{-1}}$ and of its dipole moment as 3.33 D ⟨71ZN(A)1342⟩, while the dipole moment of 3-fluoropyridine is given as 2.09 D ⟨76JSP(59)216⟩, assuming pyridine geometry and a C—F bond length of 1.354 Å. Such studies also indicate a 'fattening' of the pyridine ring, but overall electron withdrawal from both the π- and σ-orbitals of the pyridine nucleus and also a reduction in excess electronic charge at N, although one might have expected a 3-substituent to leave the π-system predominantly unaffected. The ring distortions resulting in these 'dilations' of the pyridine ring by successive fluoro substitution, as revealed by microwave spectroscopy, have been summarized ⟨76MI20400⟩.

Measurements have been made on the molecule pentafluoropyridine ⟨74MI20402⟩. The dipole moment is 0.98 D, half that of pyridine, which the authors conclude is made up of 2.08 D for μ_π and 1.10 D for μ_σ, the latter opposing the former, and the total moment having its negative end on the nitrogen atom. If C—F distances at 1.35 Å are assumed from the value in fluorobenzene, the pyridine ring must be severely contracted compared with unsubstituted pyridine, but other analyses fit the experimental data, for example with less ring-shrinkage and shorter C—F lengths. The Townes and Dailey theory indicates considerable increase in π-electron density of the nitrogen atom in going through the series pyridine, 2-fluoropyridine, pentafluoropyridine, resulting from structures of the form (**23**) and (**24**).



(**23**)



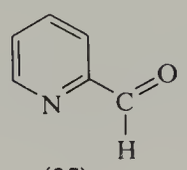
(**24**)

Some work is also available on other halogenopyridines, although as yet incomplete analyses are available. Studies on these compounds ⟨72MI20401, 74MI20403, 72ZN(A)1011, 74JSP(52)244, 75JSP(57)377, 75JST(29)33, 76MI20401⟩ show, from the nuclear quadrupole coupling constants, and assuming undistorted pyridine ring dimensions, the degree of double bond character in the carbon–halogen bond. In all cases these appear to be greater than the corresponding figure for the halogenobenzene. Thus for chlorobenzene the double bond character is 3.26%, for 2-, 3- and 4-chloropyridine the values are 5%, 3.5% and 5% respectively. For bromobenzene a value of 2.24% is to be compared with 4.77% and 3.58% for 2- and 4-bromopyridine respectively; for iodobenzene, 1.75% compared with 4.5% and 2.3% for the 2- and 4-iodopyridines ⟨76MI20401⟩. In all cases however, the values decrease for a given halogeno compound as we descend the series Cl, Br, I. These lead to values for the lengths of the carbon–halogen bonds which also involve the assumption of a basic undistorted pyridine ring. These are 2-Cl, 1.72 Å ⟨72ZN(A)1011, 74JSP(52)244⟩, and 3-Cl, 1.71 Å ⟨75JSP(57)377⟩, to be compared with 1.72 Å in chlorobenzene and 1.726 Å in vinyl chloride. For the bromo and iodo compounds the bond lengths indicated are 2-Br, 1.88 Å; 4-Br, 1.87 Å ⟨72MI20401⟩; 2-I, 2.08 Å; 4-I, 2.09 Å ⟨74MI20403⟩.

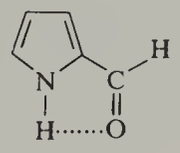
The fairly drastic assumption that the pyridine ring remains undistorted in substituted pyridines has been examined critically in a series of halogen- and cyano-substituted pyridine rings ⟨76MI20400⟩ by making the alternative assumption that here the C—X bond lengths are constant for a given X. This suggests that for all the cyano compounds and for the 3- and 4-halogenopyridines a 'dilation' or 'fattening' of the pyridine ring occurs, as noted previously for pyridine *N*-oxide ⟨70MI20401⟩ and fluoropyridines ⟨76MI20402⟩. Such studies serve to stress the assumptions that are very frequently made in deriving molecular dimensions from microwave data; only very rarely are full investigations done on all the isotopic species necessary for complete dissection into all constituent bond lengths and angles.

The conclusions arrived at for the halogenopyridines are paralleled by those for the cyanopyridines, which is unsurprising as CN is often regarded as a 'pseudohalogen'. Dipole moments ⟨75JSP(58)178⟩ obtained are recorded in Table 3. The cyanide substitution in the pyridine ring appears to produce distortions of the benzene ring analogous to those in cyanobenzene.

Studies with a further electron withdrawing group, formyl, substituted in a pyridine ring have also been carried out. In these cases, the question of the angle of twist arises, and also, in the 2- and 3-derivatives, the disposition of the carbonyl group relative to the N atom of the pyridine ring. In 2-formylpyridine the conformation is planar with C=O *trans* to the C(2)—N bond (**25**), resulting in a dipole moment of 3.56 D ⟨75BCJ2009⟩. This contrasts with, for example, 2-formylpyrrole where the *cis* form can be stabilized by hydrogen bonding (**26**).



(**25**)



(**26**)

3-Formylpyridine also exists in the vapour phase in the *trans* planar form, giving rise to a dipole moment of 1.44 D ⟨77MI20401⟩. These conformational preferences of 2- and 3-formylpyridine have been substantiated by *ab initio* MO calculations ⟨77JCS(P2)1601⟩. The energy difference for the 2-isomer is 10.2 kJ mol^{-1}, much larger than for the 3-isomer, 1.5 kJ mol^{-1}, although the energy barriers are reversed, 18.7 kJ mol^{-1} and 25.1 kJ mol^{-1} respectively. The 4-isomer is also in a planar form ⟨80JSP(82)176⟩, as is 4-vinylpyridine ⟨76JA6897⟩, with a dipole moment of 1.66 D. Here MO calculations ⟨77JCS(P2)1601⟩ predict an energy barrier of 25.3 kJ mol^{-1} for twisting of the formyl group.

In the area of electron donating groups attached to pyridine, 2-, 3- and 4-aminopyridine have been examined, in four isotopic forms, NH_2, NHD (two species observed) and ND_2. Here again conformation is of interest. For 2-aminopyridine it is found ⟨72JSP(42)320⟩ that one amino hydrogen is closer to the ring plane by 0.08 Å than the other, while the NH_2 group appears to be twisted through an angle of 32° so that the hydrogen nearer to the ring nitrogen lies closer to the plane. 2-Aminopyridine thus has a more planar NH_2 group than is the case for aniline, which has a corresponding angle of 37° ⟨66CC152, 74JST(23)253⟩. One might expect this from the increased conjugation between NH_2 and the electron withdrawing pyridine ring. For 3-aminopyridine the conformation is similar, with an amino hydrogen closer to the ring nitrogen and less out of the plane than the other. The 2- and 4-amino isomers also have similar amino configurations with flattening of the C—N$\begin{matrix}\diagup\,\mathrm{H}\\ \diagdown\,\mathrm{H}\end{matrix}$ pyramid, unlike the 3-isomer whose amino configuration resembles that of aniline ⟨75JCS(F2)438⟩. The computed (*ab initio* SCF MO calculation) barrier heights to inversion of 7.6, 8.8, 8.8 and 11.4 kJ mol^{-1} for the 4-, 3- and 2-isomers and aniline respectively are higher than the observed values, but in the correct order. The π-charge donated to the ring by the amino group is calculated to be greater for 4- and 2-aminopyridine than for 3-aminopyridine and aniline, however, while the σ-charge subtracted appears to show that the pyridine ring is most electronegative at the 3-position. This has been justified by considering further *ab initio* calculations in which the MO's are made up from linear combinations of the pyridine and amino fragments of the molecules ⟨75JCS(F2)438⟩.

Several significant studies have been made in the realm of saturated heterocycles. The microwave spectrum of quinuclidine has been measured to derive skeletal torsion values which arise from the molecule's vain attempt to escape from the boat conformation of the piperidine rings into which it is inevitably constrained ⟨72JSP(42)127⟩, and it has been shown that the earlier assignments made by Johnson ⟨60JCP(33)949⟩ should be completely reversed. The molecule thus twists through an angle of ±12° and in fact there is a small barrier of ~0.2 kJ mol^{-1} where this angle is 0°, even though this is the average conformation in the torsional vibration.

Microwave techniques give information on other saturated heterocycles. Piperidine has been shown ⟨68CC668⟩ to be 60% N—H equatorial at 25 °C in the vapour phase, this isomer being more stable than the axial conformer by 1.0 (±0.6) kJ mol^{-1} (see Section 2.04.5.1). A low resolution study on 2,6-difluoropiperidine ⟨77T1707⟩, which permits particularly simple

use of Kraitchman's equations, indicates that the molecule exists in the N—H equatorial form in the vapour phase giving a lower limit to the conformational free energy at 25 °C of 3.7 kJ mol^{-1}. This result is confirmed by high resolution measurements, and is discussed in relation to molecular mechanics calculations, with which it is not out of line.

2.04.2.2 X-Ray Diffraction

This technique is applied to crystalline structures, and as such is not suitable for pyridine itself or many simple pyridine derivatives. They can only be examined in the form of salts or complexes. The structures will thus show features due to the presence of complexing agents, as well as to the influence of forces arising from the solid phase measurements. This complicates the interpretation of the vast wealth of information that is available, although at the same time revealing detailed features of crystal geometry and packing. Thus, although both this technique and microwave spectroscopy furnish data on molecular dimensions, the limitation of the latter to simple molecules at low pressure in the gas phase means that direct comparison between results obtained by the two methods is impossible. Wheatley ⟨72PMH(5)174⟩ has summarized the data available for pyridine derivatives available at that time. He points out that in such measurements, the introduction of techniques for phase determination means there is no longer any need for the presence of a 'heavy atom' in the molecule. Hydrogen atom scattering is, however, usually insufficient to allow location of such atoms, although it can be done with very refined techniques.

It is unwise to trust any bond length determined by X-ray diffraction to better than ±0.01 Å, and sometimes errors are much greater. A very detached and realistic discussion of error limits has been given previously ⟨72PMH(5)174⟩.

Scrutiny of *Chemical Abstracts* reveals literally hundreds of structures containing pyridine or its derivatives analyzed by X-ray crystallography, and by far the greater majority are involved in complexes with metallic ions, from which the important piece of information to be gained is the geometry of coordination of the metallic ion.

Below are given two recent typical results on metallic complexes of pyridine derivatives. Figure 3 shows the structure of the dimer di-μ-bromobis[bromo(pyridine)copper(II)] ⟨80IC2321⟩. The X-ray pattern reveals a square planar copper bromide complex, with the dimer molecules stacked above each other, forming linear chains. The pyridine ring is not coplanar with the Cu_2Br_4 plane, but twisted at an angle of 54° to ensure efficient packing. Although the twisting of the pyridine rings in the rigid crystalline system could lead to differences of bond lengths in otherwise equivalent bonds, the differences reported almost certainly contain a contribution due to the inherent errors in X-ray crystallographic determinations, and similar errors arise in related structures ⟨72PMH(5)174⟩. To within this measure of inaccuracy, all that can be said is that bond lengths are similar to those in uncomplexed pyridine in the vapour phase (Section 2.04.2.1).

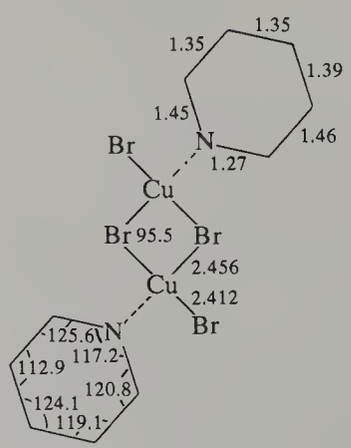


Figure 3 Dimensions of di-μ-bromobis[bromo(pyridine)copper(II)] by X-ray crystallography

The second structure is that of *cis*-[dichloro(η-ethylene)(2,6-dimethylpiperidine)platinum(II)] ⟨80MI20406⟩ given in Figure 4. *trans*-[$PtCl_2$(η-ethylene)(substituted pyridines)] had previously been studied ⟨78MI20403, 79MI20401⟩ and showed shortening and thus strengthening of the Pt—N bond possibly due to stabilizing interaction between the

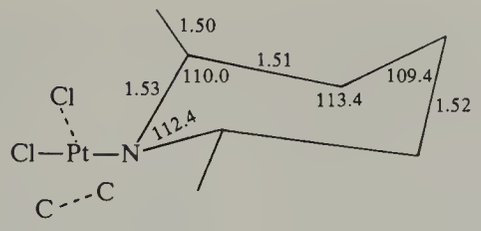


Figure 4 Dimensions of *cis*-[dichloro(η-ethylene)(2,6-dimethylpiperidine)platinum(II)]

metal orbitals and the antibonding MO's of the heteroaromatic system. The compound shown in Figure 4, with the piperidine ligand *cis* to η-coordinated ethylene, had arisen in an effort to prepare the *trans* compound to check on this proposal. The platinum is square planar coordinated, and the two methyl groups and the Pt atom are bonded to the piperidine ring in the equatorial position. The dimensions of the piperidine ring are, within experimental error, those of piperidine hydrochloride ⟨60AX72⟩ given in Figure 5, and those of 4-ethoxycarbonyl-1-methyl-4-phenylpiperidine ⟨61G754⟩ in Figure 6. Comparison of the data in Figures 4, 5 and 6 shows little indication of any influence of substitution at nitrogen or

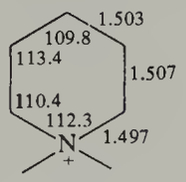


Figure 5 Dimensions of piperidine hydrochloride

carbon on bond lengths or angles, within the accuracy limits of such experiments. Figure 6 provides dimensional data for other linkages, particularly for C_6H_5 substituted at C(4) of the piperidine ring, which provides a comparison with the bond lengths in heteroaromatic species discussed here. The crystallographic structure of pyridinium hydrochloride has been determined ⟨62AX427⟩ and its dimensions are given in Figure 7. Again there is no great difference between these dimensions and those of uncomplexed pyridine in the vapour phase (Section 2.04.4.1), the shortening of the N—C bond due to the electronegativity of nitrogen being the distinctive feature in both cases, and to about the same extent (1.32 Å in solid pyridine hydrochloride compared with 1.34 Å in pyridine vapour), despite the protonation of N in the former case. The ring angle at $\overset{+}{N}H$ of 128° does however seem rather large, a value of about 120° appearing more normal for positively charged nitrogen.

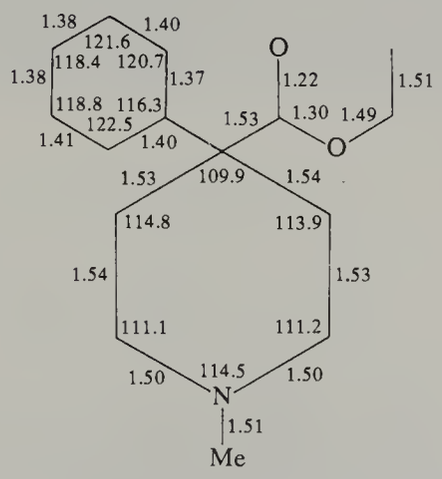


Figure 6 Dimensions of 4-ethoxycarbonyl-1-methyl-4-phenylpiperidine

The dimensions for pyridinium nitrate ⟨65JPC1915⟩ are therefore also included for comparison (Figure 7). The ternary charge transfer salt pyridinium-1-naphthylamine picrate, Kofler's complex, recently measured ⟨80AX(B)1170⟩, similarly shows pyridinium dimensions which agree with those found for pyridine from microwave spectroscopy, and these dimensions also agree with those for the pyridine ring in 2,2′-bipyridinium ⟨81AX(B)1306⟩ and complexed 2,2′-bipyridine ⟨81AX(B)1409⟩.

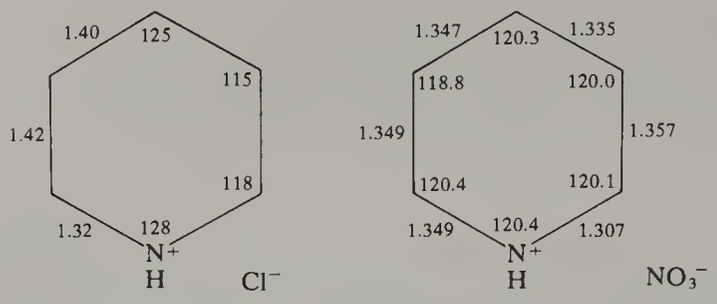


Figure 7 Dimensions of pyridinium hydrochloride and nitrate

Quinoline has also been measured in the form of a complex, $Ni(S_2PEt_2)(C_9H_7N)$ ⟨70JA3964⟩. The dimensions are shown in Figure 8. The angles show little distortion from 120°, but there is a significant degree of bond length alternation in both rings, that in the homocyclic ring matching that of naphthalene fairly closely ⟨57AX504⟩. In other complexes of quinoline, X-ray crystal determinations ⟨71AX(B)373, 73IC2939, 71BCJ1⟩ reveal significant deviations from these dimensions, particularly for the quinolinium ion $C_9H_7NH^+$. Indeed, in these latter measurements, for quinolinium 2-dicyanomethylene-1,1,3,3-tetracyanopropanediide, $2(C_9HN_8)^+(C_{10}H_6)^{2-}$, the heterocyclic ring appears distorted from planarity. Such small deviations from planarity are well revealed by these determinations. 3,5-Dinitropyridine, for example, can be shown to have one nitro group coplanar with the heterocyclic ring, but the other rotated out of plane by 7° ⟨74AX(B)2071⟩. Even in 1-isoquinolyl(phenyl)methanol, measurements reveal a small bending around the central bond, so that there is an angle of 0.7° between the pyridine and benzene ring ⟨81AX(B)768⟩.

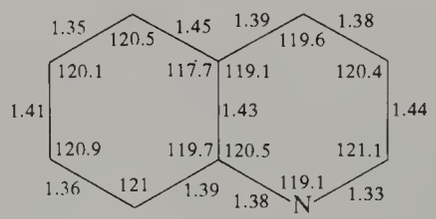


Figure 8 Dimensions of quinoline in the complex $Ni(S_2PEt_2)(C_9H_7N)$

The results of the first determination ⟨80AX(B)2076⟩ of the structure of 7,8-benzoquinoline in the form of a charge transfer complex with 7,7,8,8-tetracyanoquinodimethane is shown in Figure 9. The complex consists of mixed donor–acceptor stacks, with an interplanar distance of 3.43 Å, indicating the participants to be in the neutral ground state. Bond length alternation is again pronounced even for the homocyclic ring furthest removed from the heterocyclic ring, while a similar interesting variation in bond lengths has been discerned in 3-methylisoquinoline ⟨74CSC323⟩.

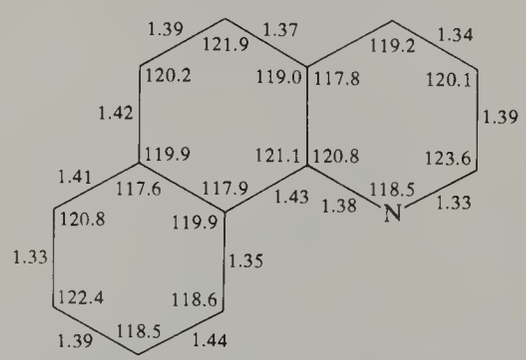
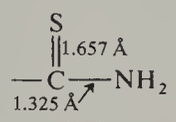


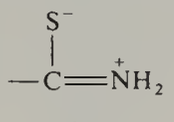
Figure 9 Dimensions of 7,8-benzoquinoline in the complex $C_{12}H_4N_4 \cdot C_{13}H_9N$

Pyridine trihydrate has recently been examined ⟨80AG(E)552⟩ and exists as an unusually hydrogen bonded structure in which five separate hydrogen bonds link the water structure in two dimensions, with the formation of four-, five- and six-membered rings in the ratio 1:2:1 respectively, and the sixth binds, alternately from either side of the layer, the N atom of a pyridine molecule. The pyridine molecules are thus enclosed between successive water layers 8.9 Å apart.

Clearly, hydrogen bonding may be an important feature in deciding the crystal structure taken up by pyridine derivatives, and the form it takes can vary quite markedly with relatively small changes in structure. For example, each molecule of nicotinamide is linked by two weak hydrogen bonds, from the amide nitrogen atom to the oxygen of a neighbor, and to the ring nitrogen atom of another, to form two-dimensional networks ⟨54AX283⟩, the angle between the plane of the pyridine ring and of the amido group being 28°. In *N*-phenylnicotinamide the molecules are also connected by strong N—H···O amide hydrogen bonds, but the phenyl and pyridine rings are twisted out of the plane of the carbonyl group in opposite directions by 31.3° and 33.3° respectively ⟨79MI20407⟩. Very similar hydrogen bonding features and carboxamide twist angle are to be found in (*S*)-*N*-(α-methylbenzyl)nicotinamide, a chiral NADH analogue ⟨81AX(B)1637⟩. For 2-(*N*-methylcarboxamido)quinoline the molecule is again planar, stabilized not only by resonance, including conjugative interaction with the aromatic ring, but also by intramolecular hydrogen bonding ⟨80MI20402⟩. In 2-thioamidopyridine, however, internal resonance within the thioamido group, giving the bond lengths shown in (**27**) and suggesting a strong contribution from (**28**), means that there is little resonance interaction with the pyridine ring, which is thus at an angle of 10.5° to the side group ⟨72AX(B)283⟩. This work also includes a good summary of interatomic distances and bond angles previously determined for a variety of pyridine derivatives.

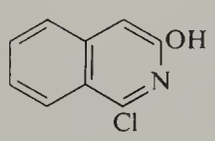


(**27**)

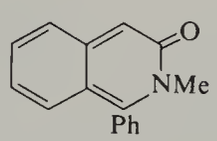


(**28**)

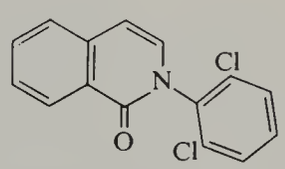
Hydrogen bonding will obviously figure prominently in potentially tautomeric structures. Among earlier work, the studies of Penfold ⟨53AX591⟩ on 2-pyridinone deserve mention. Here the atoms responsible for tautomerism are involved in an intermolecular N···O hydrogen bond which links the molecules into endless helices. On the other hand, 6-bromo-2-hydroxypyridine and 2-amino-5-chloropyridine, molecules in which the pyridine tautomer is favored (see Section 2.04.4 for discussion of hydroxy and amino tautomers), form cyclic dimers with OH···N (1.82 Å) and NH···N (2.05 Å) hydrogen bonds respectively ⟨76AX(B)220, 76AX(B)224⟩. Here the measurements on 2-amino-5-chloropyridine were carried out by neutron diffraction (see Section 2.04.2.3). Again in line with arguments presented in the tautomerism section (Section 2.04.4.2), X-ray crystallographic studies show the pyridinone form to be favored in the solid state when electron withdrawing groups are absent from the 2(6)-position of the pyridine ring: 3,5-dichloro-2,6-dimethylpyridin-4-one and 5-chloro-2-pyridin-2-one both have hydrogen located on the nitrogen atom ⟨72AX(B)3200, 72AX(B)3405⟩. The influence of an electronegative substituent is further demonstrated in structures (**29**), (**30**) and (**31**), where crystallographic dimensions clearly show ⟨74AX(B)1146⟩ that (**29**) exists as the lactim or hydroxyisoquinoline form, and (**30**) and (**31**) as the lactam, or isoquinolinone form.



(**29**)



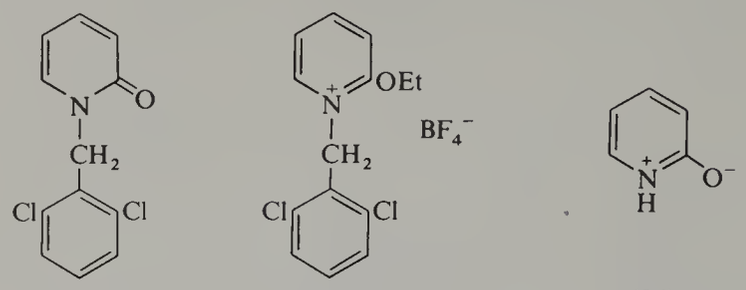
(**30**)



(**31**)

An important study in this area involved examination of compounds (**32**) and (**33**) ⟨74AX(B)680⟩. In neither compound is there any trace of interaction between the two rings, as shown by the high degree of twisting, the dihedral angles being 85° and 87° respectively. The crystallographic molecular dimensions shown are compared with other pyridine and pyridinone molecules in Table 4. The short–long–short pattern of C—C bond alternation shown by 5-chloropyridin-2-one, pyridin-2-one and (**32**) is taken to indicate a degree of π-localization in these molecules. This contrasts with the essentially equivalent C—C bond lengths found in the pyridinium ring of (**33**). A difference between N—C(2) and C(2)—O bond lengths may also be observed in (**32**) on one hand, and 5-chloropyridin-2-one and pyridin-2-one on the other. This may be taken to indicate the contribution of the resonance form (**34**) which contributes to the latter two and is stabilized in their hydrogen bonded dimers, a form which is not available to the *N*-alkylated structure (**32**). The authors

⟨74AX(B)680⟩ suggested therefore that the unassociated (**32**) exhibits bond lengths characteristic of pyridin-2-one in the gas phase and thus is the best model for MO calculations.



(**32**) (**33**) (**34**)

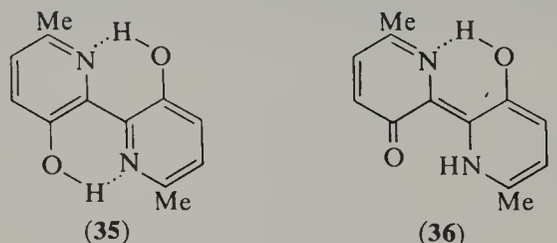
Table 4 Bond Lengths for (**30**) and (**31**) and Related Molecules of Pyridine or Pyridinone Form

Bond	*5-Chloro pyridin-2-one*[b]	*Pyridin-2-one*[a,c]	*Pyridin-2-one*[d]	*6-Chloro-2-hydroxy-pyridine*[e]	(**30**)	(**31**)	*Pyridin-2-one (calc.)*[f]
N—C(2)	1.37	1.37	1.40	1.34	1.40	1.36	1.41
C(2)—C(3)	1.43	1.41	1.44	1.39	1.46	1.41	1.46
C(3)—C(4)	1.34	1.35	1.33	1.38	1.35	1.38	1.35
C(4)—C(5)	1.41	1.39	1.42	1.38	1.39	1.39	1.46
C(5)—C(6)	1.34	1.35	1.37	1.36	1.34	1.38	1.35
C(6)—N	1.36	1.36	1.34	1.33	1.37	1.38	1.38
C(2)—O	1.25	1.26	1.24	1.32	1.22	1.32	1.26

[a] From pyridin-2-one-6-chloro-2-hydroxypyridine complex. [b] ⟨72AX(B)3405⟩. [c] ⟨71AX(B)1201⟩. [d] ⟨53AX591⟩. [e] ⟨69AK(30)71⟩. [f] ⟨70JA2929⟩.

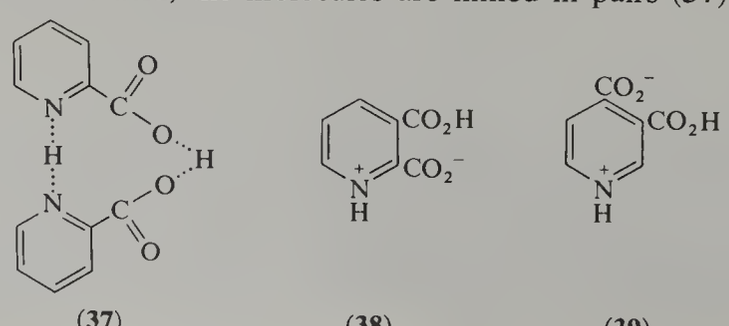
However, as we shall see in the tautomerism section (2.04.4.2), this conclusion must be tempered by the fact that in the gas phase the predominant tautomer is 2-hydroxypyridine. This also affects calculations of bond lengths in pyridin-2-one by Dewar ⟨70JA2929⟩ using a semiempirical SCF MO π-approximation given in the final column of Table 4. This will also be discussed again in the tautomerism section (2.04.4).

2,2′-Bis(6-methyl-3-hydroxypyridine) exists as discrete molecules in the crystalline form without intermolecular hydrogen bonding ⟨71JA5402⟩. There is, however, strong intramolecular hydrogen bonding (**35**) where the N···H length is 2.57 Å, while the C—C bridge length of 1.46 Å and C—O lengths of 1.35 Å, intermediate between typical single and double bond lengths, indicate an important contribution from canonical forms (**36**). This gives some explanation for the intense fluorescence of the molecule.



(**35**) (**36**)

The tautomeric form of pyridinecarboxylic acids, neutral, zwitterionic or intermediate between these two forms, in the crystalline state, is of interest, and extensive investigations exist ⟨73CL1121, 73BCJ2020, 73BCJ2292, 73BCJ2372, 73BCJ2669⟩. In the intermediate form, as exemplified by 2-picolinic acid, the molecules are linked in pairs (**37**) by two symmetric



(**37**) (**38**) (**39**)

double minimum hydrogen bonds with small potential barriers, the N···H···N length being 2.85 Å, and the O···H···O length 2.53 Å. The 2,6-dicarboxylic acid monohydrate exists in the neutral form, while the 3,5-isomer, dinicotinic acid, exists in the intermediate form, but here each molecule is joined by two kinds of hydrogen bond (O—H···O, 2.59 Å; O···H···N, 2.52 Å) to four surrounding molecules. Pyridine-2,3-dicarboxylic acid exists in the zwitterionic form (**38**), as does cinchomeronic acid, the 3,4-dicarboxylic isomer (**39**), the N—H bond distances being 0.89 Å and 1.09 Å respectively.

There is also a very strong intramolecular hydrogen bond in 2-methylpyridine *N*-oxide-6-carboxylic acid, the molecules being held together in the crystal by dipole–dipole forces ⟨75AX(B)2719⟩. 2-Hydroxymethylpyridine *N*-oxide, on the other hand, shows strong intermolecular hydrogen bonding ⟨71JHC617⟩, but intramolecular hydrogen bonding exists in 8-hydroxyquinoline *N*-oxide ⟨71AX(B)2443⟩. The C—N bond lengths of 1.35 and 1.40 Å may be compared to those of 1.33 and 1.37 Å respectively for other quinoline systems which do not have the dative bonded oxygen, the lengthening in the former case possibly due to the inductive effect of O^-.

Pyridine *N*-oxide itself has been studied ⟨71AX(B)432⟩. The crystal structure contains discrete molecules held together by van der Waals' forces and dipole–dipole interactions, and the unit cell contains two crystallographic independent units of dimensions given in Figure 10. These data clearly show how crystal packing forces can influence molecular dimensions, and indicate the pitfalls into which the inexperienced may stumble, if they attempt to ascribe bond or angle dimension variation between one compound and another as due entirely to intramolecular forces of inductive, resonance, or steric origin.

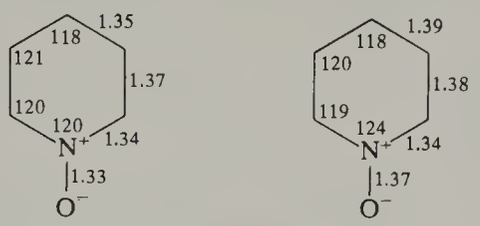


Figure 10 Dimensions of crystallographically independent molecules of pyridine *N*-oxide

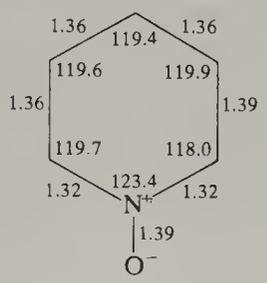


Figure 11 Dimensions of pyridine *N*-oxide in the complex $[Cu(C_5H_5NO)Cl_2{\cdot}H_2O]_2$

The dimensions derived from the dimeric complex dichloroaquo(pyridine *N*-oxide)copper(II) are given in Figure 11 ⟨80IC2519⟩. This result is in line with the suggestion that the dimensions of pyridine *N*-oxide itself are little changed on complexation ⟨71AX(B)432⟩. The dimensions recorded for pyridine *N*-oxide hydrochloride previously ⟨61AX914⟩ are also very similar *e.g.* the N—O bond length is 1.37 Å, to be compared to a length of 1.28 Å recorded

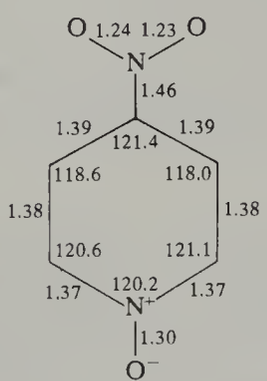
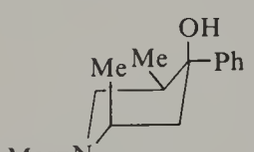


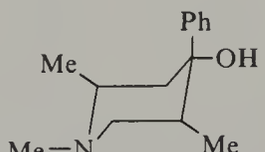
Figure 12 Dimensions of 4-nitropyridine *N*-oxide

by microwave spectra for the free molecule (Section 2.04.2.1). If, however, an electron-withdrawing group is substituted *para* to the *N*-oxide function this bond becomes shortened, due presumably to an increase in *p*-quinonoid character. This is shown in Figure 12 for 4-nitropyridine *N*-oxide, a planar molecule, measured at 30 K ⟨76AX(B)572⟩, following earlier studies ⟨56AX787⟩, and has also been observed for 4-cyanopyridine *N*-oxide ⟨74MI20404⟩.

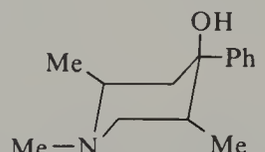
A very large number of studies involve designation of the preponderance of the chair conformation in the piperidine ring as we have seen in Figures 4, 5 and 6 (see Section 2.04.5.1 for discussion of conformation), and indicate which substituents are axial and which equatorial in the crystalline form. Torsion angles are generally in the range 53–60°, but these can be very much affected by substitution ⟨70RTC375, 74RTC164, 74JCS(P2)101, 74AX(B)240, 76AX(B)128, 76AX(B)132, 76AX(B)136, 81AX(B)712, 81AX(B)1771⟩. Such considerations are exemplified by studies on the highly substituted piperidine alcohols (±)α- (**40**), β- (**41**) and γ-promedol (**42**) ⟨71CC1102, 72AX(B)1791, 72AX(B)1796, 72AX(B)3484, 72AX(B)3489⟩. The propionate esters of these alcohols show analgesic activity, that from β-promedol being most active, and γ-promedol least, with (±)-α-promedol occupying an intermediate position. The studies reveal the molecular structures to be as shown, with each in a chair conformation, slightly distorted in structure (**40**) and skewed in chiral structure (**41**). This latter structure exists in both monoclinic and rhombohedral form in which the conformation is the same, but intramolecular hydrogen bonding is quite different. In the rhombohedral form molecules of alternating chirality are linked *via* O—H···N hydrogen bonds into hexameric rings, while in the monoclinic form the hydrogen bonding links molecules of the same chirality into infinite chains. The axial orientation of the phenyl ring in this β-isomer (**41**), which gives rise to the most active analgesic, parallels the conformation of the corresponding portions of morphine and codeine.



(40)

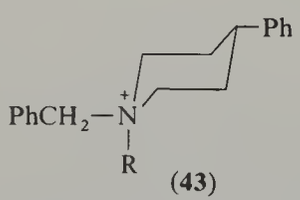


(41)

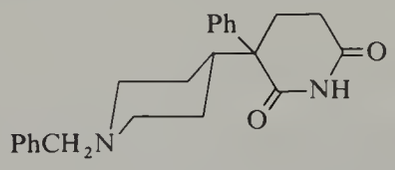


(42)

Disposition of substituents at nitrogen is also important; in compounds (**43**) where R = ethyl or isopropyl it has been shown ⟨72CC455, 73JCS(P2)1558⟩ that the phenyl group is equatorial and in a plane at angles of 52° and 79° respectively to the plane of the piperidinium ring, and that in both molecules the benzyl group occupies the equatorial position, a situation which has arisen from preferred equatorial attack of benzyl chloride on 1-ethyl- and 1-isopropyl-4-phenylpiperidine. In compound (**44**) the piperidine ring is in the normal chair conformation, but the piperidinedione ring is considerably flattened due to the two carbonyl groups ⟨73AX(B)369⟩.

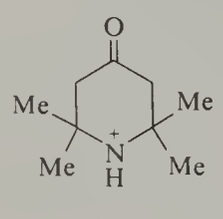


(43)

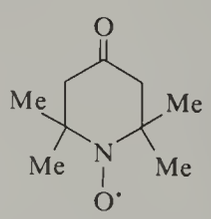


(44)

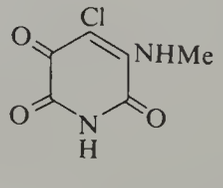
Distortion of the chair conformation by substitution occurs in 2,2,6,6-tetramethylpiperidin-4-one hydrochloride (**45**) ⟨71AX(B)932⟩, in which steric interaction between axial methyl groups leads to flattening of the ring. The resultant C(2)—C(6) intramolecular distance is 3.2 Å, to be contrasted with 2.4 Å in the non-methylated compound. A similar effect is to be found in other 2,2,6,6-tetramethyl derivatives ⟨81AX(B)1771⟩. In the related free radical nitroxide (**46**) the steric interactions are reduced by adoption of a 'symmetric twist' chair form ⟨74AX(B)790⟩. 4-Chloro-5-methylamino-2,3,6-pyridinetrione monohydrate



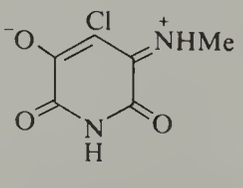
(45)



(46)



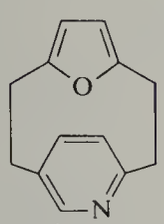
(47)



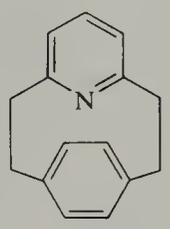
(48)

(**47**) is planar ⟨73AX(B)1971⟩, the importance of the polar canonical form (**48**) in the resonance hybrid being demonstrated by the short bond length between C and N (external) and the length of the carbonyl bond adjacent to the chloro substituent, which is the longest of the three.

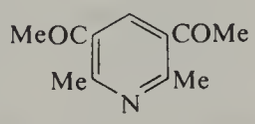
In contrast to the flattening or distortion of piperidine rings from the chair conformation, steric constraints may compel non-planarity in pyridine derivatives, as in the [2,2]cyclophane (**49**). The pyridine ring adopts a shallow boat conformation ⟨75JHC433⟩, with the substituted C atoms 0.17 Å out of the plane of the central four atoms, and the two rings inclined at 23°. In the cyclophane (**50**), however, the pyridine ring is planar, although the benzene ring suffers severe distortion, and the two rings are perpendicular to one another ⟨74JA1581⟩. Compound (**51**) is also distorted into a shallow boat form ⟨80CSC725⟩, with the methyl groups projecting outwards.



(**49**)

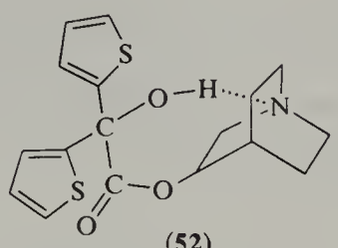


(**50**)

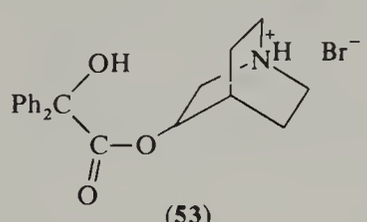


(**51**)

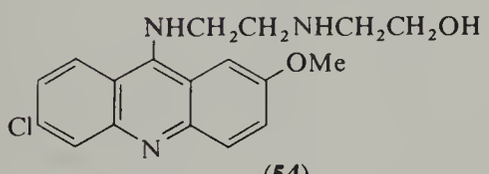
In the crystals of quinuclidinium and 4-haloquinuclidinium chlorides N—H···Cl types of hydrogen bonding are to be found, with a length of about 3 Å. The N—C bond, C—C terminal bond and N···C terminal distance are all shorter in the haloquinuclidinium cations than in quinuclidinium itself, indicating the polar effect of the halogen ⟨80MI20405⟩. An intermolecular hydrogen bond is present in quinuclidinyl di-α,α'-thienylglycolate (**52**) between the hydroxyl and the quinuclidine nitrogen atom ⟨70AX(B)341⟩, and, as above, the nitrogen atom in quinuclidinyl benzilate hydrobromide (**53**) hydrogen bonds to halogen anion $\overset{+}{N}H\cdots Br^-$ ⟨69AX(B)1119⟩. Such determinations relate the drug activity of these and related structures to theoretical considerations of stereochemical factors ⟨65JMC616⟩. The X-ray crystallographic measurements also give important structural details for the biologically active acridines (**54**) and (**55**) ⟨72AX(B)1, 72AX(B)590⟩. In both, the ring systems are buckled, by 7.4° and 10.7° respectively, and both have intramolecular hydrogen bonds between nitrogen atoms in the side chain, as well as being stabilized in the crystal conformation by intermolecular hydrogen bonds involving the terminal hydroxyl group and ring nitrogen atom.



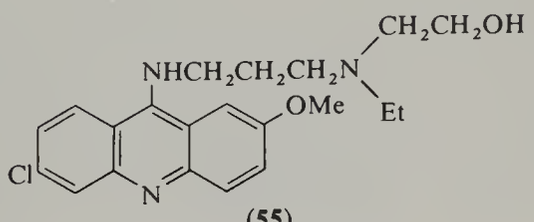
(**52**)



(**53**)



(**54**)



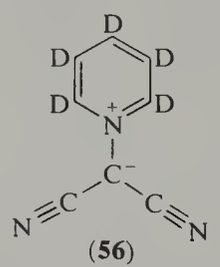
(**55**)

2.04.2.3 Neutron Diffraction

Neutrons travelling at *ca.* 3.9×10^3 m s^{-1} have a momentum of about 5.2×10^{-24} kg m s^{-1}, corresponding to a wavelength of 1 Å. Such a wavelength is about that for X-rays, and thus similar diffraction effects are observable. Both techniques are used for crystal structure elucidation, but ND is more accurate. X-rays are scattered only feebly by hydrogen atoms, whereas in ND such atoms are located with a standard deviation of ±0.002 Å, an accuracy as good as for carbon or nitrogen atoms. Thus, as we shall see, the technique is frequently

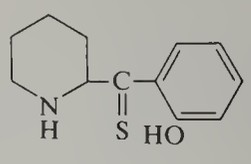
used for study of hydrogen bonding phenomena. At the same time, the technique is more involved (and therefore more expensive), and there are in consequence only a handful of relevant studies in our area of interest, compared with the large number using X-ray techniques.

Both the X-ray and ND patterns for 4-nitropyridine *N*-oxide at 30 K have been measured ⟨76AX(B)572, 76AX(B)1777, see Section 2.04.2.2⟩ and the results compared, the C—H distances being evaluated by the latter technique. These studies provide a nice comparison between the two methods. Agreement is good apart from the values for all the N—O bonds for which the X-rays lead to estimates *ca.* 0.007 Å shorter. ND of 2-amino-5-chloropyridine shows that the molecules are linked into dimers in the crystalline state by N—H···N amino–pyridine nitrogen bonds of length which can accurately be shown to be 3.058 Å between the two nitrogen atoms, 2.015 Å for N···H, and at an angle of 174° ⟨76AX(B)224⟩. In 4-aminopyridine perchlorate, almost linear hydrogen bridges $[NH_2\text{-}C_6H_4N\text{—}H\cdots NC_6H_4NH_2]^+$ are also present whose length can again be accurately found by ND ⟨80JCP(72)6117⟩, and whose influence is apparent in the N—H stretching and bending vibrations and their temperature variation in the IR spectrum. Temperature variation techniques in ND have been used to elaborate the nature of the hydrogen bonding in 2,3-pyridinedicarboxylic acid ⟨74JCP(60)3866, 79AX(B)2126⟩, previously discussed (Section 2.04.2.3). ND shows that perdeuterated pyridinium-1-dicyanomethylide (**56**) is non-planar, the cyanomethylide group being slightly twisted from the plane of the pyridine ring at 294 K by an angle of 3.94°. This increases to 5.12° at 118 K ⟨80AX(B)1807⟩. Indeed, this method is sufficiently accurate to register the very small bond length and angle changes which occur on this temperature change due to the changes in thermal motion.

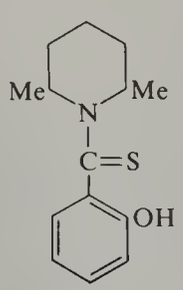


(**56**)

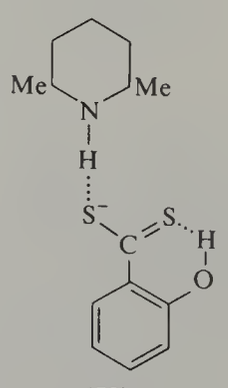
The geometry of the O—H···S bond in 1-(2-hydroxythiobenzoyl)piperidine (**57**) is also revealed by ND studies at 20 K ⟨81AX(B)1244⟩. X-ray crystallographic measurements at room temperature are also given, so the study provides another informative comparison between the two methods, albeit at very different temperatures. Moreover, the studies yield information which relates to general considerations of the structure of *N*,*N*-dialkylthiobenzamides and the effect of twisting about the amide C—N bond due to steric interactions. A previous report ⟨77CJC227⟩ also supposed to elucidate such interaction in (**58**) in which the piperidine ring would be twisted from the plane of the *o*-hydroxythiobenzoyl group, in fact pertained to salt (**59**) ⟨81AX(B)1679⟩.



(**57**)



(**58**)



(**59**)

2.04.2.4 Electron Diffraction

A good account of the methodology and instrumentation in this area has been provided previously ⟨71PMH(3)27⟩. Briefly we may note that diffraction of electrons of wavelength 0.1 Å by gases or vapors at very low pressure enables structural conclusions, including details of conformational equilibria, to be reached. Results obtained thus complement those from microwave spectroscopy. In an early study ⟨55ACS1306⟩, the average C—N and C—C

bond lengths for pyridine vapor were found to be 1.38 Å and for C—H the average length was 1.078 Å, dimensions which may be compared with those from microwave spectroscopy (Section 2.04.2.1, Figure 1). ED studies ⟨74JCP(61)1280⟩ also confirm the dimensions of pyridine *N*-oxide provided by microwave spectroscopy, and these more recent studies are given in detail for comparison in Table 5. 4,4′-Bipyridyl is shown to have about the same angle of twist (37°) as biphenyl (42°), while the 2,2′-isomer is very flexible with a much lower energy barrier than biphenyl ⟨58MI20400⟩.

Table 5 Comparison of Pyridine *N*-oxide Dimensions (Å, degrees)

Parameter	*Microwave*[a]	*ED*[b]	*Difference between ED and microwave*
N—O	1.278±0.01	1.290±0.015	0.012
N—C(2)	1.362±0.003	1.384±0.011	0.022
C(2)—C(3)	1.389±0.005	1.381±0.009	−0.008
C(3)—C(4)	1.395	1.393±0.008	−0.002
CNC	119.8±0.3	120.9±1.8	1.1
NCC	120.7±0.2	118.0	−2.7
C(2)C(3)C(4)	120.6	124.6	4.0
C(3)C(4)C(5)	117.6	114.1±2.5	−3.5
N···C(3)	2.392	2.371	−0.021
N···C(4)	2.795	2.821	0.026
C(2)···C(4)	2.418	2.454	0.036
C(2)···C(5)	2.749	2.745	−0.004
C(2)···C(6)	2.357	2.401	0.044
C(3)···C(5)	2.387	2.338	−0.049
O···C(2)	2.288	2.311	0.023
O···C(3)	3.557	3.551	−0.006

[a] ⟨75JST(27)205⟩. [b] ⟨74JCP(61)1280⟩.

The chair conformation of 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one at 120 °C has been confirmed by ED ⟨74ACS(A)671⟩. In the corresponding free radical at 125 °C the chair form is slightly flattened ⟨74ACS(A)675⟩, and is in the twisted boat form in the solid state (see Section 2.04.2.2). ED measurements on quinuclidine are also available ⟨80JST(65)297⟩.

2.04.3 MOLECULAR SPECTROSCOPY

2.04.3.1 Nuclear Magnetic Resonance

As in most areas of structural elucidation, NMR reigns supreme in importance for garnering structural evidence in pyridine and derivatives ⟨B-73NMR8⟩; so much so, that a good deal of discussion of it will be reserved until later when we confront the key areas of investigation, namely aromaticity and tautomerism in pyridines (Section 2.04.4) and stability and conformation (Section 2.04.5) in piperidine compounds. ^{1}H, ^{13}C, ^{14}N and ^{15}N magnetic resonance may all be examined. Fourier-transform instrumentation even enables the measurement of deuterium NMR at natural abundance. Figure 13 shows the resultant spectra for pyridine and quinoline ⟨77MI20405⟩, where separate resonances are found for each group of magnetically equivalent nuclei. The small ^{1}H–^{2}H couplings are unobservable even without ^{1}H decoupling, but they do contribute to line widths. Better resolution is obtained with proton noise decoupling.

We next give Tables 6, 7 and 8 to show representative values for various chemical shifts, couplings and solvent effects in ^{1}H and ^{13}C NMR spectra of pyridine and its *N*-oxide and protonated derivatives, in addition to those in the general section (Chapter 2.01), to show the general character of the results obtained and their susceptibility to variation of structure and media.

The proton–nitrogen couplings for (**60**) in Table 6 are very similar in magnitude to those for the same coupling pathway in (*Z*)-acetaldehyde ethylhydrazone (**61**), (*Z*)-acetaldoxime (**62**) and *N*-nitrosodimethylamine (**63**), and this resemblance is qualitatively maintained on protonation. Such couplings and their variation can be ascribed to the degree of *s* character in the N—C and C—C bonding orbitals. The large increase in $^{1}J(^{15}N, ^{13}C)$ on protonation accords with prediction, and the presence of the π-system appears to give significant C—N

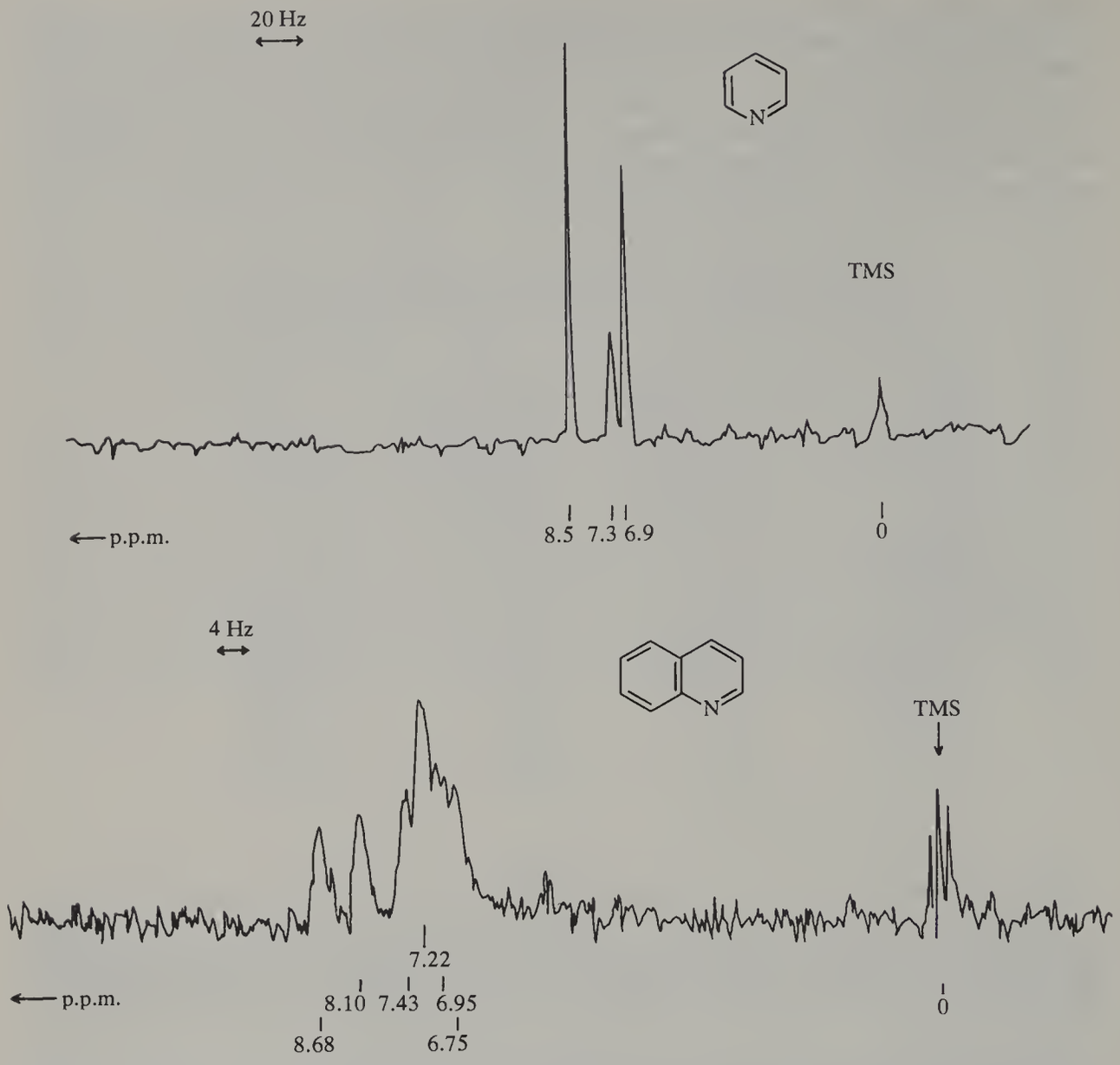


Figure 13 Fourier-transformed NMR spectra (15.4 MHz, 12 mm tube) of ^{2}H in natural abundance in neat pyridine (17 000 transients) and neat quinoline (32 000 transients) (Reproduced with permission from ⟨77MI20405⟩)

Table 6 Coupling Constants (Hz) for the Pyridine System[a,b]

$J(^{1}H, ^{1}H)$	*Neat*	*Methanol*	*Pyridinium chloride in methanol*
2, 3	4.88	4.97	5.94
2, 4	1.83	1.81	1.51
2, 5	0.97	0.90	0.67
2, 6	−0.12	−0.16	−0.55
3, 4	7.62	7.83	7.93
3, 5	−1.34	1.38	1.64
$J(^{15}N, ^{1}H)$			
1, 2	−10.76	−10.06	−3.01
1, 3	−1.53	−1.56	−3.98
1, 4	±0.21	±0.18	±0.69
$J(^{15}N, ^{13}C)$			
1, 2	0.45	0.7	12.0
1, 3	2.4	2.6	2.1
1, 4	3.6	3.8	5.3

[a] ^{15}N chemical shift upfield with respect to $H^{15}NO_3$: 56.8, 74.4, 170.1 for (a), (b) and (c) respectively.
[b] ⟨71JA5218⟩.

Table 7 ^{13}C Chemical Shifts of Pyridine Derivatives in Various Solvents[a,b]

Compound	*Solvent*	α-^{13}C	β-^{13}C	γ-^{13}C	$^{13}CH_3$
Pyridine	CCl_4	149.7	123.2	135.1	—
	$CDCl_3$	149.9	123.8	136.0	—
	EtOH (95%)	150.1	125.1	137.7	—
	$(CF_3)_2CHOH$	148.9	126.7	140.7	—
	CF_3CO_2H	141.9	128.5	148.6	—
	H_2SO_4	142.6	129.4	149.7	—
Pyridine *N*-oxide	CCl_4	138.7	125.6	123.2	—
	Me_2SO	139.0	126.7	125.2	—
	$CDCl_3$	139.4	127.2	125.7	—
	EtOH (95%)	140.3	127.9	129.5	—
	$(CF_3)_2CHOH$	140.7	128.4	132.6	—
	CF_3CO_2H	140.4	129.4	141.1	—
	H_2SO_4	141.1	130.5	145.5	—
N-Methylpyridinium iodide	EtOH	146.0	128.6	146.0	49.8
	$(CF_3)_2CHOH$	146.6	129.7	147.0	50.4
	CF_3CO_2H	146.3	129.5	146.6	50.1
	H_2SO_4	148.1	132.1	148.8	54.6

[a] In p.p.m. downfield from internal TMS, except for the protonating solvents CF_3CO_2H and H_2SO_4, where measurements were made with respect to external TMS/$(CD_3)_2CO$ (1:1).
[b] ⟨76JOC3589⟩.

Table 8 $^1J(^{13}C, ^1H)$ (Hz) for Pyridine Derivatives[b]

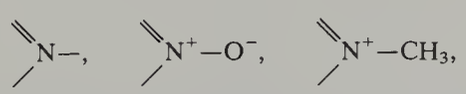
Compound	*Solvent*	α-^{13}C	β-^{13}C	γ-^{13}C
Pyridine	none	179	162	161
	$CDCl_3$	179	163	161
	$(CF_3)_2CHOH$	180	164	164
	CF_3CO_2H	192	176	172
	H_2SO_4	192	177	172
Pyridine *N*-oxide	$CDCl_3$	188	169	171
	EtOH	190	171	172
	$(CF_3)_2CHOH$	191	172	173
	CF_3CO_2H	196	178	173
	H_2SO_4	197	178	173
N-Methylpyridinium iodide[a]	CF_3CO_2H	192	176	172

[a] $^1J(^{13}C, ^1H)$ for Me is 147 Hz. [b] ⟨76JOC3589⟩.

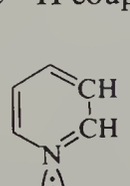
couplings over two and three bonds. However, the very small values of $^1J(^{15}N, ^{13}C)$ do not agree with equation (1), previously proposed ⟨64JA5564⟩, where $S_N S_C$ is the product of the per cent *s* character in each of the orbitals of the C—N bond.

$$S_N S_C = 80 J_{NC} \quad (1)$$

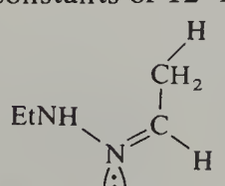
From Table 7 it may be seen that the γ-carbon resonance is at a high field for the *N*-oxide compared to the corresponding values for pyridine and pyridinium, providing the solvent is non-protonating. This points to shielding due to participation of canonical form (**64**), which is lost on protonation. Similar effects for α-C are also present, but as expected, are tempered by the proximity variation of substitution at nitrogen,



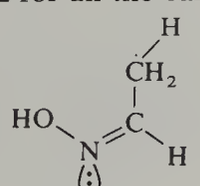
and the protonated forms of the first two. Protonation or *N*-methylation leads to an increase of C—H coupling constants of 12–15 Hz for all the carbon nuclei (Table 8).



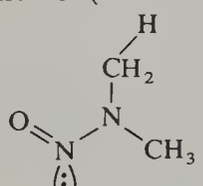
(**60**)



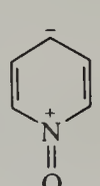
(**61**)



(**62**)



(**63**)



(**64**)

We take up now the detailed question of how the chemical shifts correlate with structure, then consider relatively recent work on nuclear spin–spin coupling in pyridine and derivatives, and finally illustrate how external influences, solvent, complexation and so on, affect NMR patterns in this area.

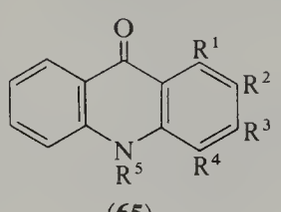
The shielding constant for an atom, σ^A, may be represented as the sum of independent contributions (equation 2).

$$\sigma^A = \sigma_d^{AA} + \sigma_p^{AA} + \sum_{B \neq A} [\sigma^{AB} + \sigma^{A,deloc}] \quad (2)$$

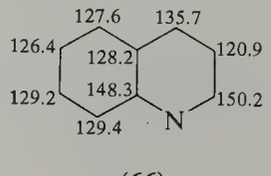
In equation (2), σ_d^{AA} is a positive term resulting from the diamagnetic shielding of electrons localized on atom A, σ_p^{AA} is a paramagnetic term (usually negative) which corrects for any deviation from spherical symmetry of the localized electrons on atom A, σ^{AB} represents a shielding or deshielding effect on atom A arising from the circulation of electrons on other atoms, and $\sigma^{A,deloc}$ is a shielding/deshielding ring current effect originating from circulating electrons in a delocalized π-system ⟨75APO(11)123, 75OMR(7)451⟩. In the case of pyridine and derivatives, such effects arise from the aromatic ring current, the perturbation of the π- and σ-electrons by the nitrogen atom, the magnetic anisotropy of the nitrogen atom, and the electrostatic influence of the lone pair dipole. These may be allied with additional influences such as substituents, fused rings, and the solvent media. Clearly, the theoretical picture is a complex one; in practice the situation may be clearer for given instances, but we are still far from any definitive knowledge in this area.

Bloor and Breen ⟨67JA6835⟩ have employed CNDO/2 MO treatment to show that total electron densities gave a better fit with ^{13}C chemical shifts of a wide variety of aromatic heterocycles, including pyridine, quinoline, and isoquinoline, than did π-electron densities alone, while proton chemical shifts in a series of monosubstituted benzenes, pyridine, pyridinium ion, and charged aromatic compounds were related to the electron density on the hydrogen atom ⟨71CJC1779⟩, also calculated by CNDO/2 MO methods. However, a generalized statement that ^{13}C chemical shifts do not correlate with charge densities, based on a wide variety of organic molecules, has been made; for example, a study of six-membered aromatic heterocycles and substituted pyridines has shown that charge density alone is insufficient to explain changes in carbon shieldings ⟨76MI20402⟩. Other workers ⟨76JCS(P2)621⟩ have also warned against a general acceptance that ^{13}C chemical shifts parallel charge distribution, because shielding parameters will be dependent on various factors such as hybridization, charge delocalization, and anisotropic diamagnetic and paramagnetic shielding effects ⟨B-72MI20400⟩. This is illustrated by an NMR study of 3- and 4-substituted *N*-methylpyridinium salts in D_2O ⟨71HCA229⟩. The ring nitrogen-14, and methyl proton and carbon substituent chemical shifts (SCS) are excellently correlated by exalted Hammett substituent constants (σ^+), further supported by measurements of the *N*-methyl chemical shift in 2-, 3-, and 4-substituted *N*-methylpyridinium salts in DMSO ⟨74OMR(6)53⟩. Extended Hückel theory reveals the nitrogen chemical shifts to originate in changes in electron density on the nitrogen atom ⟨71HCA229⟩. There is, however, no significant variation in electron density on the carbon and hydrogen atoms, and neighboring anisotropic effects are postulated to explain the SCS of these nuclei.

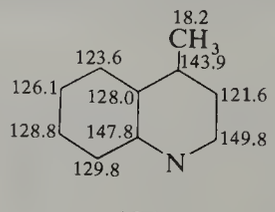
In particular cases, on the other hand, correlation between ^{13}C SCS and total electron density may be quite good; for example, 9-acridanone derivatives (**65**), where R^1, R^2, R^3, R^4 and R^5 are generally electron donating groups, produce a reasonably quantitative correspondence between ^{13}C SCS and electron densities calculated by CNDO/2 MO methods ⟨81MI20400⟩. In other polycyclic heteroaromatics, inter-ring SCS may show a variety of complex interactions. This situation has been investigated for ^{13}C chemical shifts in a range of methylquinolines ⟨76OMR(8)147, 76AJC1617, 79AJC761⟩. Values in p.p.m. are shown for the parent compound (**66**) and 4-methylquinoline (**67**) measured in $CDCl_3$; a number of effects producing both upfield and downfield shifts have been described for such cases.



(**65**)

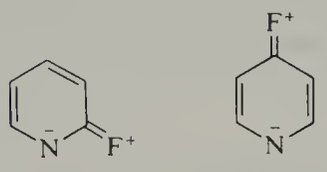


(**66**)



(**67**)

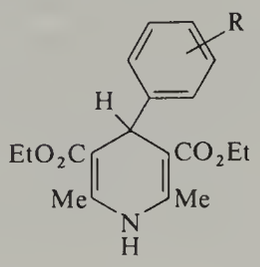
We have seen above that parameters of Hammett type may give correlations with SCS. How good are such correlations in other instances? The ^{13}C shifts *para* to the substituent in 2- and 3-substituted pyridines show a rough linear relationship with σ_p, although halogens deviate because of anisotropic effects ⟨68JPC290, 68JPC2619⟩, but no correlation with σ_m in 4-substituted pyridines was observed ⟨67JPC3592⟩. Proton chemical shifts in 2-substituted pyridines and pyridinium ions gave some degree of correlation with σ values ⟨69JPC1049⟩. 2-Fluoropyridines give ^{19}F shifts which correlate excellently with the corresponding SCS in *p*-substituted fluorobenzenes, implying a constant influence in the effects of ring nitrogen in the heteroaromatic nucleus ⟨70JCS(B)1516⟩. Likewise, ^{13}C chemical shifts for 2-, 3- and 4-fluoropyridines and pyridinium ions can be derived additively from the equivalent shifts in pyridine, pyridinium ion and fluorobenzene ⟨75JA1808⟩. The correspondence breaks down as expected however, when conjugation can occur giving rise to contribution of canonical forms such as (**68**) and (**69**).



(**68**) (**69**)

The ^{14}N chemical shifts of 3- and 4-substituted pyridines in acetone show a poor correlation with both σ and σ^+ ⟨71T3129, 72MI20402⟩. They do, however, correlate qualitatively with the overall electronic character of the substituents ⟨73MI20401⟩. The ^{15}N chemical shifts in mono- and di-amino substituted pyridines in DMSO also correlate well with the corresponding ^{13}C shifts in aminobenzenes ⟨80HCA504⟩. Comparisons of protonation and methylation of the ring nitrogen atoms in pyridines and quinuclidines reveal similar effects on the ^{13}C chemical shifts ⟨77OMR(9)53, 78HCA2596⟩ although protonation proves to be a more sensitive measure of SCS, while ^{15}N chemical shifts in substituted pyridine *N*-oxides are in line with the expected resonance and inductive influences of the substituents ⟨79OMR(12)87⟩.

Correlations with σ^+ also exist for $^{13}C{=}O$ and $^{13}CH_2$ shifts in *N*-phenacylpyridinium bromides measured in H_2O ⟨77CC119⟩, as well as for ^1H and ^{13}C shifts at the 4-position of 4-aryl-1,4-dihydropyridines (Hantzsch esters) (**70**) ⟨77BSB267⟩. This latter type of compound is of interest as an effective model for the NAD/NADH coenzyme system, and this work provides detailed analysis of ^1H and ^{13}C NMR of such compounds.



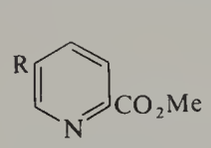
(**70**)

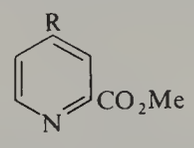
A detailed study ⟨79TH20400⟩ reveals a number of significant correlations of ^1H and ^{13}C SCS with substituent parameters. Proton SCS have been measured for 3- and 4-substituted pyridines in CCl_4 and pyridinium ions in TFA and ^{13}C SCS for 3- and 4-substituted pyridines in $CCl_4/CDCl_3$ and pyridinium ions in TFA/D_2O. However, although some correlations are good, certain substituents, such as amino, alkoxy and thioalkoxy, are anomalous, particularly in protic solvents. A variety of different types of σ value have to be employed, σ^+, σ, σ_I, and it is certain that dual substituent parameter treatments could produce better fits to the experimental data. The general probability of an improvement in such correlations by DSP treatments should certainly not be overlooked ⟨74CJC39, 75TL2113, 76JA2020, 77AJC351, 79JOC1261⟩, and indeed this has been partially explored for ^{13}C SCS in pyridines by using combinations of σ_I and σ_{II} ⟨72CPB429⟩, but there still seems some doubt as to whether this is relevant from a chemical point of view ⟨77JCS(P2)769, B-80MI20400, 81JOC2130⟩.

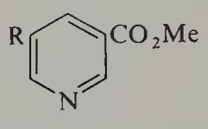
Clearly, the multifarious factors at work on SCS in pyridines as well as other aromatics can be matched by the more complex manifestations of the Hammett equation and its extensions to provide some sort of correlation, but no systematic overall correlation or related theory has emerged as yet.

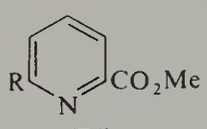
As pointed out elsewhere ⟨76OMR(8)567⟩, the general situation regarding quantitative correlation between theoretical calculation, empirical substituent parameters, and SCS has been well summarized by the White King ⟨B-11MI20400⟩: 'If any of them can explain it', said Alice, 'I'll give him sixpence. I don't believe there is an atom of meaning in it'. 'If there is no meaning in it', said the King, 'that saves a world of trouble, you know, as we needn't try to find any'. But one suspects that the White King's philosophy will not dissuade spectroscopists from attempting the search!

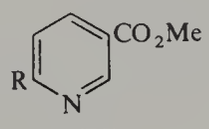
The question of additivity of SCS is difficult to probe, because *ortho* interactions, notoriously difficult to account for, are bound to arise in even disubstituted pyridine rings, apart from those with the 3,5-disposition. To test this, proton chemical shifts have been measured for six series of substituted methyl pyridinecarboxylates (**71**), (**72**), (**73**), (**74**), (**75**) and (**76**) ⟨75OMR(7)41⟩, and SCS *ortho* and *para* can be accounted for by assuming additive substituent, ester, and nitrogen effects. However, for protons *meta* to the substituent, particularly for the case where both the proton and the substituent are adjacent to N, the additivity breaks down, and there is evidence of substituent–nitrogen interactions.


(**71**)


(**72**)


(**73**)


(**74**)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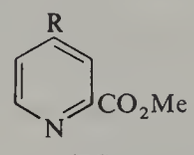
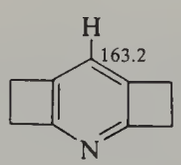
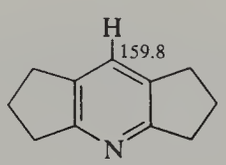

(**76**)

In a study of general additivity of substituent effects in proton pyridine NMR ⟨74MI20407⟩, a large number of 2-, 3- and 4-substituted pyridines have been examined in $CDCl_3$ or CCl_4, and the shifts obtained used to predict those of disubstituted pyridines. Agreement with measured values appears excellent, at least as good as for disubstituted benzenes, for all types of substituent located *ortho*, *meta* or *para* to one another and to the ring nitrogen atom.

For proton chemical shifts in the pyridine ring of 1-, 3- and 4-substituted isoquinolines in $CDCl_3$, there is also good additivity for a variety of different types of substituents ⟨78RTC95⟩. Shifts for disubstituted derivatives are again calculated from those for the appropriate monosubstituted compounds and these agree to a good degree of accuracy with those obtained experimentally, and are also in rough agreement with those obtained from substituted pyridines ⟨74MI20407⟩ derived as explained above.

A great deal of work has been done on nuclear spin–spin coupling in pyridine derivatives. The variety and scope of this work is illustrated in Table 9, which shows a sample of the results obtained over the last few years, and indicates the type of information available, and the way in which it can be correlated with other facets of molecular structure and interactions.


(**77**)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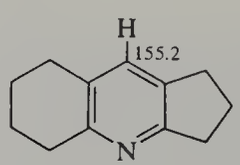
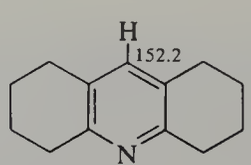
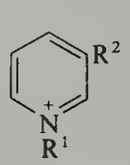

(**79**)


(**80**)


(**81**)

$R^1 = \bar{N}NO_2$; R^2 = H, Br, Me, OMe

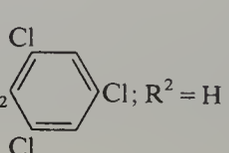

$R^1 = \bar{N}COPh, \bar{N}SO_2Ph, \bar{N}SO_2$ Cl; R^2 = H

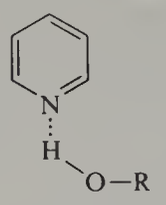
Table 9 Spin–spin Coupling in Pyridine Derivatives

Compound	*Spin–spin coupling and correlations*	*Ref.*
Pyridine, pyridine *N*-oxide, monosubstituted pyridines including fluoropyridines and pyridinones	$J(^{15}N, ^{13}C)$ correlated with SCF–INDO MO calculations. Reasonable agreement with coupling magnitude and sign: $^{2}J(^{19}F, ^{13}C)$ requires an average empirical correction for correlation between theory and experiment	76TL1621 79OMR(12)318
2-Fluoropyridine	$^{2}J(^{19}F, ^{15}N)$ of −52.64 Hz in $(CD_3)_2CO$ indicating coupling mechanism strongly influenced by proximity of N and F lone pairs	79CC478
Quinoline, isoquinoline and perfluoro derivatives	Correlation between long range inter-ring $J(^{1}H, ^{1}H)$ and $J(^{19}F, ^{19}F)$ coupling indicating transmission solely through π-electron system. Signs of inter-ring couplings alternate with number of intervening bonds, and may be correlated with CNDO/2 MO calculations of mutual polarizabilities or bond orders	79MI20405 79OMR(12)17 76OMR(8)240 76OMR(8)628 78JMR(29)65 77OMR(9)318
Bis-annelated pyridines	$^{1}J(^{13}C, ^{1}H)$ coupling constants for the aromatic C—H in compounds (**77**), (**78**), (**79**) and (**80**) decrease with size of fused ring as shown, because increasing the steric strain decreases the electron density at the bridgehead, while that at the adjacent carbon is increased, the resultant polarization of the C—H bond being reflected in the coupling constant	77JOC300 77JOC2742
Substituted pyridines	Insensitive nuclei enhanced by polarization transfer procedure (INEPT) for ^{15}N NMR with natural isotope abundance: ^{2}J, ^{3}J and $^{4}J(^{15}N, ^{1}H)$ coupling constants obtained in $(CD_3)_2CO$ and DMSO-d_6	81OMR(16)170
Polysubstituted pyridines	Additivity of substituent effects on $J(^{1}H, ^{1}H)$ and $J(^{13}C, ^{1}H)$	79JCS(P2)285 73JST(16)451
cis-[PtMe(4-X-pyridine)L]PF_6; L = 1,2-bisdiphenylphosphinoethane	$J(^{195}Pt, ^{31}P)$ correlated with σ_X	79CJC958
4-Nitroquinoline 1-oxide	Effect of substitution on $J(^{1}H, ^{1}H)$ in $CDCl_3$, including the potentially carcinogenic 2,6- and 2,7-dimethyl derivatives	72JHC1097
3-Substituted pyridine *N*-imides (**81**)	$J(^{1}H, ^{1}H)$ correlated with Pauling electronegativity for first atom of 3-substituent	75OMR(7)569
2,2′-Dipyridyltin derivatives	Adduct configuration and electronic character of Sn—C bond from $J(^{117/119}Sn, ^{1}H)$ and $J(^{117/119}Sn, ^{13}C)$	77BCJ3055
Methylacridines	Variation of $J(^{1}H, ^{1}H)$ with π-bond alternation	71OMR(3)339
Quinuclidine and azaadamantane	Large value of $^{3}J(^{15}N, ^{13}C)$ of 0.6 Hz in quinuclidine, *cf.* that of <0.3 Hz in azaadamantane, indicative of through space interaction in the former case. Poor agreement with INDO MO calculations	76OMR(8)438 75OMR(7)563

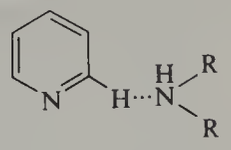
NMR patterns also throw light on details of solvation and complex formation, while in turn, NMR patterns may be clarified by complexation with lanthanide or other shift reagents ⟨71JA3922, 71CC33, 73JA3534, 73TL3127, 74JCS(P2)748⟩, although care has to be taken in drawing conclusions from such measurements in equilibrating systems, such as NH conformational equilibria of piperidine derivatives ⟨74JA682⟩.

^{14}N and ^{15}N chemical shifts and couplings in unsaturated compounds such as pyridine and quinoline are particularly susceptible to the influence of hydrogen bonding solvents ⟨71JA5218, 73JA324, 80JOC130⟩. Indeed, such upfield shifts of pyridine nitrogen-15 in both polar aprotic and hydrogen bonding media, relative to the value in the gas phase, correlate well with Kamlet–Taft solvent parameters ⟨79MI20406⟩, hydrogen bonding effects being particularly important. These are therefore a sensitive test of medium effects ⟨78JA4969, 79MI20406⟩, although ^{19}F chemical shifts for fluoropyridines correlate less well ⟨77MI20402⟩. ^{13}C shifts in pyridine are also very sensitive to solvent and dilution effects ⟨74JMR(14)286⟩.

^{13}C solvent shifts may be extrapolated to infinite dilution, and thence *via* the postulation of two types (**82**) and (**83**) of solvent interaction ⟨74JMR(14)286⟩, a scheme of parameterized solvent shifts can be prepared assuming that each type of interaction produces its own intrinsic shift.

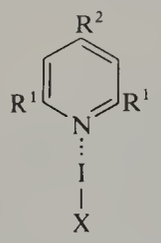


(**82**)

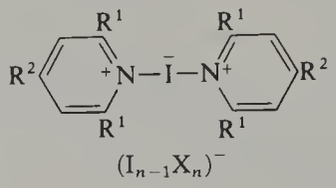


(**83**)

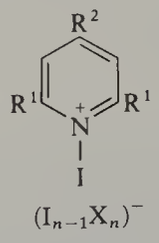
^{1}H and ^{13}C NMR studies reveal details of complexation between pyridine and methylpyridines, on the one hand, and iodine and also iodine monochloride on the other ⟨79JOC2658⟩. These yield evidence for three types of complex. In deuterobenzene, charge transfer complexes of form (**84**) are formed, while in nitrobenzene–$CDCl_3$, pyridinium compounds (**85**) and (**86**) may be formed, the relative proportions depending on the substitution of the pyridine ring, whether iodine or iodine monochloride is used, and the relative concentrations of the base and electrophile. As expected, the NMR phenomena associated with solvation or complexation of pyridines is generally influenced by the basicity of the heteroaromatic, although for ^{199}Hg shifts in (MeHg-*o*-substituted pyridine)NO_3 compounds, the solvent and counterion are influential, but not the pK_a of the pyridine ⟨78JOM(144)371, 79JOM(179)47⟩. Presumably here steric effects are all-important.



(**84**) $R^1 = R^2 = H$, Me
R^1 = Me, $R^2 = H$
X = Cl, I



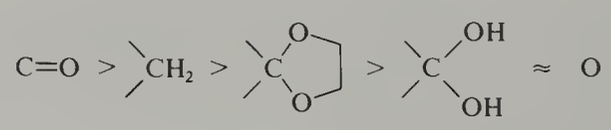
(**85**) $R^1 = R^2 = H$, Me
R^1 = Me, $R^2 = H$
X = Cl, I



(**86**) $R^1 = R^2 = H$, Me
R^1 = Me, $R^2 = H$
X = Cl, I

π-Back bonding effects in Ru(II) and Fe(II) complexes of pyridine and substituted pyridine can be detected from ^{1}H and ^{13}C shifts ⟨77JA718⟩. These can be distinguished from influences due to protonation or complexation by comparison with the shifts obtained for Co(III) or Rh(III) complexes. ^{13}C shift changes on complexation are much larger than the ^{1}H shifts for these compounds, although solvent change influences both equally.

Details of hydration of piperidin-4-ones have been established from ^{1}H and ^{13}C chemical shifts ⟨79OMR(12)399⟩. This study involves careful investigation of chemical shift with acidity of the solution as the [ketone]/[hydrate] ratio, whose value is obtained from integration of the proton NMR signals in different buffer solutions, decreases markedly if the ring nitrogen atom is protonated. The ratio also increases in the sequence $N^+Me_2 > N^+HMe > N^+H_2$ as the solvation of the charged N correspondingly increases and thus the charge density on the nitrogen atom decreases. The shift increments of the C(4) signals induced by positively charged N decrease in the order:



The carbonyl group carbon shows the largest upfield shift due to the electrostatic field effect; in the dioxolane and dihydroxy derivatives this is countered by the polarization of the free oxygen electron pairs.

2.04.3.2 Nuclear Quadrupole Resonance

The phenomenon of NQR is the origin of hyperfine structure in microwave rotational spectra (see Section 2.04.2.1), as well as in electron and nuclear paramagnetic resonance.

A rather good simple account of the origin of the phenomenon has been given ⟨B-61MI20400⟩, and its application to the study of heterocyclic molecules has been reviewed ⟨63PMH(2)89⟩. The Zeeman effect can also be observed in NQR lines, and the study of this has, for example, enabled elucidation of the crystal packing in 3-cyanopyridine ⟨80JST(58)171⟩. For use of NQR to determine molecular electronic distribution using Townes and Dailey theory (Section 2.04.2.1), measurements must be made on crystalline samples (of about 1–10 g) at liquid nitrogen temperatures. Other drawbacks to the technique have been outlined ⟨63PMH(2)89⟩, and the number of observations using it are limited.

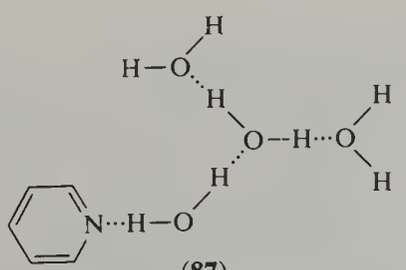
Early measurements of ^{35}Cl resonances of chlorobenzene, 2-, 3- and 4-chloropyridine, and 2-, 6- and 7-chloroquinoline ⟨58JCP(28)99, 58JCS2653, 63PMH(2)89⟩ have been interpreted in terms of the inductive effect of the nitrogen atom, which raises the frequency, *e.g.* 35.24 MHz for 3-chloropyridine compared with 34.60 MHz for chlorobenzene. The values for 2-chloropyridine and 2-chloroquinoline are, however, lower than for chlorobenzene, 34.17 and 33.29 MHz, and this is interpreted in terms of back donation of the halogen lone pair electrons. The C—Cl bond may thus be calculated to have 9% double bond character in 2-chloropyridine and 12% in 2-chloroquinoline. ^{14}N quadrupole coupling constants of a range of 4-substituted pyridines have subsequently been measured ⟨73JST(19)43⟩, and here the main changes in electron density are found to be in the π- rather than the σ-electron population, the latter varying little and only randomly through a wide variety of substituents. The electron density at the ring nitrogen atom can be correlated with CNDO MO calculations ⟨79MI20402⟩, and the π-electron populations with Taft resonance parameters ⟨73JST(19)43⟩. The degree of correspondence in the latter case is, however, rather poor, and it is perhaps a little surprising to find no contribution from the inductive effect of the substituents. Details are given in Table 10.

Table 10 Electron π- and σ-Populations Calculated by Townes and Dailey Theory from ^{14}N NQR Coupling Constants for the Ring Nitrogen Atom in 4-Substituted Pyridines

Substituent	π	σ	σ_R [a]
NO_2	1.099	1.284	0.14
MeCO	1.109	1.273	0.16
CN	1.107	1.272	0.13
H	1.148	1.290	0
Cl	1.147	1.284	−0.23
Me	1.177	1.297	−0.12
NH_2	1.344	1.319	−0.82
NMe_2	1.318	1.270	−0.83

[a] ⟨73MI20401⟩.

Some of the fine detail which is available from NQR measurements is illustrated by the results for the water–pyridine complex formed at temperatures below 190 K ⟨78MI20404⟩, which augments the conclusions drawn from X-ray measurements (Section 2.04.2.2). Double nuclear resonance techniques were used to measure ^{2}H, ^{14}N and ^{17}O NQR in isotopically enriched samples, from which structure (**87**) was ascertained. The N···HO bond distance is 1.8 ± 0.2 Å. The other half of this molecule of water and the water molecule to which it is bound have couplings which are very close to those in ice, indicating that probably only one molecular level is required in general to match a biological organic molecule to its aquatic environment. The other two water molecules are bound only weakly. Deuteron quadrupole coupling has also been used to elucidate details of charge distribution and molecular structure in other pyridine and pyridinium complexes and salts ⟨79JCP(70)5072, 80JST(58)37⟩. ^{14}N NQR studies have been made for a large number of such complexes



(**87**)

⟨77JA1384, 80IC392, 80IC398⟩, and by application of Townes and Dailey theory the extent of charge transfer from the nitrogen donor orbital to the complexing Lewis acid may be calculated. If actual proton transfer is involved, the degree of occupancy of the N donor orbital gives a measure of the extent of hydrogen bonding to the anion, and this increases in the order $HSO_4^- < NO_3^- < Cl^- < ClO_3^- < Br^- < ClO_4^-$ ⟨80IC392⟩. ^{35}Cl NQR frequency changes have also been used to study complexation and protonation of this kind in 2-, 3- and 4-chloropyridine ⟨73JST(19)43⟩.

2.04.3.3 Ultraviolet Spectroscopy

The exploration of the UV (and visible) region of the electromagnetic spectrum has been experimentally realizable for many decades, and the technique has therefore a distinguished history in the elucidation of structural problems. Figure 14 illustrates this with the UV spectra of pyridin-2-one and model compounds ⟨42CB1338⟩ from which the correct tautomeric structure for the compound was deduced many years ago (see Section 2.04.4.2), while UV spectra of nicotine and quinoline were recorded as long ago as 1910 ⟨10JCS1035⟩. Much detail of the correlation of heterocyclic structure with spectral characteristics is therefore also well known and extensively covered in previous reviews ⟨63PMH(2)1, B-67MI20400, 71PMH(3)67⟩. Details of more specialized aspects of measurements in the UV or visible region such as optical rotatory dispersion and circular dichroism ⟨71PMH(3)397⟩, and fluorescence and phosphorescence in heterocyclic derivatives ⟨74PMH(6)147⟩ have also received attention in comprehensive review form.

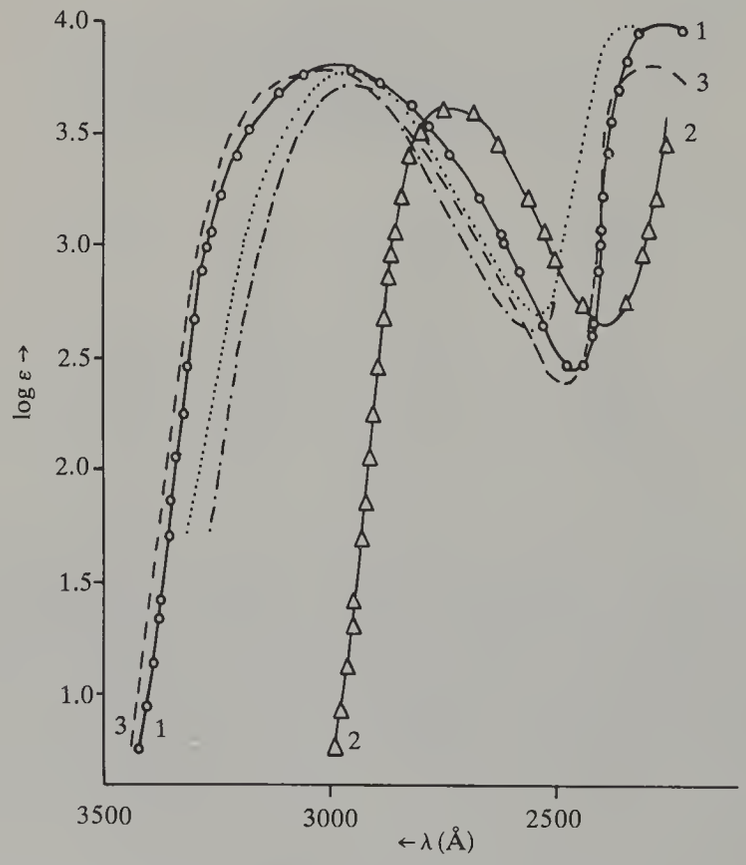


Figure 14 UV absorption spectra of (1) pyridin-2-one, (2) 2-ethoxypyridine, (3) *N*-methylpyridin-2-one, all in methanol (Reproduced with permission from ⟨42CB1338⟩)

The well-known similarity of the UV spectrum of pyridine to benzene is rationalized by saying that in the former the expected low intensity $n \rightarrow \pi_4^*$ transition comes near or under the intense $\pi_3 \rightarrow \pi_4^*$ absorption band ⟨B-78MI20400⟩, and it has been pointed out that this similarity is paralleled in the spectra of polycyclic analogues ⟨B-62MI20400⟩. Such similarities have been used in the corroboration of structure of heteropolycyclic compounds; the important feature deciding the characteristics of the UV spectra is the annelation pattern of the aromatic rings, not which methine group is replaced by nitrogen. This has been discussed in early papers, for example in the phenanthrene, phenanthridine, *o*-phenanthro-

line and 3,4-benzocinnoline series ⟨51JCS3199⟩, and the anthracene, acridine, 1- and 2-azaanthracene and phenazine series ⟨51JCS3199, 53BSF108⟩. Figure 15 shows the resultant spectra for the latter series, which clearly shows the overall correspondence of absorption maxima.

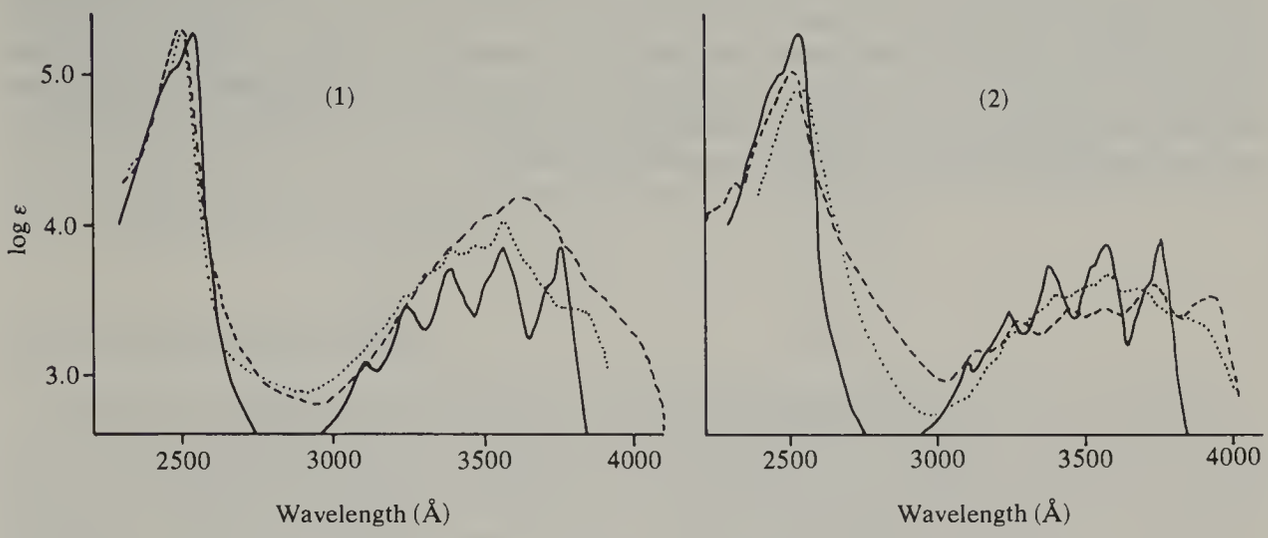


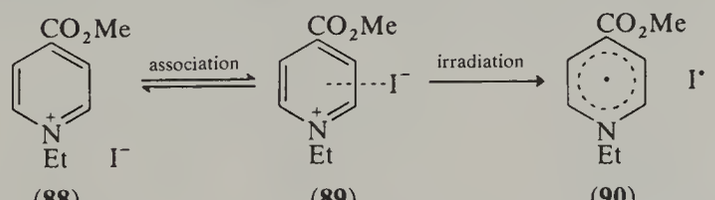
Figure 15 (1) UV absorption spectra of anthracene, phenazine and acridine in ethanol. (2) UV absorption spectra of anthracene, and 1- and 2-azaanthracene in ethanol (Reproduced with permission from ⟨51JCS3199⟩)

The $\pi \rightarrow \pi^*$ transition of azines (for pyridine $\lambda = 2510$ Å, $\varepsilon = 2000$, C_6H_{12}) is little influenced by solvation effects, but the $n \rightarrow \pi^*$ ($\lambda = 2700$ Å, $\varepsilon = 450$, C_6H_{12}) transition, arising from interaction of the N lone pair electrons with the *p* orbitals of the aromatic system, is. This band is most apparent in inert solvents, but is less evident in polar solvents which interact with the lone pair, and disappears completely on protonation. Likewise, the polar canonical forms of pyridine *N*-oxide are stabilized by polar or hydrogen bonding solvents, while electron transfer to the aromatic ring is favored in non-polar solvents. The UV spectrum is therefore profoundly influenced by solvent, which has an effect on both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions ⟨62BCJ555, 69JHC859⟩. Solvent may also influence the fluorescent properties of N heterocycles, including those of *N*-oxides ⟨70SA(A)1545⟩.

The dramatic influence of solvent effects on the UV and visible spectra of certain pyridine compounds, known generally as a solvatochromic effect, has been much utilized in the expression of solvents effects. The polarity parameter Z or E_T is defined ⟨58JA3253, B-68MI204002⟩ from the longest wavelength charge transfer band of 1-ethyl-4-methoxycarbonylpyridinium iodide (equation 3).

$$Z \equiv E_T = hc\bar{\nu}N \tag{3}$$

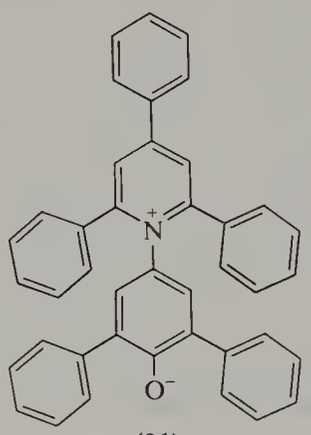
where h is Planck's constant, c is the velocity of light, ν is wavenumber, and N is Avogadro's number. This wavelength change arises from stabilization of the electronic ground state ion pair by increasingly polar solvents relative to the radical pair excited state; see structures (**88**), (**89**) and (**90**). Details of this have been elucidated using the 4-cyano compound ⟨80JA6780⟩, which has served to show that both the ground state ion pair and the excited state are destabilized on transference to a more polar solvent.



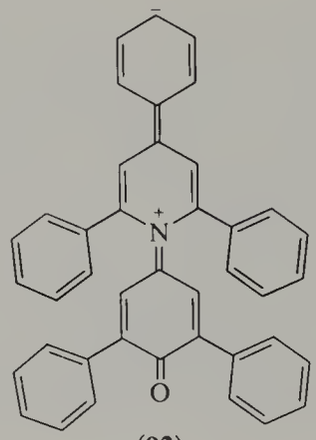
(**88**) (**89**) (**90**)

Other workers ⟨63LA(661)1⟩ have studied strong solvatochromic $\pi \rightarrow \pi^*$ transitions (a record hypsochromic shift of 3500 Å for solvent change from diphenyl ether to water!) in the pyridinium *N*-phenoxide betaine (**91**) ↔ (**92**), and these may also depend on temperature ⟨63LA(669)95⟩ and pressure ⟨73CL1251⟩. Observations on this compound lead to the $E_T(30)$ solvent parameter. Obviously, most physical properties of molecules vary with solvent; how can we choose a property which will vary most widely and give best indication of solvent interaction? The key factor here in deciding these large solvent shifts in these series of

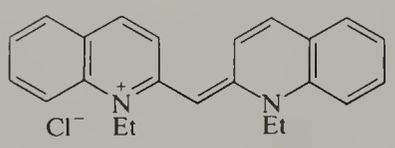
pyridine derivatives is the character of the canonical forms contributing to the resonance hybrid ⟨72JCS(F2)137⟩. One, as shown in (**91**), is non-quinonoidal and dipolar, and the others of which (**92**) is one, are delocalized and quinonoidal. The variable contribution of such extreme canonical forms is, not unexpectedly, profoundly influenced by solvent character, and absorption changes over a wide range of wavelength. Thus the pyridinium phenoxide (**91**)↔(**92**) is colored yellow and has λ_{max} 4530 Å in water, where the polar canonical form makes greatest contribution. In ether, it is blue-green ($\lambda_{max} = 8100$ Å); here the quinonoid canonical form has the largest mixing coefficient in the resonance hybrid. In support of this theory, the UV spectrum of the cyanine dye (**93**)↔(**94**) has, by contrast, only a small dependency on solvent type ⟨B-79MI20400⟩.



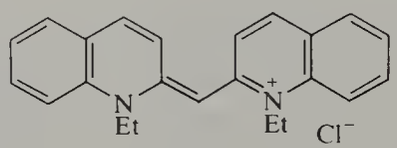
(**91**)



(**92**)

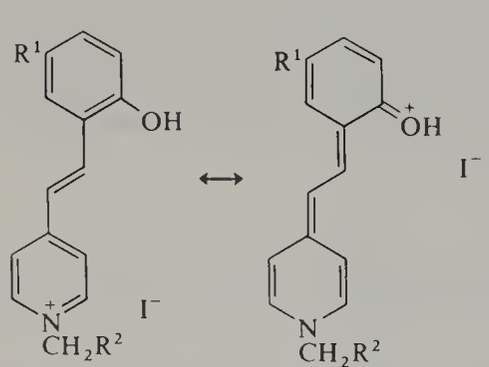


(**93**)

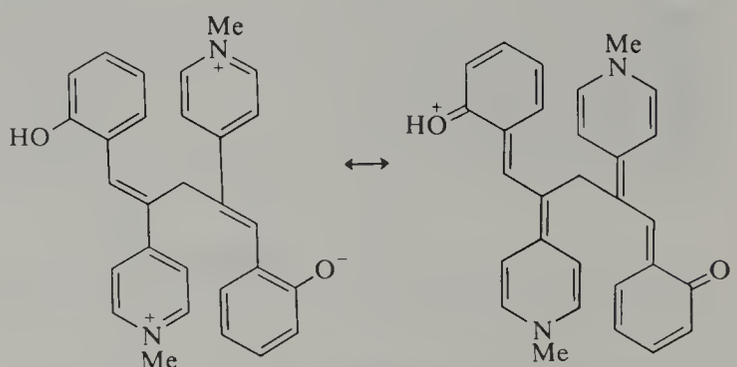


(**94**)

A variety of other solvatochromic pyridine compounds have thus been studied, including 5′-substituted 2′-hydroxy-4-stilbazole derivatives (**95**) and (**96**), types of species whose fluorescence behavior and UV spectral changes with solvent in neutral and protonated form have received much attention ⟨74T2043, 75CJC2162, 76JCS(P2)196, 76JCS(P2)1575⟩. The intramolecular hydrogen bonding interactions between the two halves of the 'double-barrelled' compound (**96**), and its unprotonated and diprotonated forms, are taken as a model for elucidation of intermolecular complexation between molecules of (**95**). The lack of fluorescence of compound (**96**) in contrast to that of (**95**) indicates alternative pathways for de-excitation ⟨74PMH(6)147⟩, and may indicate an excited state intramolecular complex or 'exciplex'. Excellent accounts of the solvatochromic properties of these and related pyridinium compounds have been provided previously ⟨B-79MI20400⟩.



(**95**) R^1 = H, NO_2, Cl, OMe
R^2 = H, Me



(**96**)

The observation of natural ORD or CD requires lack of symmetry in the molecule, but any molecule may exhibit magnetic circular dichroism (MCD). It constitutes a molecular analogy for the Zeeman effect in atomic spectra. Measurements in this area may well reveal substituent interactions which are masked in normal UV spectra. Extensive definitive papers of great interest which well illustrate this have appeared on MCD of pyridine derivatives, measured in cyclohexane, acetonitrile, and alcohol or aqueous acidic solutions for protonated

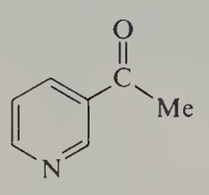
forms. These establish general rules for the interpretation of such spectra for molecules with a $(4n+2)$ electron perimeter, allowing definition of electronic effects within such systems ⟨78JA6819⟩. Treatment ⟨78JA6824⟩ of the aza analogues of benzene, for which MCD bands are very weak, show that the aza 'substituent' has no mesomeric effect but operates by the inductive effect alone. The influence of F, Cl, OH, NH_2 and CN substituents on the MCD of pyridine and pyridinium ion is very profound, however, and is in good agreement with simple PMO treatment of HOMO–LUMO energy levels as well as PPP MO calculations ⟨78JA6828⟩. In particular, the theory accords with the hydroxy derivatives being in the pyridone form ⟨78JA6834⟩ and may also be extended to interpretation of MCD of quinoline, isoquinoline and their protonated ⟨78JA6838⟩ and amino derivatives ⟨78JA6853⟩, quinolinones and isoquinolinones ⟨78JA6857⟩, acridine and other azaanthracenes ⟨78JA6861⟩, and 1-, 4- and 9-azaphenanthrenes ⟨78JA6867⟩.

2.04.3.4 Infrared Spectroscopy

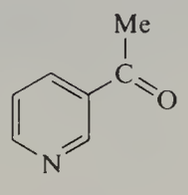
Techniques of IR spectroscopy have been previously much used in structural elucidations, although over the last decade or so the research worker seeking general structural information has turned increasingly to NMR. Some interesting structural correlations have been achieved, however, in the field of pyridine compounds, one example being substituent intensity correlations for CH stretching vibrations ⟨66SA1645, 67ZN(A)395, 67ZN(A)403, 67MI20401⟩. The intensity A for a given vibrational band is afforded by a parabolic relationship (equation 4),

$$A = a\sigma_I^2 - b\sigma_I + e \tag{4}$$

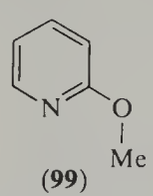
where a, b, and e are empirical parameters for a given vibration. The parabolic relationship arises because the intensity is related to the magnitude of the inductive effect of the substituents irrespective of whether they attract or donate electron density by this mechanism. The measurements are of interest in particular because they appear to show that resonance and inductive effects in substituted aromatic systems are separable. Another important intensity correlation, which again points to the justification of separate inductive and resonance mechanisms, is that of the ring breathing mode near 1600 cm^{-1} of substituted pyridines and pyridine *N*-oxides with resonance effects, quantified by the squares of expressions containing the σ_R° parameter ⟨69JA636, 77CRV639⟩. These measurements lead to σ_R° values for the ring nitrogen and its modified forms treated as a monosubstituted benzene; thus the value of N is 0.24 (in solvent MeCN), N^+—Me is 0.28 (MeCN) and for N^+—O^-($CHCl_3$) is −0.21. These values show that pyridinium nitrogen does not withdraw electrons by resonance much more effectively than pyridine nitrogen, while O^- completely reverses the effect. 4-Substituted pyridines correlate well, provided an interaction term is included for resonance donors, while potential resonance acceptors appear to conjugate far less effectively with pyridine than benzene ⟨81JCS(P2)409⟩. Measurements of 4-substituted pyridine *N*-oxides confirm the ability of the *N*-oxide to both donate and withdraw electrons according to the nature of the 4-substituent. Correlations with 2- and 3-substituents using treatments found for *ortho*- and *meta*-disubstituted benzenes are not so accurate, however, but the measurements do reveal that the preferred conformer of 3-acetylpyridine is (**97**) rather than (**98**), and is (**99**) for 2-methoxypyridine, for CCl_4 solutions; this conformation for 2-methoxypyridine had been indicated by dipole moment measurements ⟨65BSF3150⟩.



(**97**)



(**98**)



(**99**)

Details of hydrogen bonding of pyridine molecules to hydroxy groups and other details of solvation may be evaluated by IR measurements. Usually these involve measurement of the fundamental O—H stretch in the 3000–4000 cm^{-1} region ⟨67JOC407, 68T5991, 78JPC1268⟩. From such measurements the equilibrium constant K_H ([complex]/[OH donor]-[pyridine]) may be evaluated, and thence the free energy of complexation ΔG_H. Figure 16

shows the correlation obtained between *PA*, the gas phase basicities for a series of substituted pyridines ⟨76JA854⟩ and the ΔG_H values for complexation with phenol in $CHCl_3$. Only the bulkier 2-substituents show deviation, because of variable steric effects.

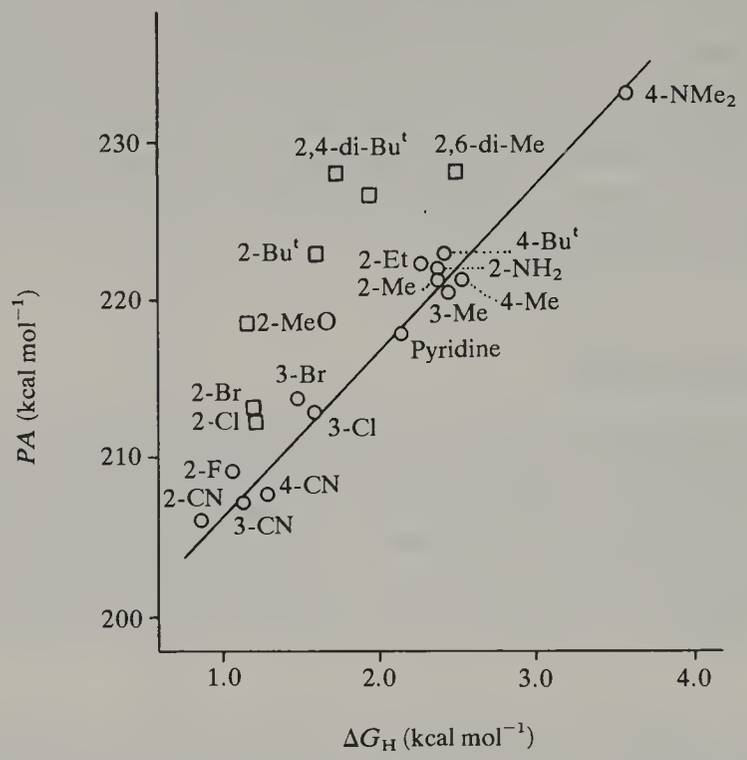


Figure 16 Correlation between gas phase basicity *PA* and free energy of complexation with phenol ΔG_H for substituted pyridines (Reproduced with permission from ⟨78JPC1268⟩)

For the cyanopyridines, two peaks appear for hydrogen bonded species; one is for complexation at the pyridine nitrogen atom and the other at cyano nitrogen. Vibrational frequency shifts of pyridine on hydrogen bond formation have also been investigated by both IR spectroscopy ⟨66JSP(21)217⟩ and the Raman effect ⟨57PIA(A)51⟩. In the former case, shifts of just about all vibrations to higher frequencies have been found due to hydrogen bonding, and this is illustrated by Table 11. It would appear that there is a considerable change in electron distribution within the pyridine molecule on complexation with hydrogen bond donors, the extent of which is not far removed from that produced by protonation at the nitrogen atom.

Calculations of vibrational spectra and conformations may be made by consistent force field theory (CFF) ⟨68JCP(49)5116⟩. This can be used, for example, in elucidating the fundamental vibrational frequencies of piperidin-2-one ⟨70JSP(33)84⟩ and thus to demonstrate that the molecule has a 'flattened' or 'twisted' chair conformation, to accommodate the tendency of the amide bond to planarity. Agreement between calculated and observed fundamental frequencies is good; the barrier to inversion into the mirror image form is only about 0.4 kJ mol^{-1}, much less than the zero point vibrational energy. Force constants may also be calculated by other approaches: the vibrational spectra of pyridine and its 4-d_1, 2,6-d_2, 3,5-d_2 and d_5 deuterated derivatives can be calculated by a CNDO/2 force method ⟨80JST(65)141⟩. Agreement with the experimental IR spectra and the assignments in Table 11 is excellent, and confirms previous reassignments ⟨63JCP(38)127, 77JST(37)321⟩ of the original data ⟨53JCP(21)1170⟩.

2.04.3.5 Mass Spectrometry

The stability of aromatic nuclei leads to molecular ions of high abundance compared to fragment ions, the reverse being true for saturated compounds. This is well illustrated in Figure 17, which shows the mass spectrum of 3-methylpyridine compared with that of 3-methylpiperidine ⟨B-71MS364⟩. Thus, *N*,*N*-disubstituted 2- and 4-aminoethylpyridines give only weak molecular ions, as they are derived from tertiary amines with long aliphatic chains ⟨78OMS203⟩. Cleavage of these molecular ions can occur β to the aliphatic N as

Table 11 Pyridine Vibration Solvent Shifts

Vibration[a]	*Assignment*[a]	*Wavenumber* (cm^{-1})	*Calc.*[b]	*H_2O* (2.5)[c]	*D_2O* (2.5)	*MeOH* (2.5)	*EtOH* (2.5)	*$CHCl_3$* (1.25)	*CCl_4* (0.13)
ν_{20b}	ν(CH)	3080 (3)[d]	3072	—[e]	+14	—	—	+4	+2
ν_2	ν(CH)	3054	3067	—	+11	—	—	+3	+3
ν_{20a}	ν(CH)	3027 (36)	3037	—	+20	—	—	—	0
ν_{8a}	ν(CC)	1583 (0)	1637	+12[f]	+11[f]	+12[f]	+10[f]	+4	0
ν_{8b}	ν(CN), ν(CC)	1576 (2)	1599	0	0	0	0	0	0
ν_{19a}	β(CH), ν(CN)	1483 (2)	1499	+4	+4	—	—	+2	−1
ν_{19b}	β(CH)	1438 (9)	1428	+5[f]	+5[f]	—	—	+1	0
ν_{9a}	β(CH)	1217 (18)	1203	−1	—	−2	−1	—	−2
ν_{15}	β(CH)	1146 (8)	1157	+4	+4	+4	+4	0	−1
ν_{18a}	β(CH), ν(CN)	1068	1055	0	0	—	—	0	0
ν_{12}	α(CCC), α(NCC)	1029	1004	+4	+4	—	—	+2	0
ν_1	α(CCC), ν(CN), ν(CC)	992	993	+9[f]	+10[f]	+9[f]	—	+1	0
ν_{10b}	—	750 (49)	–	—	+2	+2	—	—	—
ν_{11}	—	703	–	—	+3	+2	+3	—	−1
ν_{6a}	α(CCC), α(NCC)	606 (5)	588	—	+11[f]	+11[f]	+11[f]	+3	0
ν_{16b}	—	406 (5)	–	—	—	+2	+2	0	0

[a] For vibrational assignment see ⟨53JCP(21)1170, 80JST(65)141⟩.
[b] See ⟨80JST(65)141⟩ for details of calculation.
[c] Concentration of pyridine in ml^{-1}.
[d] Value in brackets indicates frequency as measured elsewhere ⟨53JCP(21)1170⟩.
[e] Dash indicates band obscured by solvent absorption.
[f] A new band replaces the original band.

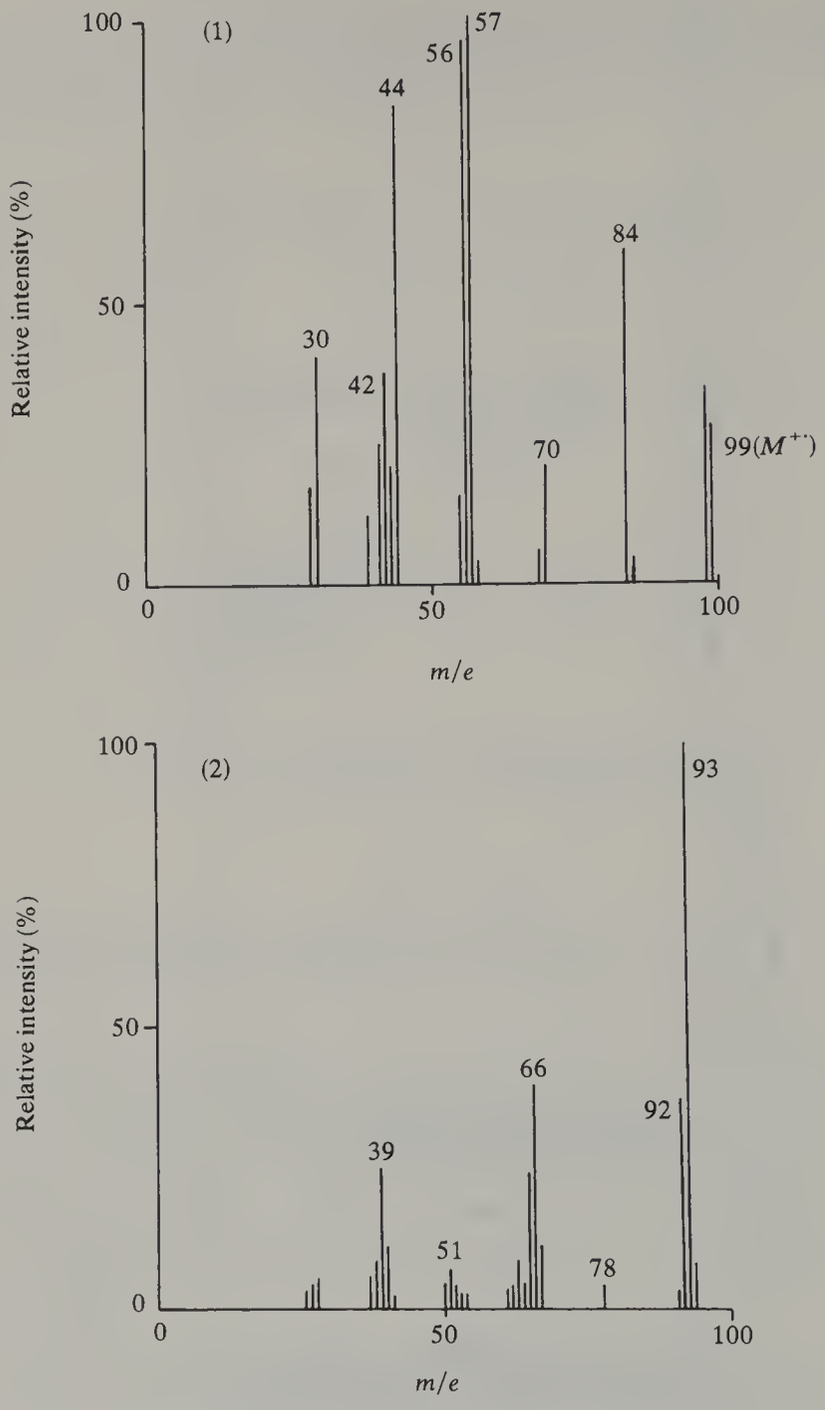
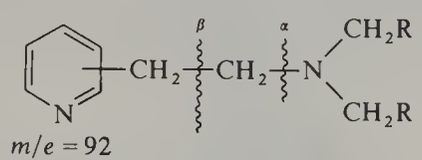


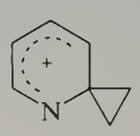
Figure 17 Mass spectra of (1) 3-methylpiperidine and (2) 3-methylpyridine (Reproduced with permission from ⟨B-71MS⟩)

in (**100**), so that the base peaks for the spectra are frequently $(M-92)^+$ due to loss of the radical ($CH_2C_5H_5N$). Peaks at $m/e = 106$ arising from α cleavage indicate, by analogy with related fragmentations ⟨73JOC1114⟩, that ion (**101**) and its *p*-isomer may be involved. Nitrogen may be implicated directly in fragmentation of 2-substituted pyridines (**102**) to give bicyclic structures (**103**).

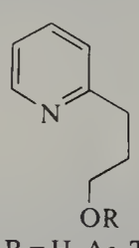


$m/e = 92$

(**100**)

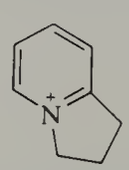


(**101**)



R = H, Ac, Ts

(**102**)

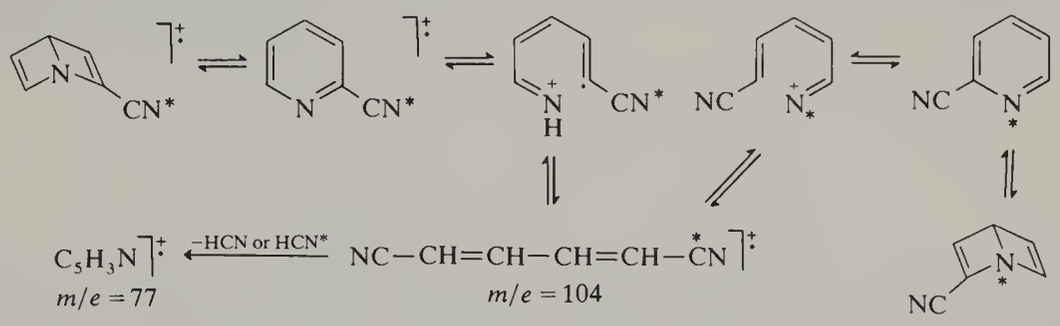


(**103**)

The fragmentation mode of pyridine itself involves initial loss of HCN from the molecular ion ⟨67CC1129⟩. Deuterium labelling shows that this process is preceded by randomization

(104) (105) (106)

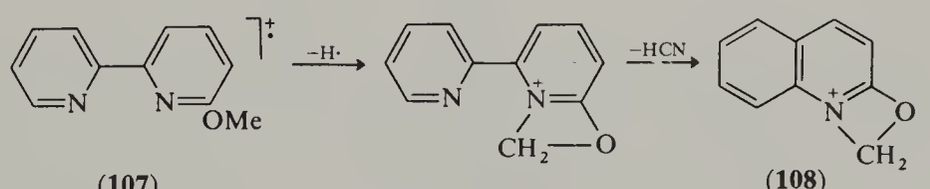
of the pyridine hydrogen atoms, possibly involving positively charged forms of Dewar pyridine (**104**), azaprismane (**105**) and azabenzvalene (**106**), by analogy with the photochemistry of pyridine. However, simultaneous ^{13}C and ^{2}H labelling of pyridine indicates that this cannot be the full picture, because the carbon and hydrogen atoms scramble independently ⟨72JCS(P2)1363⟩, although pentaphenylpyridine fluorine labelling, using alternative *p*-FC_6H_4 groups, reveals that the phenyl groups retain their positional identity ⟨70JOC793⟩. Open chain molecular ions for decomposing pyridine structures have also been proposed, while for methylpyridines, azatropylium cations may be involved, arising from azabenzyl cations ⟨B-71MS364⟩. ^{13}C and ^{15}N labelling in 2-, 3- and 4-cyanopyridine ⟨79OMS524⟩ shows that initially all three molecular ions become equivalent, firstly through cyano migration, involving Dewar pyridine, azaprismane and azabenzvalene rearrangements, and possibly also stepwise migration of CN around the ring, followed by equilibrated interchange of ring carbons at positions 2, 4 and 6 *via* Dewar pyridines. HCN loss occurs subsequently, predominantly from the ring, both open chain and Dewar structures being involved as shown in Scheme 1, with the fate of the CN group being indicated by ^{15}N labelling.



Scheme 1

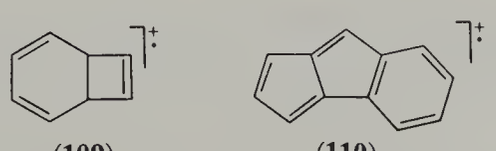
Note the key role of the 2-cyanopyridine ion in promoting the course of the subsequent fragmentation. Proximity effects in 2-substituted pyridines are often instrumental in dictating the nature of decomposition on electron impact, for example in 2-dimethylaminopyridine ⟨68TL3689, 73CS(3)139, 74JOC285⟩ and in other amino, chloro, and -one derivatives ⟨68JHC647⟩.

Polycyclic derivatives of pyridine display a number of interesting rearrangements and readjustments of structure in the MS tube. As we have seen for other pyridine derivatives above, 2,2′-bipyridyls, *e.g.* molecular ion (**107**), readily lose HCN to give quinoline derivatives, *e.g.* (**108**) ⟨76JHC369, 76JHC513, 77JHC551, 77JHC545, 79JHC1431⟩.



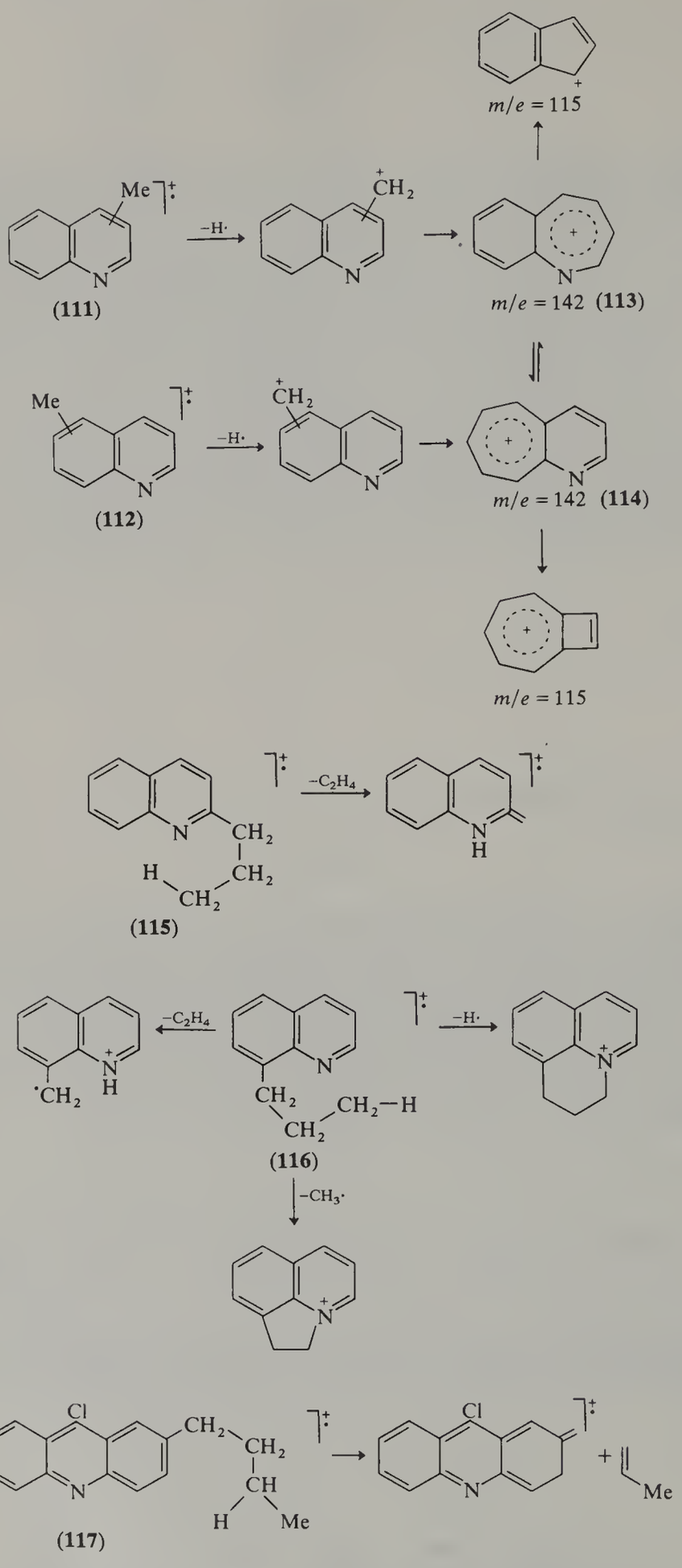
(107) (108)

Both quinoline and isoquinoline molecular ions lose HCN to yield radical cation (**109**), while loss of HCN from acridine gives structure (**110**) ⟨B-71MS364⟩.

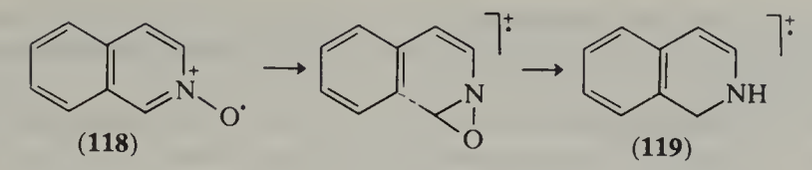


(109) (110)

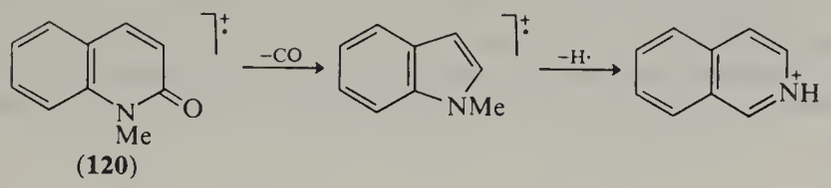
Methylquinoline radical cations (**111**) and (**112**) may involve azabenzotropylium (**113**) or pyridotropylium cations (**114**) in their decomposition routes ⟨67JOC997⟩, while McLafferty rearrangements are well represented, for example where three-carbon side chains (or longer) are present ⟨67JOC997, B-71MS364⟩, as shown for molecular ions (**115**), (**116**) and (**117**).



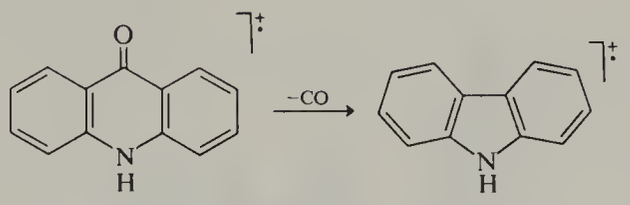
For pyridine *N*-oxides, direct oxygen loss may occur, but for quinoline and isoquinoline *N*-oxides (**118**) a 1,2-shift is an alternative, giving the corresponding -one radical cation (**119**) ⟨68T3139⟩, while -one derivatives themselves readily lose CO, as shown for *N*-methylquinolin-2-one (**120**) and acridinone (**121**) molecular ions ⟨67AJC1179, B-71MS364⟩.



(118) (119)

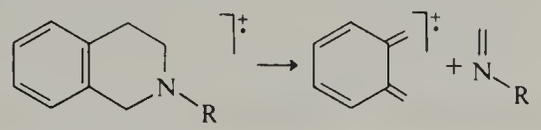


(120)



(121)

Retro-Diels–Alder decompositions may be encountered in the fragmentation patterns of reduced polycyclic pyridine derivatives, as in 1,2,3,4-tetrahydroisoquinoline and its *N*-acetyl derivative (**122**) ⟨78HCA1730⟩. Other studies leading to details of tautomerism are discussed in the relevant section (2.04.4).



R = H, COMe

(122)

Finally in this section, we refer to classic studies on gas phase interactions carried out with a pulsed electron beam high ion source mass spectrometer, which have yielded details of hydrogen bonding of substituted pyridinium ions to water in the gas phase ⟨79JA1675⟩. These measurements afford thermodynamic data for the stepwise hydration of pyridinium ions $XC_6H_4\overset{+}{N}H(OH_2)_n$ for values of n varying between 0 and 4. The attenuation of substituent effects is much less than for aqueous solution, because although the water molecules cluster round $\overset{+}{N}H$ in the gas phase, they cannot provide an overall solvation network, the dielectric constant of which in the liquid phase serves to reduce the influence of the substituent dipole.

2.04.3.6 Photoelectron Spectroscopy

If a photon of frequency ν collides with a single molecule, electrons may be ejected, the energy of which depend on the orbitals they occupy, as well as on ν. These ejected electrons are known as photoelectrons, and the determination of their spectrum of energies is known as photoelectron spectroscopy. Measurement of such spectra enables determination of ionization potentials, and these by Koopmans' theorem ⟨34MI20400⟩ are equated to the energies of filled orbitals, thus apparently constituting a direct method of evaluation of molecular orbital energy levels. The values obtained may be used to check theoretical calculations of such energy levels, so that they constitute a direct test of our theories of molecular bonding.

The ionization potentials are several electron volts even for the outermost valence electrons, and thus it is necessary to work in the UV region of the spectrum. Commonly, the necessary light is generated by a discharge through helium, which gives a band at 584 Å, corresponding to a photon energy of 21.24 eV. If the electrons to be studied lie in the core of the molecule, more energy is required to force them out, and in this case X-rays are employed, sources frequently used being chromium (5400 eV) and aluminum (1490 eV). These core electrons are too tightly bound to be influenced by the outer valency electrons involved in bonding. They are thus characteristic of the individual atoms and give information on the elements present. This mode of analysis is thus known as ESCA (electron spectroscopy for chemical analysis); it is not particularly relevant in a section on the structure of pyridine

and derivatives, and thus we concentrate here mainly on UV PE spectroscopy. A good general account of PE spectroscopy has been given, as well as of its application to heterocyclic molecules ⟨74PMH(6)1⟩.

Figure 18 gives the PE spectrum of pyridine ⟨72HCA255⟩. The diagram consists of a plot of electron current incident on the detector in counts per second *vs.* kinetic energy of these electrons, which is proportional to the ionization potential of the electrons.

The main bands which can be assigned to energy levels in the pyridine molecule are numbered; it can be seen that they are complicated by vibrational fine structure, although these can sometimes be resolved, and may indeed aid in the assignment and interpretation of the bands.

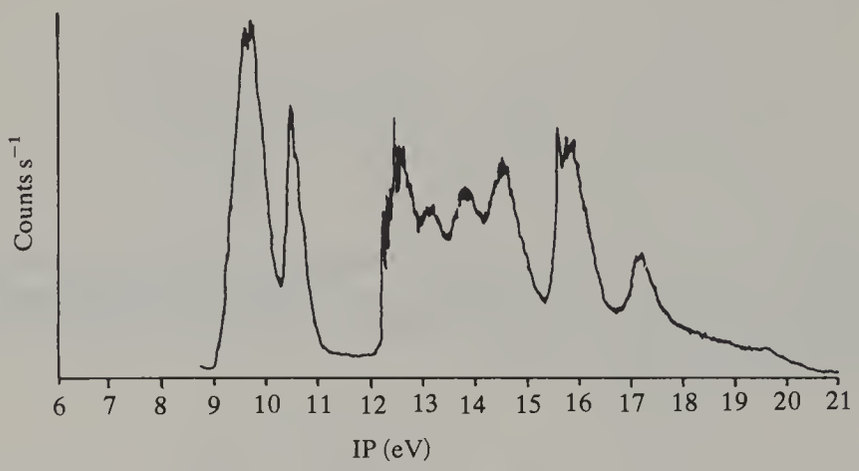


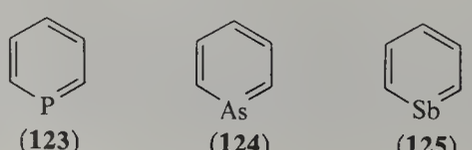
Figure 18 PE spectrum of pyridine (Reproduced with permission from ⟨72HCA255⟩)

These bands may be compared to those in benzene, in particular those which correspond to the highest occupied degenerate pair, bands 2 and 3 in Figure 18. The energy may be calculated by simple Hückel MO theory using the Coulomb integral of $\alpha_C+\delta\alpha_N$, where $\delta\alpha_N=-3.3$ eV, for the nitrogen atom, and $\alpha_C+\frac{1}{3}\delta\alpha_N$ for adjacent carbon atoms, with the second term accounting for the inductive effect of the adjacent nitrogen atom. This gives almost perfect agreement with experiment ⟨72HCA274⟩. This is shown in Table 12, where

Table 12 Calculated and Experimental Energy Levels in Pyridines and Related Aromatic Compounds

Compound	*IP (expt.)*	*IP (calc.)*
Pyridine	9.73	9.68
	10.50	10.43
Benzene	9.24	9.16
Pyridazine	10.61	10.57
	11.30	11.32
Pyrimidine	10.41	10.57
	11.39	11.32
Pyrazine	10.18	10.19
	11.77	11.70

benzene, pyridine and the three diazabenzenes are compared. Comparison of the ionization potentials of pyridine with benzene and with phosphabenzene (**123**), arsabenzene (**124**) and stibabenzene (**125**) further enables the assignment of all five bands in Figure 18 to their electron (σ, π or n) and symmetry class. These are 9.7 eV, lone pair electrons; 9.8 eV, π-electrons; 10.50 eV, π-electrons; 12.5 eV, σ-electrons; 12.6 eV, π-electrons ⟨74PMH(6)1⟩.



(**123**) (**124**) (**125**)

They are illustrated, together with orbital designation, in Figure 19. Figure 20 gives the drawings for these and the remaining MO's in pyridine ⟨B-73MI20400⟩. It must be noted that in this latter figure the energies were calculated by the SCF method ⟨68JCP(48)953⟩, and agreement with the calculations previously given is relatively good.

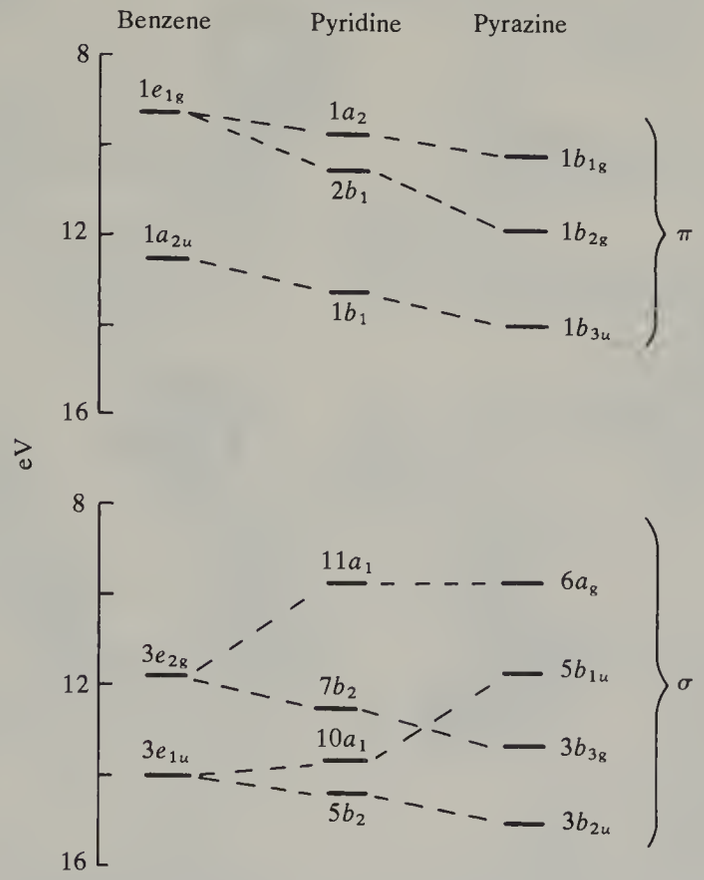
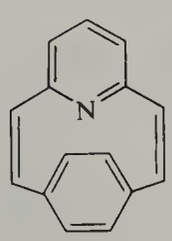
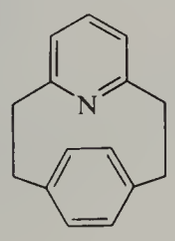


Figure 19 Ionization energies of the upper orbitals of benzene, pyridine and pyridazine. The assignments and correlations are tentative. The point group of pyrazine is D_{2h} and that of pyridine is C_{2v} (Reproduced with permission from ⟨B-78MI20410⟩)

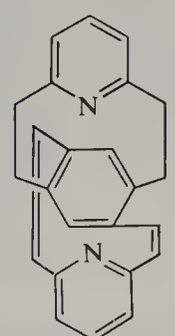
Murrell ⟨72JCS(D)564⟩ has corroborated these assignations by examination of the series pyridine, 2- and 3-fluoropyridine, 2,4- and 2,6-difluoropyridine, 2,4,6-trifluoropyridine and pentafluoropyridine. Calculations of LCAO coefficients for pyridine as carried out by various workers are well summarized in this paper, and the different methods found to give quite large differences for the π_2 level. The PE spectrum of pyridine as well as of other azabenzenes has been correctly predicted ⟨79MI20408⟩ using *ab initio* many-body Green's function calculations, showing rather significantly that Koopmans' approximation turns out to be useless for this purpose. Confirmation of the assignment of the first and fourth band of pyridine has also been provided by a study of the angular distribution of the PE spectra of pyridine, pentafluoropyridine and 2,6-lutidine ⟨78BCJ3482⟩. The PE spectra of 2- and 4-*trans*-styrylpyridines and 4-OMe-, 4-Me-, 4-Br- and 4-NO_2-3-styrylpyridine as well as the parent molecule have been correlated with CNDO and PMO calculations ⟨75JCS(F2)1583⟩. In these compounds the substituent effect on the first ionization potential is much lower than the influence of substituents on benzene ionization, as in the former case it is spread over a much larger π-system. The related structures (**126**) and the saturated partners (**127**) together



(**126**)



(**127**)



(**128**)

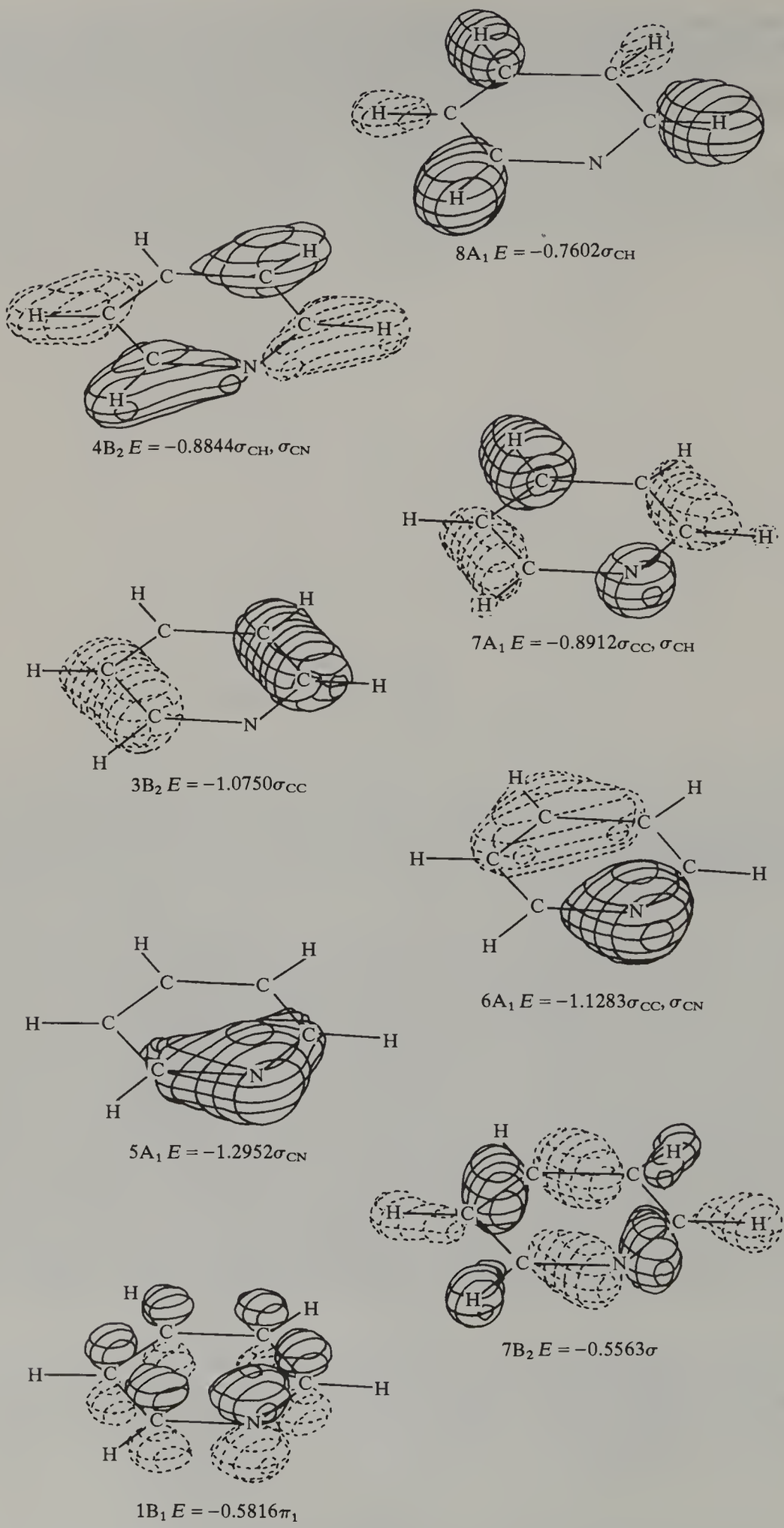
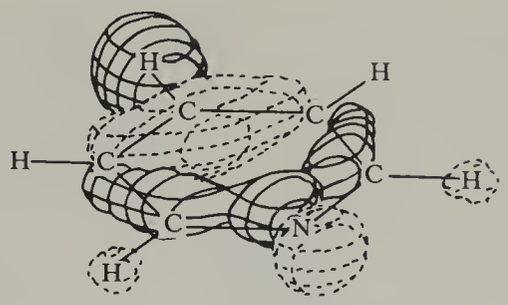
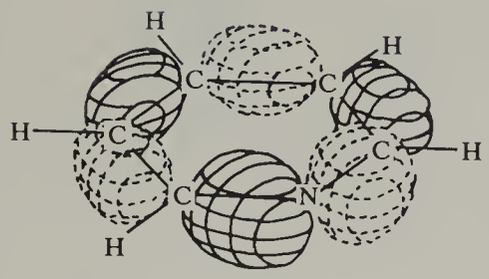


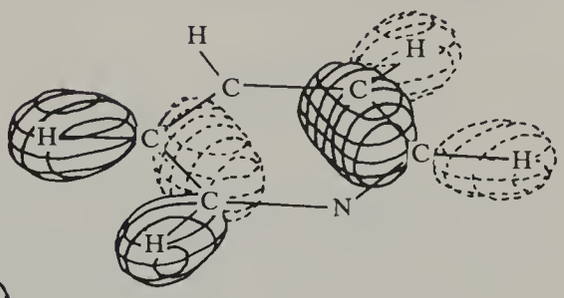
Figure 20 MO drawings for pyridine. Energies are in a.u. (1 a.u. = 27.21 eV) (Reproduced with permission from ⟨B-73MI20400⟩).



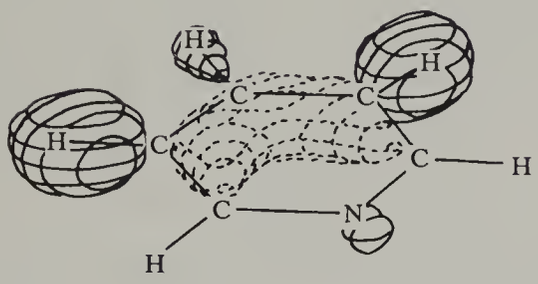
$10A_1\ E = -0.6193\sigma$



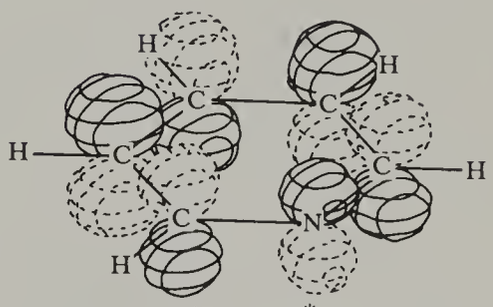
$6B_2\ E = -0.6483\sigma_{CN}, \sigma_{CC}$



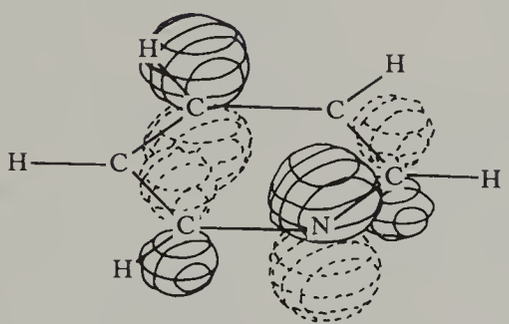
$5B_2\ E = -0.6914\sigma_{CC}, \sigma_{CH}$



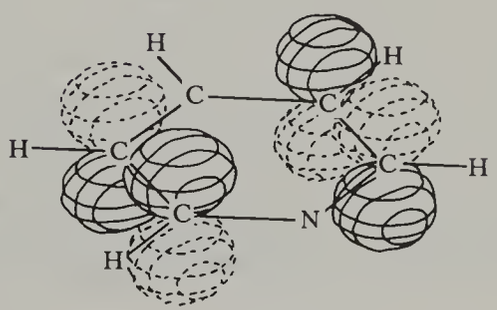
$9A_1\ E = -0.6945\sigma_{CC}, \sigma_{CH}$



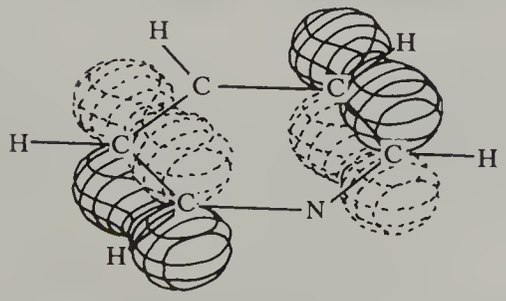
$4B_1 \quad \pi_6^*$



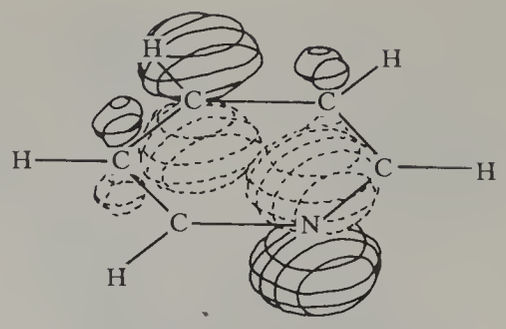
$3B_1\ E = 0.1107\pi_5^*$



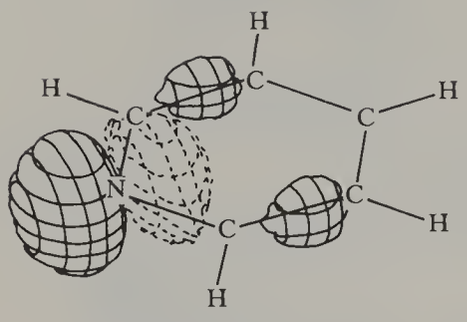
$2A_2\ E = 0.1099\pi_4^*$



$1A_2\ E = -0.4062\pi_3$



$2B_1\ E = -0.4260\pi_2$



$11A_1\ E = -0.4425n$

Figure 20 (*cont.*)

with various methylated derivatives were found to give PE spectra in good correspondence with one another and with no unusual features ⟨79JA2121⟩. There was thus no evidence for interactions between the benzene π-electrons and the pyridine π-electrons or lone pairs in these compounds, although temperature-dependent NMR measurements showed that in saturated derivatives (**127**) the pyridine and benzene rings were parallel to each other, whereas for dienes (**126**) the two rings are mutually perpendicular. The triple-layered cyclophane (**128**) did show a remarkably low first ionization potential of 6.97 eV; X-ray crystallographic examination showed that the central benzene has a twist-boat conformation, with the pyridine rings bent 15° from true perpendicularity with it.

The PE spectra of hydroxy- and mercapto-pyridines have been examined, together with the model *N*-alkyl and *S*- or *O*-alkyl compounds, to elucidate the tautomeric equilibria in the vapor phase ⟨77JCS(P2)1652⟩ (Section 2.04.4.2). Figure 21 and Table 13 show details of the PE spectra of 1-methylpyridin-2-one, 2-methoxypyridine and the tautomeric mixture at equilibrium of pyridin-2-one and 2-hydroxypyridine. This indicates that there is approximately 25% of oxo form present; once adjustment has been made for the expected influence of methylation, similar measurements reveal *ca.* 10% of the thione form in the mercapto–thione equilibrium. Other spectra indicate that 3- and 4-hydroxy- and 3- and 4-mercapto-pyridine exist in the vapor phase with less than 5% of the alternative tautomer present.

A good deal of attention has been directed at the PE spectrum of pyridine *N*-oxide. We have already referred to the correlation between various MO calculations and the PE spectrum of this compound (Section 2.04.1). Initial assignments ⟨74TL1709⟩ of the bands for pyridine *N*-oxide were subsequently corrected ⟨74TL2987, 74JCS(F2)1991⟩, and it was shown for a series of substituted *N*-oxides that the substituent effects were easily discernible because the first four or five bands showed clear separations. The first three bands are ascribed to π_O, σ_O and π-electron transitions respectively, and the ionization energies of all three showed correlations with MINDO/2 calculations, dipole moments and Hammett σ or σ^+ substituent constants. Such substituent effects on PE spectra, as well as UV spectra and dipole moments, may be correlated with modified PPP, IEH (iterative extended Hückel) and MINDO/2 MO calculations ⟨81JST(71)253⟩; these calculations also include data for 4-nitroquinoline *N*-oxide. Other dipolar structures studied included the imines (**129**) and

Table 13 PE Spectra of 1-Methylpyridin-2-one, 2-Methoxypyridine and Pyridin-2-one/2-Hydroxypyridine Tautomeric Mixture

Compound	*Ionization potential*							
1-Methylpyridin-2-one	8.41π		9.54n		10.42π		11.63π	
2-Methoxypyridine	8.82π		9.82n		10.20π		11.45π	
Pyridine-2-one–hydroxypyridine	8.62π	9.11π	9.77n	10.08π	10.48π	10.78π	11.72π	12.22π

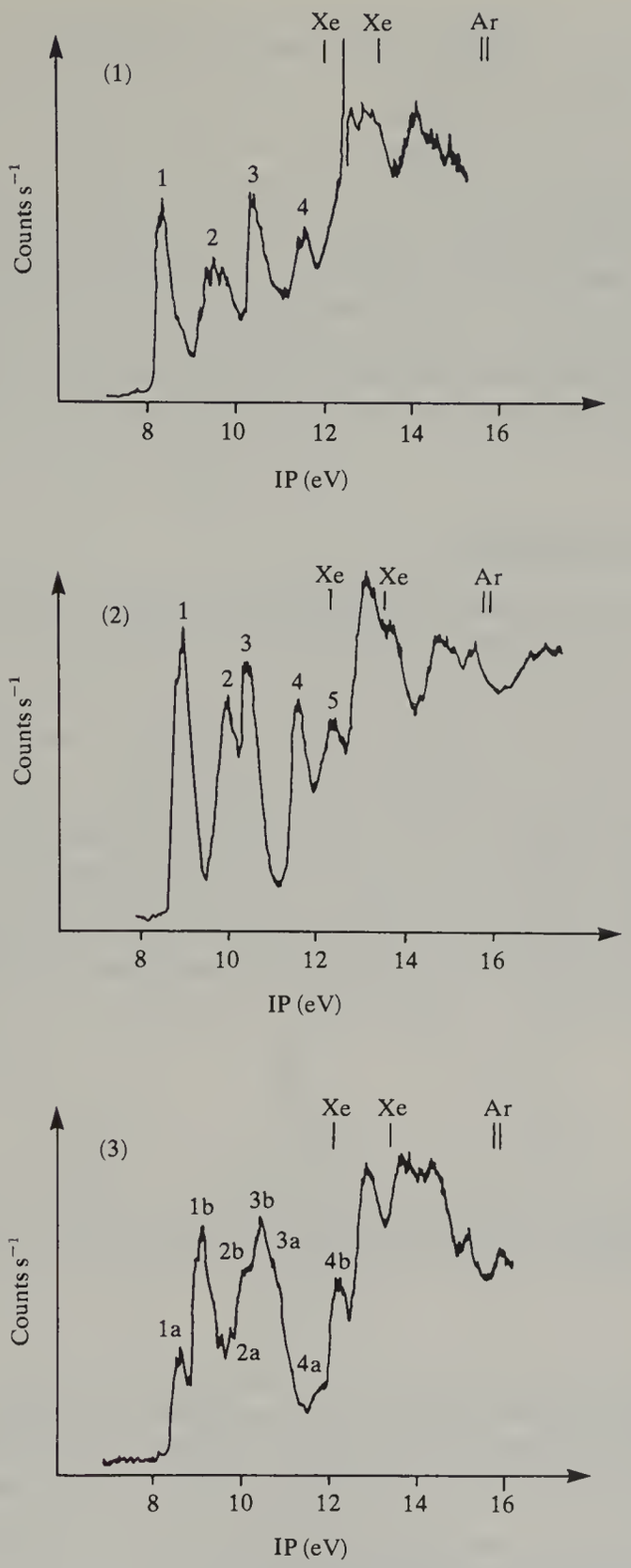
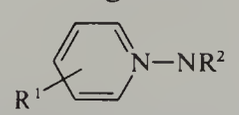
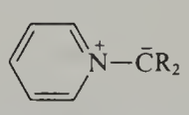


Figure 21 (1) PE spectrum of 1-methylpyridin-2-one; (2) PE spectrum of 2-methoxypyridine; (3) PE spectrum of the mixture at equilibrium of pyridin-2-one and 2-hydroxypyridine (Reproduced with permission from ⟨77JCS(P2)1652⟩)

ylides (**130**) ⟨75T2909⟩. From the binding energies of the 1*s* electrons in an ESCA determination it was deduced that the negative charge resides entirely on N in structures (**129**), but is delocalized on to the electronegative substituents in (**130**).



(**129**) R^1 = H, Me, CO_2Et
R^2 = COPh, SO_2Ph, CO_2Et, CO_2Pr^i, Tos

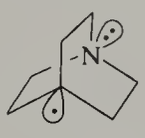


(**130**) R = CN, CO_2Et

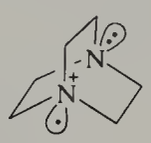
For the application of PE spectroscopy to conformational questions in piperidine derivatives, little information is available. For example, no conclusion can be drawn as to the conformational equilibria in piperidine, or *N*-chloro- or *N*-bromo-piperidine ⟨79AJC475⟩, because of the broad overlapping character of the bands. The spectra do, however, confirm the NQR experiments that indicate that in the chloro compound the N—Cl bond is polarized towards Cl with an excess charge of 0.20 electrons ⟨56JCP(25)1286, 65T1095⟩. A comparison of the PE spectra of azaadamantane and quinuclidine reveals no large differences ⟨74HCA546⟩, although ^{15}N–^{13}C NMR couplings do suggest a difference in through-space interactions (Section 2.04.3.1, Table 9). The vertical lone pair ionization potentials for 15 4-substituted quinuclidines ⟨74HCA546⟩ show a good correlation with pK_a values for the quinuclidinium ions, however, and thus with substitutent parameters σ^* or σ_I, which measure group inductive effects. The substituents appear to exert their influence on the ionization potential by virtue of their dipole moments, but the rationale of the ionization potential–pK_a correlation is obscure.

2.04.3.7 Electron Spin Resonance

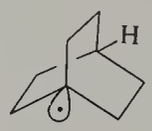
Electron spin resonance or electron paramagnetic resonance occurs when the spin magnetic moment of the odd electron in a radical couples with an applied radiation field in the microwave region. The radical may be present in the gas phase, as a solid, or in solution (which can be very dilute). The spectra reveal hyperfine structure which arises from the presence of nuclear magnetic moments. This gives important information. It may be used as a fingerprint to disclose the identity of the radical present, and it also bears testimony to the type of molecular orbital that the unpaired electron occupies. For example, the hyperfine coupling constant α^N for the quinuclidin-4-yl radical (**131**) (generated at −80 °C in cyclopropane from the bromide by photochemically produced alkyltin radicals) is 1.80. This can be compared with a corresponding value of 16.96 for (**132**), indicating no spin delocalization to the N atom in (**131**), but extensive delocalization between the two N atoms in radical (**132**) ⟨79JA3409⟩. This is further substantiated by an undetectably small value for α^H for the γ-position of (**131**), compared with a corresponding value of 0.89 for radical (**133**).



(**131**)



(**132**)



(**133**)

There is a relationship (the McConnell equation) between the unpaired electron density on a given atom and the polarization interaction with each attached proton:

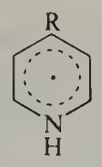
$$\alpha^H = Q^H \rho_\pi \tag{5}$$

Here α^H is the hyperfine splitting, Q^H is the value of α^H for $\cdot CH_3$ (−23 G) and ρ_π is the spin density. McLachlan ⟨60MI20400⟩ has used the Hückel approximation (which gives just as reliable results as SCF theory in this case) to calculate the electron spin distribution in π-electron radicals, and this method has frequently been used by subsequent workers, as we shall see.

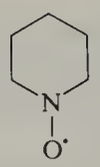
Equation (5a) governs the magnitude of the magnetic field which must be applied for resonance at the frequency ν to take place.

$$h\nu = g\beta H_0 \tag{5a}$$

Where β is the Bohr magneton and both this and h are fundamental constants; H_0 is the applied magnetic field. Factor g is 2.0023 for the free electron and ranges from 1.9 to 2.1 for the particular paramagnetic species under investigation. It yields information on the extent of odd electron delocalization within heterocycles. For *p*-substituted 1-hydropyridinyl radicals (**134**) in isopropanol/acetone at room temperature, for example, the g values vary as follows with changing electronic character: Bu^t, 2.0029; Et, 2.00288; Ph, 2.00278; NO_2, 2.00472; NO_2^- (anion radical with KOH), 2.00491; CO_2H, 2.00331 ⟨78JMR(32)353⟩. This work also shows that in this particular case spin densities calculated from equation (5) do not correlate with McLachlan spin density calculations.



(134)



(135)

Line widths and line broadening can also give important details of rate processes such as ring inversion, as for example, in the ring inversion of piperidine nitroxide (**135**) ⟨74PMH(6)95⟩, leading to an estimation of the enthalpy of activation $\Delta H^{\neq}$ as 22.6 kJ mol^{-1} for this process ⟨69JCP(50)2630⟩. The relevant spectra are shown in Figure 22, and we give these results in detail because they afford a nice example of the interpretation of ESR phenomena. At −103 °C the rate of inversion is slow compared with the ESR time scale, and the molecule is frozen in one conformation. The spectrum results from hyperfine coupling to N to give three equal intensity lines and to the axial and equatorial β protons to give two sets of triplets with intensity ratio 1:2:1, but with widely different coupling constants. The total of 27 lines expected are not all observable due to some overlapping. Each line is further split into a 1:3:3:1 quartet attributed to equal coupling to two γ and one δ proton. At 110 °C the rate of interconversion is sufficiently rapid to average couplings to axial and equatorial β protons, and thus each N line is split into a 1:4:6:4:1 quintet. Again overlapping occurs to reduce the number of lines observed from fifteen to thirteen.

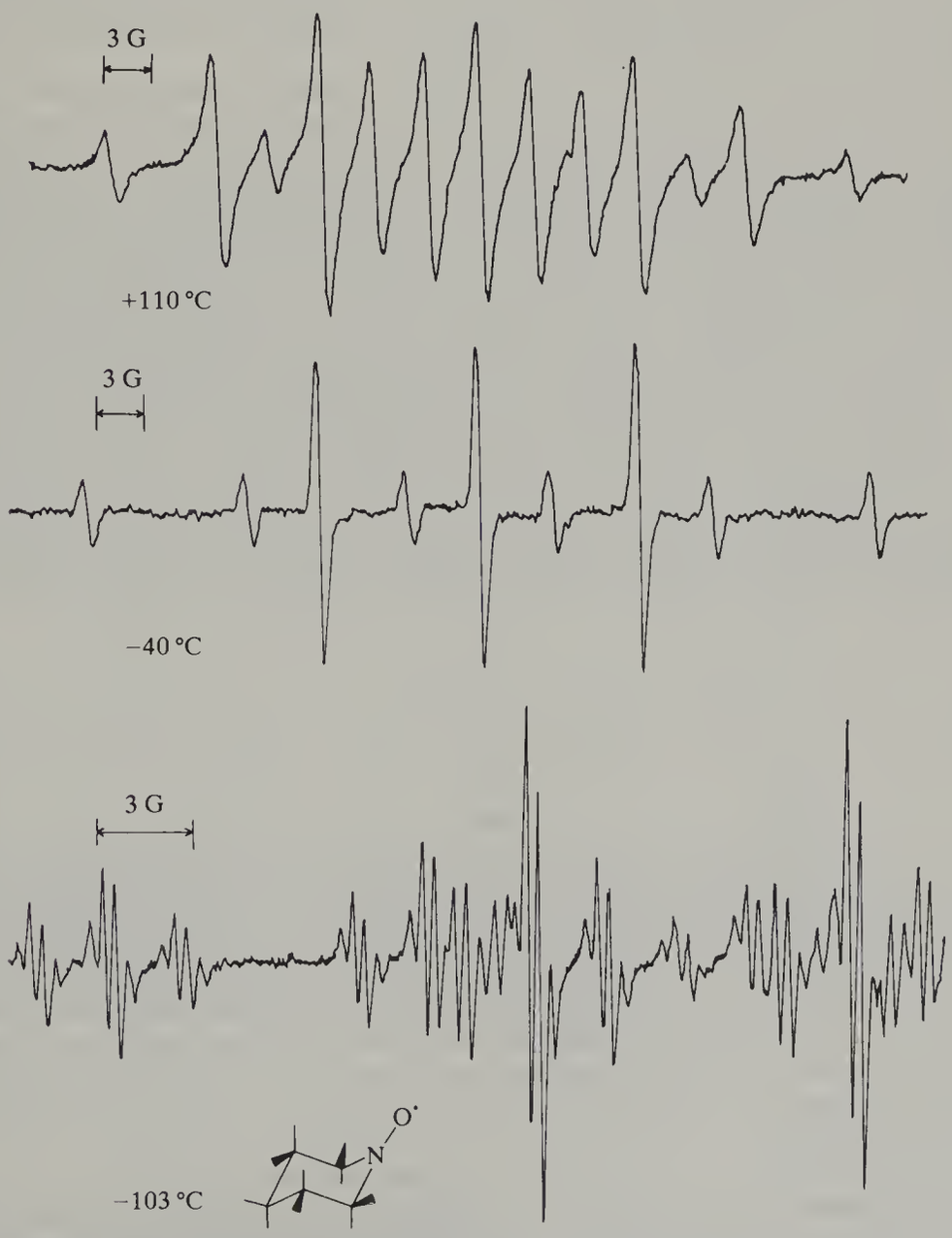


Figure 22 ESR spectra for piperidine nitroxide at different temperatures. Note that only the left half of the spectrum is shown for −103 °C to better illustrate the γ- and δ-proton hyperfine coupling. For the other two temperatures the complete spectra are shown (Reproduced with permission from ⟨69JCP(50)2630⟩)

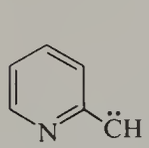
At −40 °C the spectrum corresponds to an intermediate rate of interconversion. The outer lines and four of the six components of the central line retain the same spin assignment upon ring inversion and remain fixed and narrow, while the remaining lines broaden and disappear.

The ENDOR technique refers to electron–nuclear double resonance. This consists of the effect on a partially saturated ESR line of simultaneously irradiating the sample with a radiofrequency to induce nuclear resonance transitions of hyperfine coupled nuclei. It may enable one to obtain information about signs of coupling constants. ELDOR is the technique corresponding to electron–electron double resonance. Such techniques, coupled with TRIPLE resonance, have been utilized and well described in a discussion of pyridine and 4,4-bipyridyl radical anion ESR spectra measured in sodium/liquid ammonia ⟨80JMR(41)17⟩.

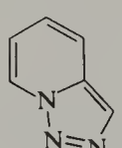
The subject of ESR spectroscopy of heterocyclic radicals has been the topic of a previous review ⟨74PMH(6)95⟩. We consider here mainly the results which have appeared subsequently, and also draw attention to a fine review by Hansen ⟨79AHC(25)205⟩. Neutral heteroaromatic radicals require stabilization by delocalization of the odd electron, or they may be generated by continuous *in situ* photolysis, or trapped in an inert matrix, and examples of these techniques have been discussed ⟨74PMH(6)95⟩.

The ESR hyperfine coupling constants have been established experimentally ⟨67MI20402⟩ for the pyridinyl radical (**134**; R = H) and deuterated analogues, produced by γ irradiation of a solid solution of pyridine in ethanol at 77 K, but the signs of the couplings are not known experimentally and are made solely on the basis of Hückel MO calculations. INDO MO calculations on this radical, together with the radical anions of quinoline, isoquinoline and acridine have also been carried out ⟨74OMR(6)5⟩.

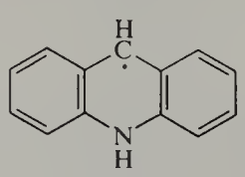
The ESR spectrum of triplet 2-pyridylmethylene (**136**) has been observed ⟨78JA6245⟩ when phenyl azide or the triazolopyridine (**137**) matrices in argon at 10 K are irradiated. Irradiation of 3- and 4-diazomethylpyridine gives the corresponding 3- and 4-pyridylmethylenes; the former exists in two conformational forms, both of which are observed, but only one of the two possible conformers is observed for 2-pyridylmethylene, presumably because of preferential stabilization by the adjacent nitrogen atom. The polarized absorption and ESR spectrum of the acridine *C*-radical (**138**) have been measured ⟨78MI20406⟩ at room temperature, the radical having been produced at 77 K by irradiation in polyvinyl alcohol film. The absorption spectrum is shown to be quite different to that of the *N*-radical (**139**) ⟨69BCJ1197⟩, and this is in good agreement with MO calculations. The radical is dark red; between 0 and 20 °C there is no change in the ESR spectrum, but at 30 °C the intensity of the spectrum decreases and at the same time the colour disappears. Temperature effects have also been studied in the case of the radical anion of 4-cyanopyridine. 4-Cyanopyridine reacts with alkali metals at −70 °C to give red solutions in which the hyperfine splittings are broadened by a dynamic process which appears to involve the cation 'jumping' from the vicinity of one nitrogen atom of the radical anion to the other ⟨78MI20402⟩.



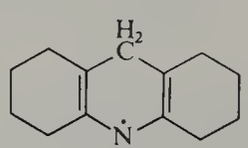
(**136**)



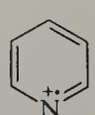
(**137**)



(**138**)



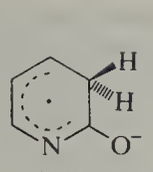
(**139**)



(**140**)

The elusive radical cation of pyridine (**140**) has been obtained by irradiation of pyridine in $CFCl_3$ at 4 K ⟨79MI20403⟩ and *g* values and hyperfine coupling constants have been measured for the parent molecule and deuterated derivatives. This species is of σ-type, the odd electron spending most of its time in the N sp^2 'lone pair' orbital. Radical cations and anions of pyridinium bis(alkoxycarbonyl)methylides have been produced: in the former case ⟨78CC817⟩ as a cyclopropenone complex, and in the latter by reduction of pyridinium bis(methoxycarbonyl)methylide with sodium ⟨79JMR(35)171⟩. The coupling constants in the ESR spectrum of both the radical cation and the anion agree to some extent with simple Hückel MO calculations.

The anions of 2- and 4-hydroxypyridine were generated by irradiation in argon matrices at 4 K in the presence of sodium atoms ⟨74JA2342⟩. They were found to exist in the keto forms (**141**) and (**142**), probably due to the resulting stabilization of the negative charge by both O and N. The 3-hydroxypyridine anion, however, is in the hydroxy form (**143**); here the negative charge on O in the alternative anionic keto forms (**144**) and (**145**) cannot be communicated to N.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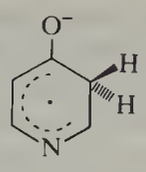
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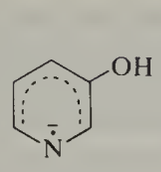
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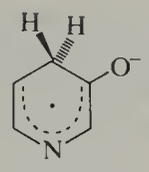
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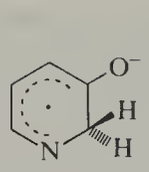
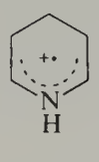

(145)

ESR of phosphorescent triplet states of 2,2′-bipyridyl, and its methylated derivatives, and 2,2′-biquinolyl have been studied at 77 K in ethanol glasses and all shown to be in the (*E*) conformation ⟨80BCJ890⟩. The ESR spectra of 1-aza- and 4-aza-phenanthrene, together with the cation of the latter can also be observed, in its lowest molecular triplet state, by continuous irradiation in rigid glasses at 153 K ⟨74MI20400⟩. The technique of continuous irradiation, this time in the case of the pyridinium cation, shows the possibility of a transannular bond being formed in glassy solutions with concentrated hydrochloric acid at 77 K. The resultant structure (**146**) and its mechanism of formation from pyridinium cations or by photolysis of azacyclohexadienyl radicals (**147**), derived by photolysis of 2- or 4-polyvinyl pyridines, has been examined ⟨74JPC899, 74CC579,′ 76JCS(F1)143⟩. The spectral characteristics were checked by INDO MO calculations, and the formation of (**146**) shown to involve an azaprismane ammonium radical intermediate (**148**), by experiments involving various deuterated derivatives.


(146)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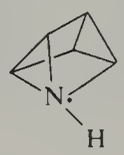
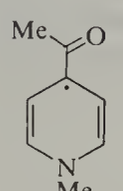

(148)

The three 1-hydropicolinyl radicals can be produced at room temperature by photoreduction of picolines in isopropanol/acetone ⟨75MI20400⟩. Hyperfine coupling constants have been assigned using McLachlan MO calculations, but INDO calculations did not give good agreement with experiment. A good deal of interest has centred on pyridyl and pyridinyl radicals because of the marked effect of solvent on their ESR spectra. For example, the ESR spectra of 1-hydropyridinyl radicals (**134**), on whose *g* values we have commented earlier, produced transiently by photochemical reduction in isopropanol, acetone and water mixtures, show variable *g* values and hyperfine couplings as the water content is changed ⟨78JMR(31)69⟩, for cases where R = HCO and MeCO. McLachlan MO calculations revealed that the solvent effect was due to the redistribution of π-spin population produced by hydrogen bonding between the carbonyl oxygen atom and water molecules.

The 4-acetyl-1-methyldihydropyridyl radical (**149**) also shows large variations of hyperfine splitting constants with solvent, which were explained in terms of resonance ⟨77JCS(P2)943⟩. Solvents of low polarity encourage non-polar canonical forms such as (**150**) and (**151**), which are distinguished by large spin densities at the 2- and 6-positions, whereas polar solvents promote zwitterionic canonical forms such as (**152**), which show increased methyl and 3- and 5-position couplings. This solvent-induced variation by THF, HMPA, DMSO, MeOH and H_2O in spin density leads to a good correlation of ring proton splittings with Kosower *Z* values (see Section 2.04.3.3), while the hyperfine splitting constants of the 4-methoxycarbonyl-1-methyldihydropyridyl radical ⟨78JPC2739⟩ correlated with Dimroth–Reichardt $E_T(30)$ values (see Section 2.04.3.3) for a very wide variety of solvents of apolar, dipolar protic and protic types. Other dihydropyridyl radicals exhibit solvent induced variation in characteristics. For example, the stability of the 4-cyano-1-methyldihydropyridyl radical is profoundly influenced by solvent; apolar solvents stabilize it, but polar solvents promote its decay to the cation radical (**153**) ⟨77JCS(P2)943⟩.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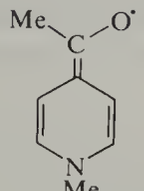
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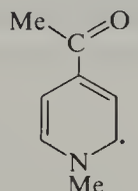
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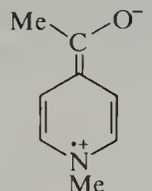
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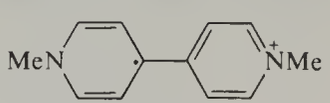
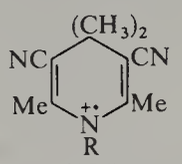
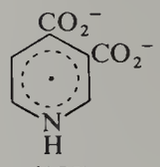

(153)

The significance of 1,4-dihydropyridine derivatives in reduction of biological substrates involving the intermediacy of a radical cation has led to much interest in such species. Such radical cations (**154**) have been generated by electrolytic oxidation in aqueous acetonitrile

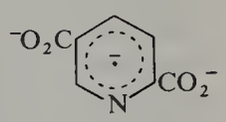
at 24 °C ⟨77TL2725⟩, and the influence of R on their stability and thus the intensity of their ESR spectra have been studied. All nine possible mono- and di-carboxy-1-hydropyridine anion radicals, *e.g.* (**155**), have been formed by photolytic reduction of anions of pyridinecarboxylic acids in alkaline aqueous acetone and/or alcohol solution at room temperature ⟨76JMR(21)9⟩. Values of *g* varied with the pattern of substitution; hyperfine coupling constants did not correlate well with McLachlan MO calculations. In more strongly basic solution the pyridine proton may be lost, giving trianionic species (**156**), the ESR spectrum of which has been reported ⟨77JMR(25)67⟩; the 3,5-isomer has also been prepared and characterized ⟨79JMR(34)543⟩.



(**154**)



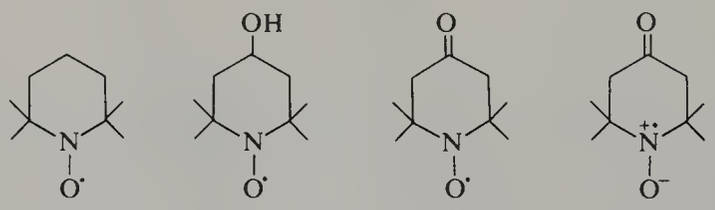
(**155**)



(**156**)

R = Me, CH_2Ph, $CH_2C_6H_4$*p*-Cl, $CH_2C_6H_4$*p*-OMe, $CH_2C_6H_4$*p*-NO_2

Due partly at least to their importance in spin labelling experiments, much attention has been directed at the ESR spectra of nitroxide radicals, particularly 2,2,6,6-tetramethyl derivatives of form (**157**), (**158**) and (**159**) and their derivatives. These studies have included investigation of their structure, including conformation (see previously in this section) and the influence on it of structural variation, particularly at position 4 ⟨71MI20400, 73ZN(B)488, 74JPC1410, 74MI20406, 75TL1469, 79MI20403, 79JCR(S)106, 80IZV413⟩, and complex formation ⟨79MI20406, 80MI20404⟩.



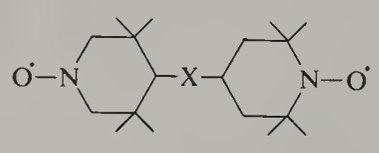
(**157**) (**158**) (**159**) (**160**)

Solvent interactions, in both organic and aqueous media, are also of interest ⟨74MI20401, 77MI20400, 77MI20404, 79MI20404, 80IZV449⟩. Thus, for nitroxide (**159**) containing labelled oxygen, the α^{14N}, α^{17O} and *g* values vary as solvent polarity is varied ⟨73JPC72⟩. Effects favouring dipolar structure (**160**) over (**159**) will lead to an increase in α^{14N} and a decrease in α^{17O}, associated as they are with the unpaired electron density at N and O respectively, thus producing the observed variations as given in Table 14. The small decrease in *g* is associated with the diminution of spin density on the oxygen atom with increasing solvent polarity.

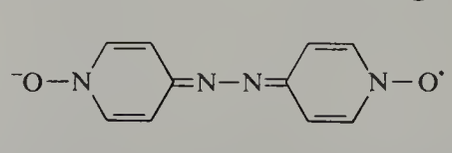
Table 14 Solvent Effects in ESR Spectra of 2,2,6,6-Tetramethylpiperidin-4-one *N*-Oxide (**159**)

Solvent	*g value*	α^{11N}(G)	α^{17O}(G)
Benzene	2.0062	14.45	19.29
DMF	2.0062	14.66	19.40
Bu^nOH	2.0060	15.01	19.11
$HCONH_2$	2.0060	15.28	18.88
$(CH_2OH)_2$	2.0061	15.40	18.72
H_2O	2.0058	16.01	17.86

Alkoxy nitroxide radicals (**161**) have been formed, and structurally characterized by ESR, from photolyses of nitropyridines in triethylsilane ⟨77JCS(P2)1132⟩. In other significant work,



(**161**) X = $-C{\equiv}C-C{\equiv}C-$
p-$C{\equiv}C-C_6H_4-C{\equiv}C-$
$-C{\equiv}C-Hg-C{\equiv}C-$



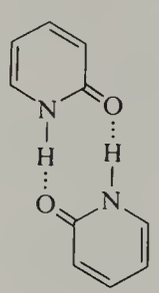
(**162**)

ESR has been used to study new polyyne derivatives of (**157**), in particular spin conduction through the diethynyl and mercury bridges in (**161**) ⟨80IZV128⟩. Radicals from aromatic *N*-oxides may also be useful as spin labels; in this context the anion radical (**162**) of azobispyridine *N*-oxide was studied by ESR ⟨75OMR(7)33⟩.

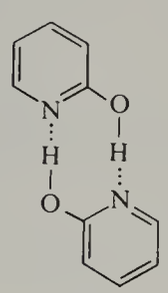
2.04.4 AROMATICITY AND TAUTOMERISM

2.04.4.1 General

The study of tautomerism was given an early impetus by work on the structure of DNA, in which the tautomeric form taken up by the base pairs proved of key importance in deciding the correct structure ⟨B-68MI20401⟩. An article ⟨65CI(L)331⟩ entitled 'Calling a Spade a Spade' emphasized the need to name and represent potentially tautomeric heterocyclic structures in their correct form, but although this requirement remains an important one, the issue is complicated by the fact, recently emphasized by Beak ⟨77ACR186⟩, that the position of tautomeric equilibrium can be very profoundly influenced by the solvent in which the molecules are dissolved, whether polar or non-polar, protic or aprotic, and also compared with the position in the gas phase. Self-association, particularly in non-polar solvents or in the solid state, may also cloud the issue; thus, for example, the dimeric form of pyridin-2-one may be written as in form (**163**) or (**164**). Therefore the correct naming of the compound becomes less certain and lost in rather difficult arguments as to whether there is a true equilibrium between (**163**) and (**164**), with the hydrogens actually 'mobile', and in which case where they spend the majority of their time, or whether the two structures represent canonical forms of a resonance hybrid, in which case the decision must be taken as to which has the greater mixing coefficient. Even if it is decided to name a compound as it exists free from solvent, do we name it as the form assumed by the isolated molecule in the gas phase, or as it is 'in the bottle'? While Katritzky's original point ⟨65CI(L)331⟩ thus remains valid to a considerable extent, additional considerations revealed in this area, particularly by his own group ⟨63AHC(1)311, 63AHC(1)339, 63AHC(2)1, 63AHC(2)27, 70C134, 76AHC(S1)1⟩, and that of Beak ⟨77ACR186⟩ show clearly that the issue is a complex one, and that a prime necessity in specifying a tautomeric structure is to state the conditions under which it has been measured, and also whether in those conditions it exists as a monomer or dimer.

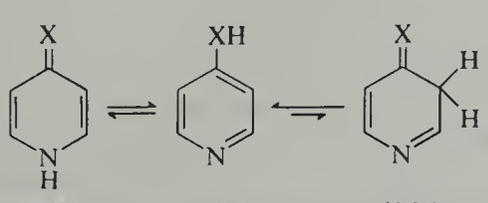


(**163**)

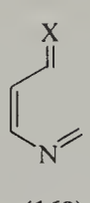


(**164**)

In a description of tautomerism in pyridines and their benzo derivatives there is little need to consider the possibility of transfer of hydrogen from the ring nitrogen to a ring carbon atom, in the ground state neutral molecules, even though this form of tautomerism is of great importance in five-membered ring heterocycles (see Chapters 3.01 and 3.04). This is because the loss of aromaticity of the pyridine ring in form (**167**), for example, is in no way compensated for by the conjugation of structures such as (**168**). Closely analogous structure sequences and reasoning can also, of course, be advanced for the 2-substituted isomers. As we shall see, however, such forms may be of importance in charged excited structures, and also in polyhydroxypyridines.

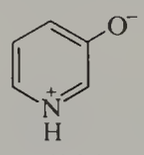


(**165**) (**166**) (**167**)



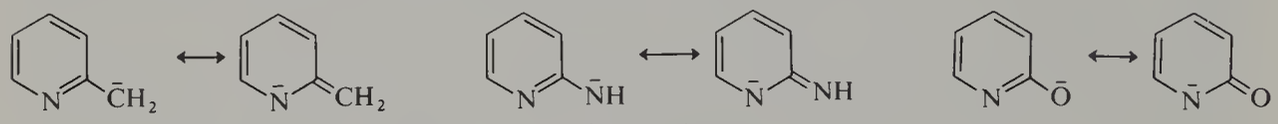
(**168**)

The main area of consideration will therefore be that of tautomerism between forms of type (**165**) and (**166**). Let us consider first the sort of substituents X which can participate in this sort of situation, and secondly what influence the position of the substituent will have. Substituents of the requisite character will be those for which the hydrogen in XH has a measure of acidic character, particularly therefore OH, SH, NH_2 and Me (or amino or alkyl groups in general in which N or C bears at least one hydrogen atom). Where such substituents are in conjugation with the heterocyclic nitrogen, *e.g.* the 2- and 4-position in pyridine, or the 2-, 4-, 6- and 8-positions of quinoline, both tautomeric forms may exist



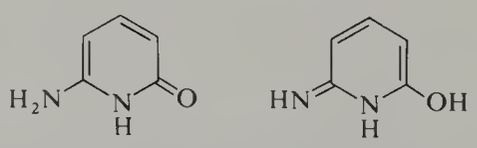
(**169**)

in neutral representations, but in non-conjugated positions, the 3-position of pyridine and the 3-, 5- and 7-positions of quinoline, for example, the *N*-protonated form may only be represented by a zwitterionic structure such as (**169**).



Scheme 2

Considering the anions derived from pyridines with hydrogen bearing substituents at sites conjugated with the ring N (Scheme 2), which will be the more strongly basic site, the ring N or the external C, N or O atom? Clearly as one moves to the right along the Periodic Table in providing the atom directly joined to ring C in the substituent, one should expect more of the form protonated on the ring N at equilibrium. To a considerable extent this situation is in practice realized. However, the question is not as simply answered as such arguments would suggest, where for example, structural modifications, such as additional substitution, are made, and solvent is varied, and we now take it up in detail. As the above rationale holds in general, however, and thus for example the tautomer (**170**) of 2-amino-6-hydroxypyridine is far more likely to exist in this form than in the alternative (**171**), we shall consider such compounds under pyridinone tautomerism (Section 2.04.4.2); similarly, the tautomerism of 2-amino-6-methylpyridine, for example, will be treated in Section 2.04.4.3, which deals with tautomerism of aminopyridines. Moreover, the possibility of observing experimentally the relative amounts of pyridine/pyridinone and of pyridine/pyridinethione tautomers, means that much more work has been done in this area (and we therefore devote a good deal more space to it), than in the amino and alkyl cases, where the pyridine form generally overwhelmingly predominates.



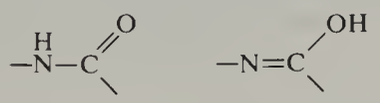
(**170**) (**171**)

In our discussion, we will divide tautomeric compounds according to the type of substituent involved, and under that heading consider all the various possibilities including structures of both neutral form and those for which only charge-separated forms can be written, and both pyridine and benzopyridine derivatives, and polysubstituted heterocycles.

2.04.4.2 Potential Hydroxy and Thiol Groups

As we shall see later, the pyridine ring is more 'aromatic' than the pyridinone ring, and thus more stable, but one must also consider how this is tempered by the inherently greater stability of the amide (**172**) over the imidate (**173**) functionality, with corresponding consequences for the vinylogous pyridinone and -thione situations. For some time it was generally agreed that the 2- and 4-pyridinones exist in that form and not as the alternative 2- and 4-hydroxypyridines, and that substitution of S for O did not change the situation, the greater acidity of SH over OH being compensated by the greater strength of the C=O

over the C=S double bond ⟨63AHC(1)339⟩. But this situation has been the subject of much speculation and argument, and it amply illustrates the contention already emphasized, that much depends on the phase and solvent in which the situation is investigated ⟨77ACR186⟩. Early work on these structures sometimes relied on the use of reactivity data to deduce the predominant tautomer ⟨63AHC(1)339⟩, and the variable conclusions thus produced illustrate quite nicely the pitfalls in this process, for obviously a minority form may have a much greater reactivity factor than a majority form in any given reaction. More reliable spectral determinations were, however, also made very early on, and in particular the UV spectrum of quinolin-2-one with its *O*- and *N*-methylated derivatives showed that the compound was indeed in its oxo form ⟨1899JCS640⟩. This work was later criticized, but the conclusion was correct and it clearly demonstrated at an early date the strategies which were to be much used in the elucidation of such situations, namely the use of spectral determinations and the use of model alkylated 'fixed forms'. Subsequent investigations employing these techniques revealed the predominance of the oxo forms of 2- and 4-pyridinone in ethanol ⟨42CB1338⟩ (for spectra of pyridin-2-one and model compounds measured in this work see Figure 14, Section 2.04.3.3), and of quinolin-4-one in benzene ⟨51JA1923⟩ and isoquinolin-3-one in alcoholic and aqueous media ⟨61JOC803⟩.



(172) (173)

Another useful technique has involved the use of IR spectra, and here the presence of amino and carbonyl stretching frequencies for 2- and 4-pyridinones and 2- and 4-quinolinones suggest the predominance of the oxo tautomer, certainly in inert solvents ⟨57JCS4874⟩. These conclusions were supported by dipole moment measurements on 4-pyridinone and its model compounds in dioxane ⟨56JCS1294⟩, and by NMR measurements in aqueous solution ⟨60CI(L)870⟩.

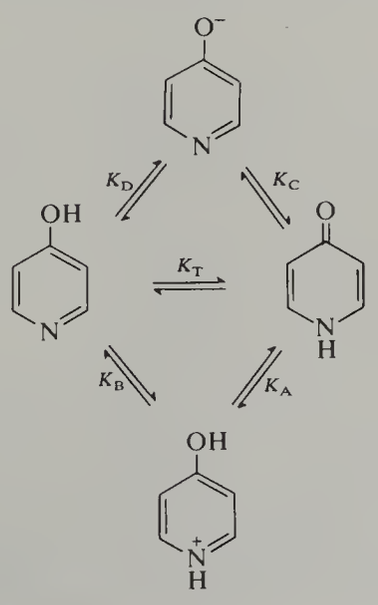
Another method much used in elucidation of these equilibria involves comparison of the pK_a of the compound under investigation with those of the model methylated derivatives. Scheme 3 illustrates the situation for pyridin-4-one. Consideration of the various equilibria allow equations (6)–(8) to be written.

$$K_1 = K_A + K_B \tag{6}$$

$$\frac{1}{K_2} = \frac{1}{K_C} + \frac{1}{K_D} \tag{7}$$

$$K_T = \frac{K_A}{K_B} + \frac{K_C}{K_D} \tag{8}$$

Here K_1 refers to proton loss from the tautomeric system, and K_2 to proton addition to the system, both of which can be experimentally determined. We assume that the substitution



Scheme 3

of methyl for hydrogen will have little or no effect on pK_a values, and the relevant pK_a data for such model compounds are obtained, *i.e.* $K_B(=K_{OMe})$, and $K_A(=K_{NMe})$, for which the pK_a values of *N*-methylpyridinone and 4-methoxypyridine are required. This method and the approximations involved in its use have been previously rigorously discussed ⟨76AHC(S1)1⟩ and it has been used extensively. In particular, it is unique in that it gives a quantitative estimate of the tautomeric ratio in cases where one form greatly predominates over the other; no other methodology can accomplish this.

Mason ⟨58JCS674⟩ used all three equations (6), (7) and (8), so that the effect of Me in the two model compounds cancelled out to some extent. Albert ⟨56JCS1294⟩ employed modified equations (9) or (10), which were subsequently criticized by Mason because the effect of Me no longer cancels.

$$K_T = (K_{OMe}/K_1) - 1 \tag{9}$$

$$K_T = K_1/(K_{NMe} - K_1) \tag{10}$$

In an important application of this method, Katritzky and coworkers ⟨67JCS(B)758, 68JCS(B)556⟩ have attempted to estimate the influence of substituent effects on the tautomeric equilibrium of pyridin-4-one. They utilized equation (8) in the form of equation (11), by considering the pK_a values of the appropriate methylated model compounds in water.

$$\begin{aligned} \log K_T &= [\text{oxo form}]/[\text{hydroxy form}] = [\text{NH}]/[\text{OH}] \\ &= pK_a(\text{oxo form}) - pK_a(\text{hydroxy form}) \end{aligned} \tag{11}$$

3-Substituents were found to alter the position of equilibrium very little from the parent compound, *e.g.* $\log K_T$ (unsubstituted) = 3.3, $\log K_T$ (3-amino) = 3.6, $\log K_T$ (3-nitro) = 3.4, but 2-substitution did have an influence, halogen atoms for example displacing the equilibrium in favor of the hydroxypyridine; thus $\log K_T$ (2-chloro) = −0.1 while 2,6-dichloro-4-hydroxypyridine exists almost entirely in this form in water. Attempts were made with some success to calculate quantitatively K_T values by assessing the influence of substituents in the relevant model pK_a values using σ constants. Other workers have also attempted the Hammett approach for tautomeric elucidation in the pyridin-4-one ⟨77BCJ710⟩ and -4-thione system ⟨77BCJ3295⟩, as well as generally for heteroaromatic systems ⟨64QR295⟩. However, as substituents must be located *ortho* to one or other reaction site, there are discrepancies between calculation and experiment, and the treatment has been criticized ⟨68JCS(C)2656, 68TL5691, 71JCS(B)296⟩.

If the amounts of the two forms are similar, determination of K_T for the mixture of tautomers becomes feasible by direct UV analysis, given that extinction coefficients for the two forms may be satisfactorily substituted by the extinction coefficients for the model compounds, as in equation (12).

$$K_T = (\varepsilon_{OH} - \varepsilon)/(\varepsilon - \varepsilon_{NH}) = (\varepsilon_{OMe} - \varepsilon)/(\varepsilon - \varepsilon_{NMe}) \tag{12}$$

K_T was thus evaluated in solvents C_6H_{12}, $CHCl_3$ and MeCN ⟨76JCS(P2)1428⟩, for 2- (0.78) and 4-pyridinone (0.11), 2,6-di-*t*-butylpyridin-4-one (0.96), quinolin-4-one (1.11, 1.63), and 3-decyl-2,8-dimethylquinolin-4-one (0.57, 0.99). The numbers in brackets are log [NH]/[OH] in $CHCl_3$. Where two values are given, they represent the estimates from measurements at two different wavelengths. These $\log K_T$ values were found to vary with solvent and to give an approximately linear correlation with Z values (see Section 2.04.3.3), the value for water also being included. Although some attempt was made to take measurements at different wavelengths, their accuracy has been criticized ⟨77ACR186⟩; for example, multiwavelength analysis on the pyridin-2-one equilibrium in C_6H_{12} gives a value of >10 for the pyridinone–pyridine ratio, compared to 1.7 given by measurements at 2950 Å alone. Calorimetric measurements of heats of solution in cyclohexane and heats of protonation in aqueous media indicated that K_T was 2.5 ± 1.5 in favor of 2-hydroxypyridine ⟨76TL2685⟩. Despite these discrepancies, however, it seems generally agreed that the amount of hydroxy form increases as solvent polarity is reduced, and that ambiguities in estimations as detailed above may occur due to increasing amounts of molecular association which will vary with concentration and is only negligible at concentrations lower than 10^{-3}M. The general increase in the amount of hydroxypyridine to pyridinone form, as solvent polarity is reduced, suggests that in the gas phase in the absence of intermolecular association the pyridine form should become predominant, and the advent of methods for investigating gas phase equilibria has enabled demonstration that this prediction is correct, as we shall see later.

Other techniques previously described for general investigation of tautomeric equilibria ⟨76AHC(S1)1⟩ involve heats of combustion, relaxation times, polarography, refractive index, molar refractivity, optical rotation, X-ray diffraction, electron diffraction, neutron diffraction, Raman, fluorescence, phosphorescence and photoelectron spectroscopy, and mass spectrometry. The application of several of these techniques to tautomeric studies has been discussed in previous sections. Other results from the more important of these will be referred to later in this section.

The results of some of these techniques are summarized in Table 15 for the situation in pyridin-2-one tautomerism; representative results are also included which show how electron withdrawal by insertion of electronegative atoms at position 6 leads to shift of the tautomeric equilibrium towards the hydroxy form.

Table 15 Tautomerism: the Pyridin-2-one–2-Hydroxypyridine Equilibrium

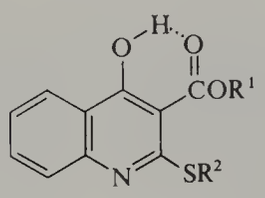
Compound	*Method of Study*	*Solvent (temperature if other than ambient)*	*Predominant tautomer*	*Ref.*
Un-	Reaction with diazomethane	$EtOH/Me_2O$	hydroxy	1895CB1624
substituted	UV (Section 2.04.3.3, Figure 14)	EtOH	oxo	42CB1338
	pK_a	H_2O (20 °C)	320:1 oxo	56JCS1294
			910:oxo	58JCS674
			3300:1 oxo	71JCS(B)279
	IR	CCl_4, $CHCl_3$, solid state (Nujol)	oxo	55JCS4340
				57JCS4874
				60JCS2947
	IR and Raman	H_2O	oxo	60JCS1221
	X-ray (Section 2.04.2.2)	crystal	oxo	53AX591
	UV	C_6H_{12}	1.74:1 oxo	76JCS(P2)1428
		$CHCl_3$	6.03:1 oxo	
		MeCN	148:1 oxo	
	^{14}N NMR	Me_2CO	oxo	71T3129
	^1H NMR	$CDCl_3$	oxo	69JPC2465
	^{13}C NMR: $J(^{13}C, ^1H)$	DMSO-d_6	oxo	75OMR(7)244
	^{13}C NMR: chemical shifts	DMSO-d_6	oxo	74OMR(6)663
	^{14}N, ^{13}C and ^1H NMR using	Me_2CO	12:1 oxo	76T1065
	N- and *O*-methyl derivatives	MeOH	24:1 oxo	
	Heats of solution	C_6H_{12}	hydroxy	76TL2685
	UV and IR	gas phase	hydroxy	73JA1700
				76JA171
	Ion cyclotron resonance (ICR)	gas phase	hydroxy	76JA6048
				79JA1361
	PE spectroscopy (Section 2.04.3.6, Figure 21)	gas phase	hydroxy	77JCS(P2)1652
	MS 'CID/MIKE'	gas phase	hydroxy	79BSB395
6-Cl	pK_a	H_2O	1.5:1 oxo	67JCS(B)758
	UV	H_2O	20:1 oxo	
	UV	EtOH	hydroxy	67DOK(177)592
				67JCS(B)758
	IR	CCl_4	1:1	
	IR	solid	1:1	
	X-ray	crystal	oxo	69AK(30)71
	UV and IR	gas phase	hydroxy	73JA1700
				76JA171
5-Me	pK_a	H_2O	400:1 oxo	68JCS(B)556
6-OMe	pK_a	H_2O	28:1 oxo	71JCS(B)289
	UV	H_2O	>20:1 oxo	
		EtOH	1.1:1 hydroxy	
		$CHCl_3$	2.1:1 oxo	
		dioxane	19:1 hydroxy	
		THF	3.6:1 hydroxy	
		C_6H_{12}	3.5:1 hydroxy	
6-NH_2	pK_a	H_2O	320:1 oxo	71JCS(B)1425

The overall influences favoring OH forms in pyridinone–hydroxypyridine tautomerism have been well summarized ⟨76AHC(S1)71⟩.

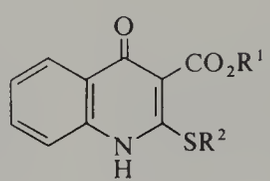
(i) Electron attracting substituents near the nitrogen atom (these include substituents like NH_2 and OMe in which the electronegative N or O atoms provide a very powerful

short range inductive effect). This is illustrated by the figures in Table 15, as well as by previous detailed discussion ⟨76AHC(S1)71⟩. Recent data on ^{14}N NMR also show, for example, that tetrafluoropyridines with OH, SH or NH_2 groups in conjugation with the ring N exist in the pyridine form ⟨78MI20409⟩. Similarly, UV, NMR and pK_a results for 3-ethoxycarbonyl-, 3-ethoxycarbonyl-6,7-methylenedioxy-, and 3-cyanoquinolin-4-one, and their model *O*- and *N*-ethyl derivatives, show that the oxo form is favored in aqueous solution, as for quinolin-4-one itself ⟨81RTC30, 81OMR(16)280⟩.

(ii) Substituents intramolecularly hydrogen bonded to the OH group. These selectively stabilize the hydroxy form. Thus, 2-alkylthio-4-oxoquinoline-3-carboxylate esters exist predominantly in the hydroxy form (**174**) in an inert solvent, where intramolecular hydrogen bonding is favored, and predominantly in the oxo form (**175**) in a protic solvent ⟨68JCS(C)2656⟩.



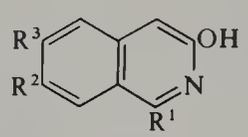
(**174**)



(**175**)

$R^1 = R^2 = Me$
$R^1 = Et$; $R^2 = Me$, Pr^n, Pr^i, CH_2Ph

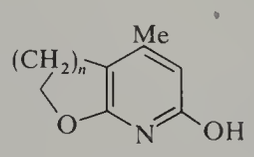
(iii) Benzene ring annelation causing a low N—CO bond order. For example, 3-hydroxyisoquinoline is the favored form over isoquinolin-3-one in most non-hydroxylic solvents, predominance of isoquinolin-3-one requiring aqueous media. For 1-chloro-3-hydroxyisoquinoline, the OH form is the predominant tautomer in all types of solvent, showing the additional influence of factor (i) ⟨67JCS(B)590, 69JCS(C)1729, 71T4653⟩. This annelation effect is supported by SCF MO calculations ⟨70JA2929⟩, and the interplay of factors (i) and (iii) have been further interestingly elucidated for substituted 3-hydroxyisoquinolines (**176**) ⟨74LA1802⟩.



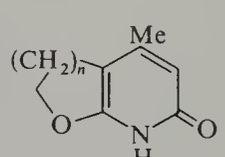
(**176**)

$R^1 = Cl, Br, I$
$R^2 = H, Me, OMe$
$R^3 = H, Cl, Br, Me, OMe$

(iv) Fusion with a five-membered or smaller saturated ring. Influences here favoring the hydroxy form include both Mills–Nixon–Brown ring strain, which is present in a five-membered ring, and which can be relieved by conversion to the hydroxy form, and strain induced electron withdrawal, ascribed to the tendency of small rings to be more electron withdrawing as they decrease in size ⟨71JCS(B)279, 71JCS(B)289, 71JCS(B)296⟩. Thus, the ratio of (**177**) to (**178**) is reduced by a factor of 15–30 in a variety of different solvents when n is changed from 1 to 2.



(**177**)



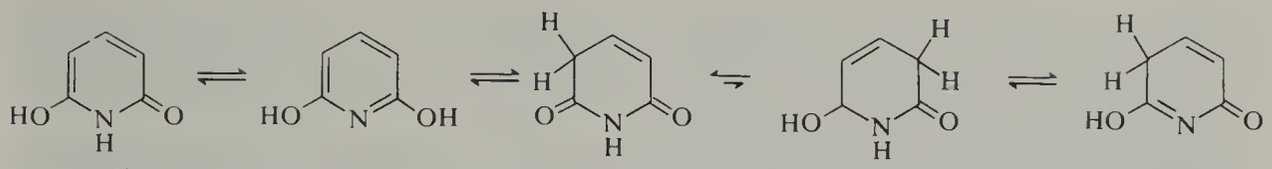
(**178**)

(v) Non-polar solvents or gas phase. See Table 15 and subsequent discussion for examples.

(vi) High temperature in polar solvents or low temperature in non-polar solvents ⟨70DOK(192)1295, 72JCS(P2)1295⟩.

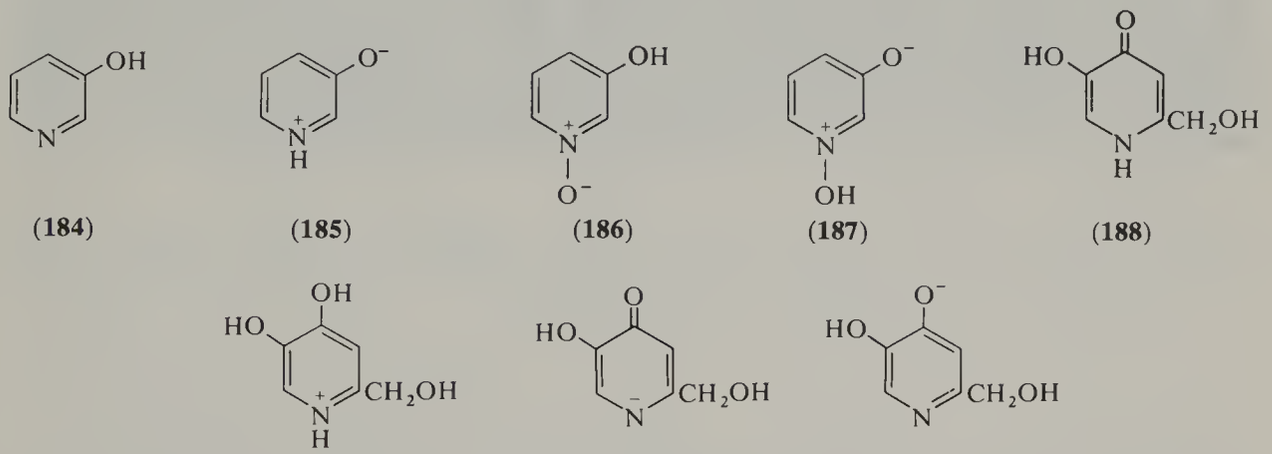
As far as one can tell from the rather limited data, and as we shall see later, much the same factors as listed above appear to be at work in deciding the amount of thiol form in 2- and 4-pyridinethione tautomerism.

Substitution of hydroxy groups into a pyridinone constitutes a special case, because now alternative tautomeric structures can arise. Glutaconamide, for example, can exist in any of five structures (**179**), (**180**), (**181**), (**182**) and (**183**), of which the first three predominate. Again, the situation has been admirably discussed previously ⟨76AHC(S1)71⟩, as has the tautomeric situation in 3-hydroxypyridines (**184**) and (**185**) and in 3-hydroxypyridine



(179) (180) (181) (182) (183)

1-oxides (**186**) and (**187**), where the *N*-oxide form (**186**) is preferred. The polyhydroxy compounds (**188**) have recently been discussed ⟨79BCJ107⟩: UV spectra in aqueous media at various pH values, and their comparison with those for model compounds, reveal that the neutral species is in the pyridinone form (**188**), and the conjugate acid in the pyridine form (**189**) precisely as expected; the additional substitution has no observable influence. The conjugate base is said to exist in significant amounts of both forms (**190**) and (**191**), but it is hard to see exactly what is meant by this as they are both canonical forms of the same resonance hybrid. Possibly some dissociation of the *m*-hydroxy group is involved. The tautomeric equilibrium of 1-hydroxypyridin-2-one lies well on the side of the keto form, as shown by IR and UV studies ⟨49JCS2091, 57JCS4375⟩, and supported most recently by PE spectroscopy ⟨80JA1174⟩. Here the technique was ESCA (Section 2.04.3.6); the N_{1s} and O_{1s} core ionization regions were measured together with those for the model alkylated systems. Measurement of phosphorescence spectra of 1-hydroxypyridin-2-one and of the model ethoxy compounds in methylcyclohexane at 77 K also suggest the presence of the tautomeric equilibrium in the excited triplet state ⟨81CC1004⟩.



(184) (185) (186) (187) (188)

(189) (190) (191)

Closely related to solvent effect, and governed by the same or similar factors, are the phenomena of dimerization *via* self-association, and association with other species present in solution, such as cations or anions, in definite stoichiometric proportions. Studies of such associations lead to further knowledge of such interactions involving the more complex bases in nucleic acid structures. One of the earliest workers to study dimerization systematically was Shindo ⟨59CPB407⟩, who examined the broad N—H stretch region 3300–2400 cm^{-1} in the IR spectra of a variety of substituted pyridin-2-ones and quinolin-2-ones in perfluorocarbon mulls and CCl_4 solution.

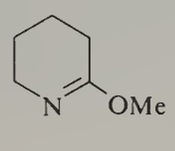
The hydrogen bonding dimerization of pyridin-2-one has been studied ⟨66JA1621⟩ in dioxane, dioxane–CCl_4 and dioxane with 1% water, and also ⟨70JA7578⟩ the association in $CHCl_3$/DMSO and CCl_4/DMSO by ultrasonic attenuation, UV, IR and NMR. IR has been used ⟨71JPC1129⟩ to study the association of quinolin-2-one with itself, and also with various carboxylic acids. Stoichiometric associations have also been demonstrated for pyridinones and substituted derivatives with water in a variety of different solvent systems ⟨78TL2221, 79JA2423⟩, with alcohols ⟨78CPB1403⟩, with carboxylic acids ⟨80JCS(P2)620⟩, with cationic species such as Na^+, Li^+, Mg^{2+} ⟨78JA7055⟩, and in complexes with electron-rich aromatics ⟨77MI20403⟩. All the above studies reveal that the oxo tautomer is favored; thus, in dimerization processes, for example, the hydrogen is predominantly bound to N and the carbonyl oxygen accepting the weaker hydrogen bond from its partner, *i.e.* structure (**163**) is favored over (**164**). However, although the oxo form is favored also in lauryl sulfate micelles in water, in cetylmethylammonium bromide the hydroxy form predominates ⟨75G431⟩. Also, in acetonitrile, association of 6-chloro- and 6-methoxy-pyridinone with halide ions Cl^-, Br^- and I^-, with counter ion NBu_4^+, shifts the equilibrium towards the hydroxy form although the oxo form is still predominant ⟨80JA401⟩. A study of the UV PE

spectra of Cr(II) and Mo(II) complexes (M_2L_4) of 6-methylpyridin-2-one also indicates that the enol form better describes the structure of the ligand in the complexes ⟨80JCS(F2)885⟩. Incidentally, this work also aids in the assignment of the PE bands for the pyridin-2-one system (see Section 2.04.3.6) ⟨77JCS(P2)1652⟩.

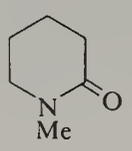
The influences at work on these interactions have been discussed in two important papers ⟨80JOC1347, 80JOC1354⟩. It is found that influences of media can be expressed in terms of two effects, differential stabilization of the different dipoles of the two tautomeric species by the dielectric constant of the medium, the dipole reaction field and by differential hydrogen bonding. For self-association pyridin-4-one is shown to form oligomers, in contrast to the well-known dimerization of pyridin-2-ones. This self-association can shift the position of apparent tautomeric equilibrium (hence the warnings previously noted about effect of concentration on K_T).

The concept of aromaticity has been linked to that of tautomerism and equilibration in pyridinone derivatives in a series of important studies by Beak ⟨68JA1569, 69JOC2125, 72T5507, 73JA1700, 76JA171, 77ACR186, 79JA1361⟩ and by Katritzky ⟨72JCS(P2)1295, 73JCS(P2)1080, 74AHC(17)255, 75BSB465, 76TL2685, 76JA6048, 77TL1777⟩ and their coworkers. Their studies also strongly emphasize the dominant role of solvent in affecting the positions of tautomeric equilibria, as we have already seen, and demonstrate the importance of measurements in the gas phase, the point at which, in Beak's words ⟨77ACR186⟩, 'understanding can begin'. Further, both groups of workers show the influence of substituents on such equilibria.

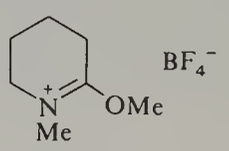
In an initial study ⟨68JA1569⟩, Beak equilibrated pairs of compounds (**192**) (**193**), (**195**) (**196**), (**198**) (**199**), and (**201**) (**202**) in the liquid phase, at 130 °C using as catalyst the appropriate common alkylated derivatives (**194**), (**197**), (**200**), (**203**) respectively. Such reactions are probably more appropriately referred to as rearrangements, but we discuss them here because of their close relevance to studies on tautomerism; moreover, their description does fall within the strict definition of tautomerism ⟨B-78MI20405⟩.



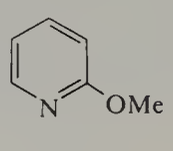
(**192**)



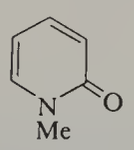
(**193**)



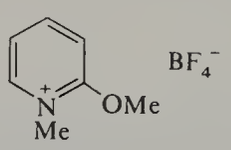
(**194**)



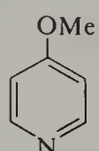
(**195**)



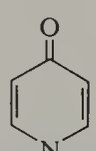
(**196**)



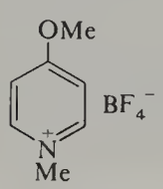
(**197**)



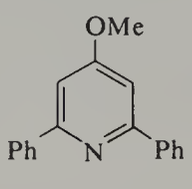
(**198**)



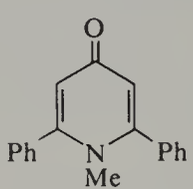
(**199**)



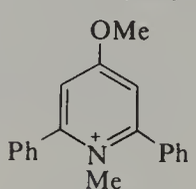
(**200**)



(**201**)

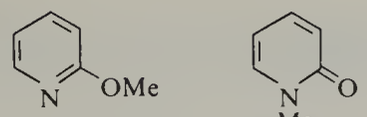


(**202**)



(**203**)

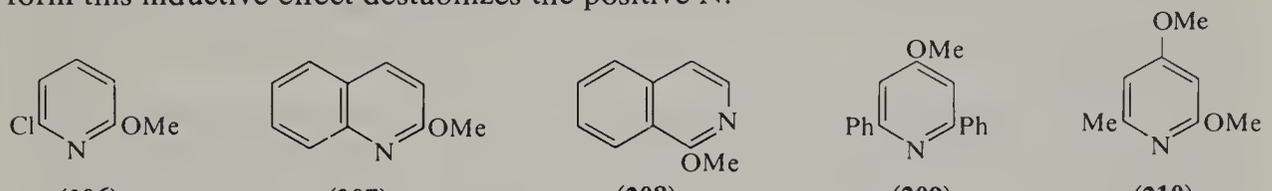
For the final pair of compounds, the equilibrium was found to favor (**201**). Presumably the phenyl groups in (**202**) sterically impede the N—Me group thus destabilizing the pyridinone form, but for the other pairs the equilibria lay so far in favor of the pyridinone form that no imidates could be detected, allowing calculation of only limiting values of $\Delta G°$ for these conditions. Quantitative information on the relative enthalpies $\Delta H°$(130 °C) of the first three pairs of isomers in the liquid phase was obtained by measuring the heats of reaction by calorimetry. To convert these values to $\Delta H°_g$, the equivalent quantities for the gas phase, Beak estimated the heats of vaporization of each of the compounds (**192**), (**193**), (**195**), (**196**), (**198**), (**199**), and gave evidence that the kinetic energy and zero point energy contributions to the energy differences between the pairs of isomers were negligible (although a statistical factor to take account of the twofold degeneracy of **199** relative to **198** is required). The results thus obtained may be summarized as follows. The chemical binding energy difference between (**192**) and (**193**) is 59 kJ mol^{-1}, and between (**195**) and (**196**) is 34 kJ mol^{-1}. If it is assumed that the chemical binding energy difference between (**192**) and (**193**) is that between (**204**) and (**205**), in which the ring double bonds are



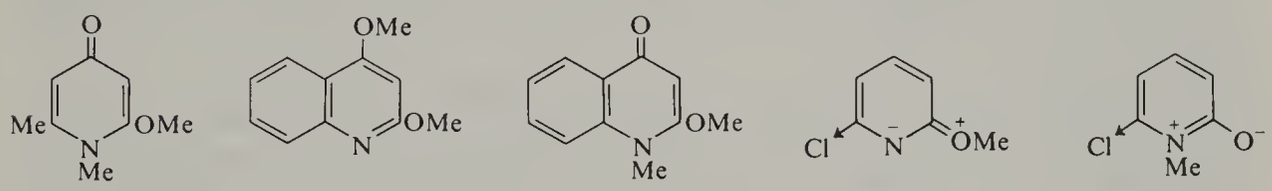
(204) (205)

completely localized, then there is therefore an approximate π-stabilization energy of (**195**) over (**194**) of 25 kJ mol^{-1}, in agreement with Hückel MO calculations. In contrast, isomers (**198**) and (**199**) are calculated to be of very similar intrinsic stability. These deductions, however, consistently emphasize the importance of environmental factors in influencing the relative stability of isomers in the liquid phase relative to the gas phase. By the same *modus operandi* ⟨69JOC2125⟩, equilibration of *N*-methyl-2-thiopyridinone and 2-methylthiopyridine, under the catalytic activity of *N*-methyl-2-methylthiopyridinium fluoroborate, shows that the latter is favored in the liquid phase by an enthalpy of about 12 kJ mol^{-1}.

In a subsequent study employing the same techniques ⟨72T5507⟩, Beak looked at compounds (**206**), (**207**), (**208**), (**209**), (**210**), (**211**), (**212**) and (**213**), and their equilibrating Me isomers to establish the effect of substitution on the methoxypyridine–1-methylpyridinone equilibria. In all cases the pyridinone form was found to be the more stable isomer in the liquid phase. In all cases but one the substitutions produced, within the limits of accuracy of the experiments, only small changes in the estimated gas phase enthalpy differences ΔH_g° and ΔE chemical binding compared to the parent equilibria. The one exception is the 6-chloro compound (**206**) where the enthalpy is shifted from strongly favoring the pyridinone towards the pyridine form so that the two isomers have similar ΔH_g° values and thus ΔE chemical binding energies. This may be explained in terms of structures (**214**) and (**215**). In the former canonical of the pyridine form the electron withdrawing inductive effect of Cl stabilizes the negative charge on N, but in the latter canonical of the pyridinone form this inductive effect destabilizes the positive N.

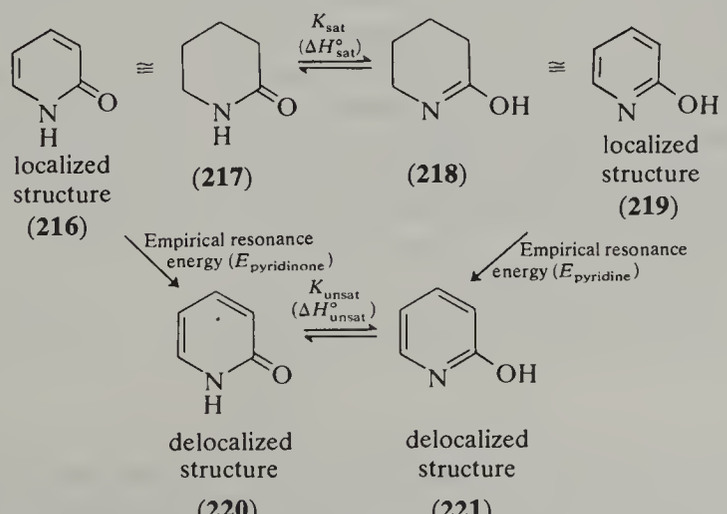


(206) (207) (208) (209) (210)



(211) (212) (213) (214) (215)

An approach using much the same rationale and assumptions as Beak has been adopted by Katritzky, but in the latter case prototropic equilibria have been utilized, for which experimental data are much more accessible ⟨72JCS(P2)1295, 73JCS(P2)1080, 74AH(17)255⟩. Scheme 4 shows the relevant equilibria in which the suffix 'sat' means saturated and 'unsat' unsaturated.



Scheme 4

The difference ($E_{\text{pyridine}} - E_{\text{pyridinone}}$) is a measure of the difference in binding energy, and therefore aromaticity, between (**220**) and (**221**), and this from the cycle given in Scheme 4 is ($\Delta H_{\text{sat}} - \Delta H_{\text{unsat}}$). Now

$$-RT \log_e K_{\text{sat}} = \Delta H_{\text{sat}} - T\,\Delta S_{\text{sat}} \tag{13}$$

$$-RT \log_e K_{\text{unsat}} = \Delta H_{\text{unsat}} - T\Delta S_{\text{unsat}} \tag{14}$$

$$(E_{\text{pyridine}} - E_{\text{pyridinone}}) = RT \log_e \left(\frac{K_{\text{unsat}}}{K_{\text{sat}}}\right) + T(\Delta S^{\circ}_{\text{sat}} - \Delta S^{\circ}_{\text{unsat}}) \tag{15}$$

The first term on the right hand side of equation (15) can be evaluated using the pK_a values of the corresponding methylated model compounds, since equations (16) and (17) hold.

$$\log_e K_{\text{unsat}} = pK_a(\text{NMe})_{\text{unsat}} - pK_a(\text{OMe})_{\text{unsat}} \tag{16}$$

and

$$\log_e K_{\text{sat}} = pK_a(\text{NMe})_{\text{sat}} - pK_a(\text{OMe})_{\text{sat}} \tag{17}$$

Estimates can be made of the second term of equation (15), not usually by direct substitution, but by invoking various empirical linear correlations between $\Delta G°$ and $\Delta H°$ previously established for protonation of nitrogen and oxygen bases.

An important assumption involved in this work was that solvation effects, although present, would tend to cancel in the comparison of similar prototropic equilibria, while associative intermolecular interactions would be negligible in the dilute solutions employed.

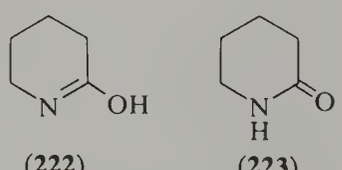
In line with Beak's finding, pyridin-2-one was estimated to be 31 kJ mol^{-1} less aromatic than the pyridine, and a similar figure of 25 was estimated for pyridine-2-thione. Subsequent results ⟨73JCS(P2)1080, 76AHC(S1)71⟩ on the pyridin-4-one, quinolin-2-one and isoquinolin-1-one series showed that aromatic resonance energy difference for the pyridin-4-one/4-hydroxypyridine system was very similar to that for the 2-substituted compounds, in contrast to Beak's findings.

For the bicyclic compounds the differences in aromaticity between the two possible forms were smaller, about 8 and about 18 kJ mol^{-1} for the quinolin-2-one and isoquinolin-1-one systems respectively. Similar values were found for the corresponding bicyclic thiones.

As we have already seen in Table 15, recent work on pyridinone tautomerism has focused on the gas phase, and finally a brief account of some of the measurements made in this area will be given.

Beak has measured the UV spectra of 2- (0.4) and 4-hydroxypyridine (<0.1), 6-chloro-2-hydroxypyridine (0.05), 2- (<0.1) and 4-mercaptopyridine (<0.1) and acridin-5-one (>10) ⟨73JA1700, 76JA171⟩. A heated cell was employed with vacuum jacketed windows, over the temperature range 120–140 °C. It was thus demonstrated that these compounds exist predominantly in the form named above (the figure in brackets after each name gives the value of K_T = [NH]/[OH], or [NH]/[SH]), using the methylated compounds as model chromophores.

Supplementary IR measurements in the gas phase showed sharp NH and OH stretching frequencies, serving to demonstrate the absence of hydrogen bonded species and thus of molecular association. The temperature variant measurements gave, from a plot of $\log_e K$ *vs.* $1/T$, a ΔH°_g value of 1 kJ mol^{-1} in favor of the hydroxy form of pyridin-2-one. Comparison of this value with that of −32 kJ mol^{-1} for the corresponding N and O methylated compounds ⟨68JA1569⟩ gives a value of about 33 kJ mol^{-1} due to the difference in localized bond energies. Applying this value to the value of 59 kJ mol^{-1} reported for the equilibrium of saturated derivatives (**192**) and (**193**) yields a ΔH°_g value of 25 kJ mol^{-1} between valerolactim (**222**) and valerolactam (**223**) in favor of (**223**).



(**222**) (**223**)

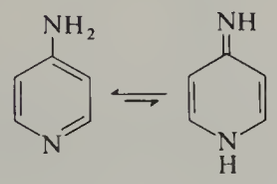
It is of interest to note ⟨76JA171⟩ that various MO calculations, SCF, MINDO/2 and CNDO/2, give widely different predictions with regard to pyridinone tautomerism in the gas phase, none of which is correct. This is particularly worrying, because they relate to

the isolated molecules, and therefore should be particularly relevant to these measurements. The CNDO/2 method does however predict correctly the shift in tautomeric equilibrium in going from aqueous solution to the gas phase ⟨78MI20407⟩.

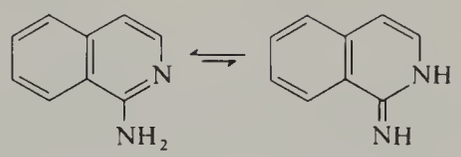
Application of pulsed ion gas-phase cyclotron resonance (ICR) spectroscopy to proton affinities of the derivatives 2-methoxypyridine and *N*-methylpyridin-2-one confirm previous deductions on the enthalpy of 2-hydroxypyridine–pyridin-2-one tautomerism ⟨76JA6048⟩, provided that the difference between the influences of *O*-methylation on 2-hydroxypyridine and *N*-methylation in pyridin-2-one are taken into account. These measurements have been further clarified and extended to other gas phase basicity measurements ⟨79JA1361⟩. A similar estimation of the gas phase basicities of 2- and 4-pyridinethiols and 2- and 4-pyridinethiones confirms that the thiol form is predominant in the gas phase ⟨77TL1777⟩, in line with previous studies involving mass spectrometric deuterium isotope studies ⟨75BSB465⟩. Photoelectron spectroscopy has also been employed in such studies (see Section 2.04.3.6 and Figure 21 for details) ⟨77JCS(P2)1652⟩.

2.04.4.3 Potential Amino Groups

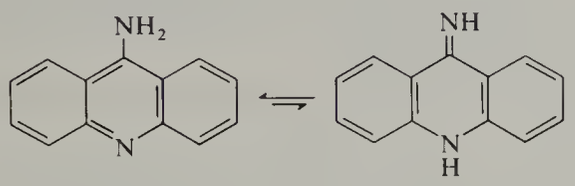
As discussed previously (Section 2.04.4.1), the tautomeric equilibrium in aminopyridines and their benzo analogues lies well in favor of the amino form, whether in solid or gas phase, or in inert or polar solvents. The evidence has been well documented and discussed ⟨76AHC(S1)71⟩. Thus, in the respective examples of tautomeric equilibria (**224**) through (**231**), the favored form is on the left hand side in all cases.



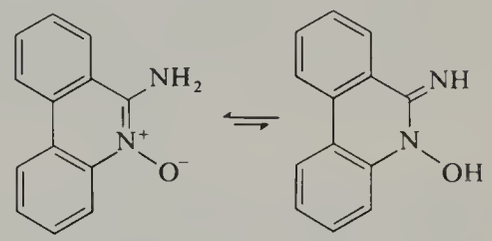
(**224**) (**225**)



(**226**) (**227**)



(**228**) (**229**)

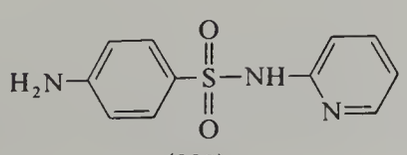


(**230**) (**231**)

The situation in substituted amino compounds may be different, however. Electron withdrawing groups R will increase the acidity of the hydrogen atom in NHR, and the imino form may thus become favored. The sequence is as follows in order of increasing acidity, full confirmatory evidence having been presented ⟨76AHC(S1)71⟩:

$$R = \text{alkyl} < \text{aryl} < \text{COalkyl} < \text{COaryl} < \text{COCCl}_3 < \text{SO}_2\text{R} < \text{NO}_2 < \text{CN}.$$

Thus, the imino form tends to predominate for the last three groups, particularly in polar or protic media, although clearly this deduction must be tempered with consideration of other adjustments of structure. Thus, the MS of compound (**232**) and its methylated model compounds indicates the amino form with no imino form detectable ⟨80MI20403⟩. Here, presumably, the electron donating NH_2 group reduces the electron withdrawing power of the sulfonyl linkage. Further to the left along the above series, moreover, the amino form quickly establishes itself as the predominant tautomer. Thus, 2-anilinopyridine exists predominantly in that form in all varieties of solvents ⟨76BCJ2770⟩. The value of K_T (=[amino]/[imino]) is 2×10^5, for example, in water as determined by pK_a measurements of model compounds using standard procedures (Section 2.04.4.2). Introduction of a 5-nitro



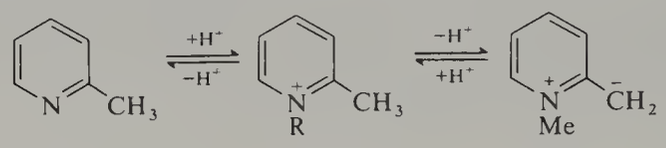
(**232**)

group into the pyridine ring lowers the amount of amino tautomer as expected from the analogous effect in pyridinone tautomerism (Section 2.04.4.2). Thus, $K_T = 8 \times 10^3$, but the amino form still predominates ⟨80BCJ717⟩.

The aromatic energy differences between the aminopyridine and pyridinone imine form ($E_{\text{pyridine}} - E_{\text{pyridine imine}}$) can be found as detailed previously (see Section 2.04.4.2) ⟨72JCS(P2)1295⟩. The pyridinone imine form retains much aromaticity, but less so than in the case of the oxygen compounds, as can be seen from the following figures for the above quantity: 2-aminopyridine/pyridin-2-one imine, 42; 4-aminopyridine/pyridin-4-one imine, 61; 2-aminoquinoline/quinolin-2-one imine, 21; 1-aminoisoquinolinone/isoquinolin-1-one imine, 26 kJ mol^{-1}.

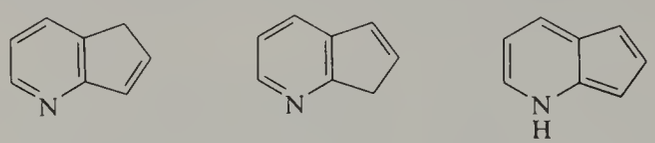
2.04.4.4 Potential (Substituted) Methyl Groups

Moving further to the left along the Periodic Table in seeking the central atom of the substituent, *i.e.* the one by which the substituent is anchored to the heterocyclic nucleus, we expect to find that nucleus overwhelmingly in the pyridine form. Generally this turns out to be true ⟨76AHC(S1)71⟩. Measurements of pK_a values have been made in aqueous solution of model systems such as (**234**)⇌(**233**) and (**233**)⇌(**235**), from which K_T may be



R = H (**234**) R = H, Me (**233**) R = Me (**235**)

evaluated ⟨76AHC(S1)71, 76CJC900⟩, using the procedures detailed in Section 2.04.4.2. These measurements, recorded in Table 16, amply confirm the stability of the pyridine form. This table also records values of ($E_{\text{methylpyridine}} - E_{\text{pyridinone methide}}$), from which it can be seen that the pyridinone methide tautomer has lost much of its aromaticity, *cf.* the pyridinone, thione, and imino cases (Sections 2.04.4.2 and 2.04.4.3) ⟨72JCS(P2)1295, 76CJC900⟩. Similarly, pyrindine, which is a cyclized alkylpyridine, exists as a mixture of (**236**) and (**237**), with only a very small amount of (**238**) in all media examined ⟨73AHC(15)187⟩.



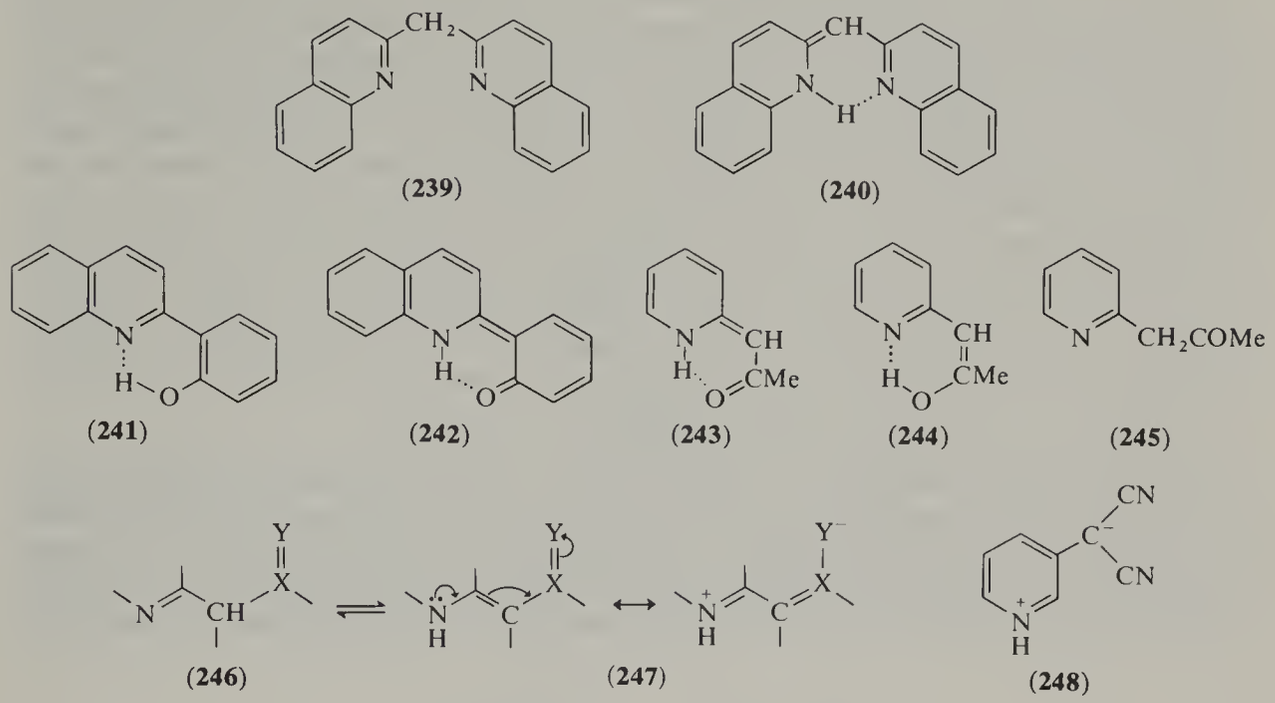
(**236**) (**237**) (**238**)

Table 16 Methyl–Methide Tautomerism

Compound	pK_a (*pyridine*)	pK_a (*methide*)	pK_T	($E_{\text{methylpyridine}} - E_{\text{pyridinone methide}}$) (kJ mol^{-1})
2-Methylpyridine	5.97	19.3	13.3	73
4-Methylpyridine	6.02	20.2	14.2	82
2-Methylquinoline	5.83	15.7	9.9	33
1-Methylisoquinoline	6.42	15.9	9.5	31
2-Benzylpyridine	6.18	16.9	10.7	—

In bisheteroarylmethanes the NH tautomer (**240**) may be favored over the alternative (**239**) in the solid and in certain solvents ⟨76AHC(S1)71⟩, particularly, it would seem, in inert solvents in which there is a strong stabilizing N—H · · · N hydrogen bond. *o*-Hydroxyphenyl derivatives exist predominantly in the phenolic hydrogen bonded form (**241**), although they can absorb light to form the photoexcited NH tautomer (**242**) ⟨76AHC(S1)71⟩. For methyl substituted with electron withdrawing groups the NH tautomer may become favored; thus 2-phenacylpyridine exists in form (**243**) and/or (**244**) rather than (**245**) in non-polar solvents and in the solid, although the 4-substituted derivative is predominantly in the pyridine form ⟨76AHC(S1)1⟩. Thus in any general case (**246**)⇌(**247**), where X=Y is electron withdrawing by virtue of resonance to give a polar canonical form, the NH tautomer is potentially

favored, depending on the contribution of this polar canonical form. The situation has again been critically surveyed for alkoxycarbonyl-, iminoylmethyl-, cyanomethyl-, azomethyl-, sulfonylmethyl-, nitromethyl- and phosphinylmethyl derivatives ⟨76AHC(S1)99⟩. Thus 2- and 4-cyanomethylpyridines exist mainly in the $-CH_2CN$ tautomeric form under most experimentally observable conditions, but for the dicyanomethyl compounds the NH tautomer becomes predominant, including the zwitterionic form (**248**) in 3-dicyanomethylpyridine.



2.04.4.5 STABILITY, AROMATICITY AND CONFORMATION

2.04.5.1 Conformation and Stability in Piperidine and Derivatives

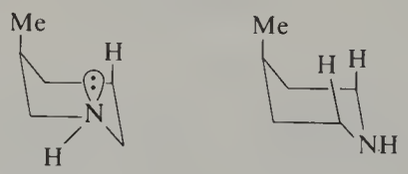
The conformational problem in piperidine and its substituted derivatives is that of cyclohexane derivatives, compounded by the additional complication of a ring nitrogen. This modifies the cyclohexane ring geometry by virtue of the fact that a C—C single bond (1.53 Å) is longer than a C—N single bond (1.48 Å), and that the nitrogen atom has a smaller van der Waals' radius (1.50 Å) than carbon (2.00 Å). There is thus a resulting influence on chair⇌boat and equatorial⇌axial type equilibria (**19**)⇌(**20**), although the system follows its carbocyclic analogue in generally eschewing boat forms ⟨67QR364⟩. Moreover, the question of whether the nitrogen lone pair is axial or equatorial in any given situation is not readily answered. These complexities have led to some rather detailed experimental work, and some lively discussion and controversy. The subject has been well reviewed ⟨75ACR300, B-80MI20401⟩; we shall deal with the main points here. Early work up to about 1965, based predominantly on molecular polarizability and dipole moment studies in benzene solution ⟨65JA1232, 67JCS(B)493, 67BSF3585⟩, indicated that N–H was equatorial in piperidine and therefore that the lone pair was axial, although initial conclusions had been that the hydrogen was axial ⟨56QR44, 58JCS3002⟩. The N—H equatorial preference appeared in the free molecule to give rise to a $\Delta G°$ value of about 1.7 kJ mol^{-1} ⟨65JA1227, 70JCS(B)127, 73JCS(P2)332⟩. It should be noted, however, that one of the 'N—H axial' proponents ⟨64CI(L)1713⟩ stressed the influence of solvent on lone pair 'size'; clearly the extent to which the lone pair enters into solvent interactions such as hydrogen bonding is going to influence its effective steric requirements.

Subsequently it was proposed ⟨66JA620, 67JA3761⟩ that the N—H might be axial: the chemical shift of 0.94 p.p.m. between the geminal H atoms at positions 2 and 6 in the NMR of *N*-methylpiperidine, in which the bulk of the N—Me grouping would force the lone pair axial, was compared to that of 0.44 in piperidine itself, in solvent methanol, the enhancement in the former case being ascribed to electronic interaction between the axial CH and the vicinal axial lone pair. Further NMR measurements ⟨69TL2023, 70JA1267, 71JA3922, 72JA3812⟩

as well as calculations ⟨67TL3729⟩ appeared to support the conclusion. However, IR intensities of NH and CD bands ⟨67CC625, 68CPB702, 68CC244, 68JCS(B)1470⟩ in piperidine derivatives, including 2,6-dideuteropiperidines, and related perhydroquinolines, perhydrophenanthridines and perhydroacridines, calorimetric data ⟨71MI20401⟩, microwave analysis ⟨68CC668⟩, and further NMR work ⟨67T291, 68TL1153, 68CC802, 77JA2794, 79JOC1081, 72JCS(P2)615⟩ all tended to show that, in the vapor phase and most solvents at least, the NH is equatorial with a preference amounting to *ca.* 0.8–2.0 kJ mol^{-1}.

If NH prefers the equatorial conformation, it is obvious that other substituents on N will also take up this conformation, although proton NMR and CD measurements indicate that in CCl_4 the nitro group may be axial in some *N*-nitro-2-alkylpiperidines ⟨77ZC177⟩. For methyl the free energy difference in favor of the equatorial form has been estimated at 2.7 kJ mol^{-1} ⟨67JCS(B)493, 70JCS(B)122⟩, based on dipole moment measurements, together with 3.8 and 5.9 kJ mol^{-1} for *N*-ethyl and *N*-isopropyl groups respectively. However, more recent measurements afford a value of 15 kJ mol^{-1} for *N*-methyl ⟨74CC825, 76JA292, 77T915⟩. Interestingly, these are based on kinetic measurements of protonation and nitrene capture rates at the N lone pair, and as such are potentially fraught by the same errors as apply to the elucidation of tautomerism by reaction rates discussed previously (Section 2.04.4.2). Nevertheless, here the possibility of the intervention of such errors is carefully considered and adjudged absent, because both reactions appear very rapid compared to the rate of that of the conformational equilibrium, and both are irreversible.

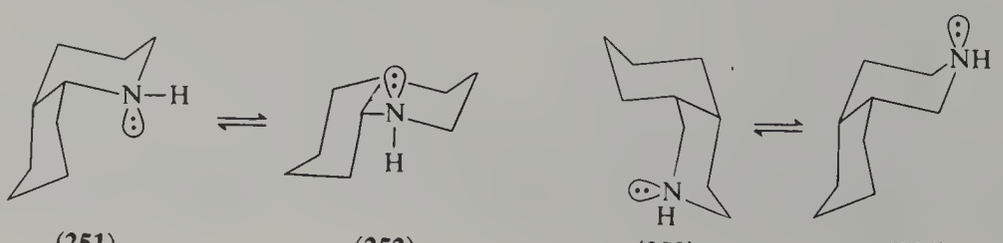
Investigations of *C*- and *N*-methylpiperidines and piperidinium compounds have been made by ^{13}C NMR ⟨78OMR(11)418⟩. Variable temperature proton and ^{13}C NMR shows the free energy difference to be 6.3 kJ mol^{-1} for the *N*-chloro substituent ⟨75T2621, 77TL3207⟩. For Me groups at C(3) and C(4) the free energy difference is 6 and 7.9 kJ mol^{-1} respectively, the former value being lower than the latter because a 1,3-diaxial interaction has been removed (compare **249** with **250**) in the axial conformation ⟨75CC844, 79NJC145, 79CC34⟩.



(249) **(250)**

The value for the 4-Me group of 7.9 contrasts with that of 7.3 kJ mol^{-1} for the methyl group in cyclohexane, possibly because the piperidine ring is more puckered round the N atom, due to the C—N bonds being shorter than the C—C bonds, so that the axial C—H bonds at C(2) and C(6) are drawn inwards, increasing interaction with the C(4) methyl group. A similar effect is observed in decahydroquinolines ⟨76JCS(P2)751⟩ and dialkylpiperidines ⟨76TL3765⟩.

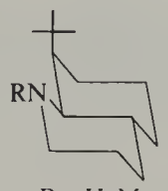
There has also been some related work on the conformational analysis of *trans*- ⟨74JA2257, 76JA7013, 76JOC199⟩ and *cis*-decahydroquinoline (**251**)⇌(**252**) ⟨73JCS(P2)842, 77JOC51⟩. For *cis*-decahydroquinoline, structure (**251**) rather than (**252**) is preferred by a factor of 4.4 kJ mol^{-1}, in which N occupies an *endo* position, presumably again reflecting the smaller size of the N lone pair compared to hydrogen. For *cis*-decahydroisoquinoline, ^{13}C NMR shows conformation (**253**) rather than (**254**) is preferred, again where the nitrogen lone pair occupies the hindered inside position ⟨79JCS(P2)510⟩. If the nitrogen is protonated the distinction between hydrogen–hydrogen and hydrogen–lone pair interactions is lost, and thus the equivalent equilibria for (**251**)⇌(**252**) and (**253**)⇌(**254**) with the protonated species indeed shows the two forms in both cases to have equivalent energies ⟨79JCS(P2)510⟩, in that ^{13}C NMR showed each conformer to be present in equal amounts for both equilibria. This again provides good evidence that the smaller size of the nitrogen lone pair is responsible for the conformational features discussed above.



(251) **(252)** **(253)** **(254)**

These conclusions are reinforced by measurement of natural abundance ^{15}N chemical shifts in piperidines and decahydroquinolines ⟨77JA8406, 78JA3882, 78JA3889⟩. Lack of correlation between ^{13}C shifts of cyclohexanes and ^{15}N shifts of piperidines bearing the same methyl substituents are attributed to, among other factors, solvent effects and the difference between H–lone pair and H–H interactions. Protonation served to cancel these stereoelectronic effects. Correspondence between ^{15}N shifts in *N*- and *C*-methyl substituted piperidines and decahydroquinoline hydrochlorides and the analogous ^{13}C values were, however, generally much closer than for saturated aliphatic amines.

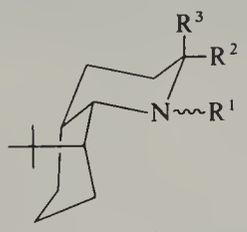
Recently, piperidine derivatives have been reported which bear axial Bu^t groups, a rare occurence. X-ray crystallographic analysis of a phenylcyclidine derivative, 1-phenyl-*cis*-4-*t*-butyl-*r*-cyclohexylpiperidine, shows it to have the conformation with the Bu^t group axial in the solid, although equatorial in solution ⟨81TL949⟩. NMR and X-ray data also show the Bu^t group axial in 8β-*t*-butyl-*trans*-decahydroquinoline (**255**) ⟨79JOC1081⟩. The Bu^t group



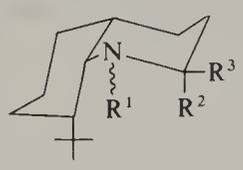
R = H, Me

(**255**)

also prefers the axial disposition in the 8β-*t*-butyl-*cis*-decahydroquinoline system given above ⟨81TL5161⟩. Scheme 5 shows the results obtained from proton and ^{13}C NMR for the equilibrium process; presumably the preference for (**256**; $R^1 = R^2 = R^3 = H$) is due to severe interaction in (**257**; $R^1 = R^2 = R^3 = H$) between the nitrogen lone pair and the Bu^t group, which must in consequence be greater than 22 kJ mol^{-1}.



(**256**)



(**257**)

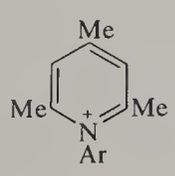
	[(**256**)]	[(**257**)]	Temp. (°C)	$\Delta G°$ (kJ mol^{-1})
$R^1 = R^2 = R^2 = H$	>97%	<3%	−75	<−5.7
R^1 = Me, $R^2 = R^3 = H$	62	38	−80	−0.8
$R^1 = R^3 = H$, R^2 = Me	>99	<1	−70	<−7.8
$R^1 = R^2 = H$, R^3 = Me	<2	>98	−65	>6.7

Scheme 5

2.04.5.2 Conformation and Stability in Pyridine and Derivatives

We have already discussed methods of estimating aromatic chemical binding energy differences for pyridine tautomeric systems (Section 2.04.4). Measurements of aromatic stability and resonance energy have been thoroughly and critically reviewed previously ⟨74AHC(17)255, 74PMH(6)99⟩, and representative values obtained have been recorded in the general section. It is important to note that values will vary widely for the same compound depending on the method of assessment, but fairly uniform comparisons are obtained if one considers series of values measured or calculated by the same method.

A novel method for estimating ring current in aromatic molecules has recently been provided ⟨79TL437⟩. This involves measurement of the ^1H NMR α- and γ-methyl chemical shifts in compounds (**258**), readily prepared from $ArNH_2$ and 2,4,6-trimethylpyrylium perchlorate. Quantity *D* defined by equation (18) is a qualitative measure of ring current



(**258**)

in Ar, and from this the relative ring current RRC is defined by equation (19) allowing for the number of *ortho* groups (x) in Ar by equation (20).

$$D = \delta(\gamma\text{-methyl shift}) - \delta(\alpha\text{-methyl shift}) \quad (18)$$

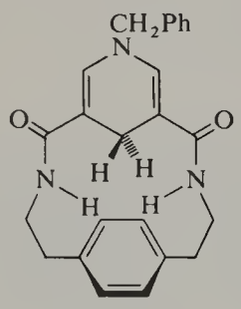
$$\text{RRC} = 200(D + 0.25) - T \quad (19)$$

$$T = 71.7x/(1 + 2.26x) \quad (20)$$

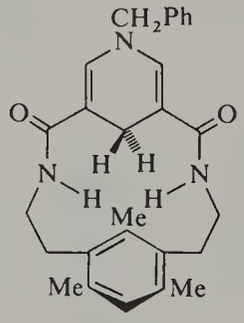
Some values of RRC are as follows: Me, 2; *p*-anisyl, 92; phenyl, 100; 2-pyridyl, 98; 3-pyridyl, 96. These figures support previous estimates of ring current which suggest pyridine is about as 'aromatic' as benzene.

A number of aspects of conformational stability and their elucidation by physical techniques have been recorded in previous sections. Further examples are now provided of the use of these methods.

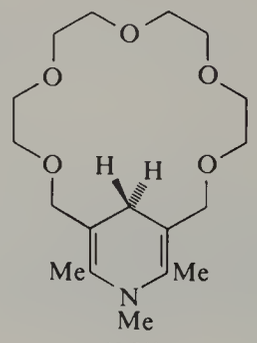
We referred previously to NMR examination of dihydropyridines (**70**) as models for the NAD/NADH coenzyme system (Section 2.04.3.1). In other studies directed at elucidation of this type of stereoselective hydride transfer ⟨80TL1549⟩, compounds (**259**) and (**260**) were synthesized and their proton NMR spectra measured. 1,4-Dihydropyridine (**259**) showed isochrony of the protons at C(4), even at 360 MHz and −80 °C in $CDCl_3$. X-ray crystallographic analysis of the stereochemistry of structure (**259**) revealed, as in other cyclophane type structures (see Section 2.04.2.2), that the heterocyclic ring was in a boat conformation, and thus the lack of diastereotopy of the C(4) protons must indicate a rapid inversion of the dihydropyridine, a conclusion supported by the isochrony of the phenyl ring and the methylene protons of the bridge. In contrast, structure (**260**) displayed an AB pattern for the C(4) protons, and this was accompanied by the observation that deuterium exchange from 1-benzyl-1,4-dihydronicotinamide-4,4-d_2 to the pyridinium precursor of (**260**) occurred stereoselectively at the magnetically most shielded diastereotopic C(4) position. X-ray crystallographic work has likewise shown that in the dihydropyridine (**261**) the dihydropyridine ring is also in a boat conformation ⟨78CC923⟩.



(**259**)

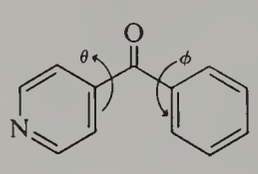


(**260**)

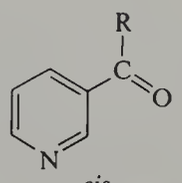


(**261**)

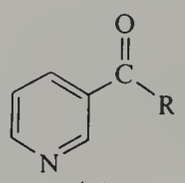
Dipole moment studies and molar Kerr constants, in C_6H_{12} at 25 °C, have proved of much use in adducing the conformations of acylpyridines ⟨73JCS(P2)1461⟩. 4-Formylpyridine is planar, but the acetyl group appears to be twisted about 25° from the plane of the pyridine ring in 4-acetylpyridine. The conformation of 4-benzoylpyridine must be defined by two angles θ and ϕ as in (**262**). The preferred conformation is calculated to be $\theta = \phi = 25°$, consistent with the result for 4-acetylpyridine.



(**262**)



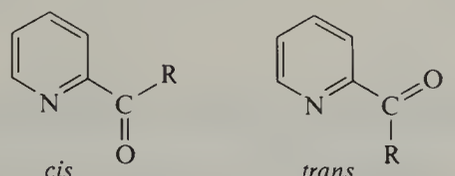
cis
(**263**)



trans
(**264**)

3-Formylpyridine is 30% in the planar *cis*-form (**263**; R = H), and 70% in the planar *trans*-form (**264**; R = H). Similar proportions are found for 3-acetylpyridine (**263**, **264**; R = Me), in agreement with previous conclusions ⟨69JA636⟩ (see Section 2.04.3.4), but here the group is again twisted 25° from the plane in both cases. 3-Benzoylpyridine probably has significant quantities of both *cis* (**263**; R = Ph) and *trans* (**264**; R = Ph) forms, but the molecule is twisted ($\theta = \phi = 25°$ and $\theta = \phi = 155°$ respectively).

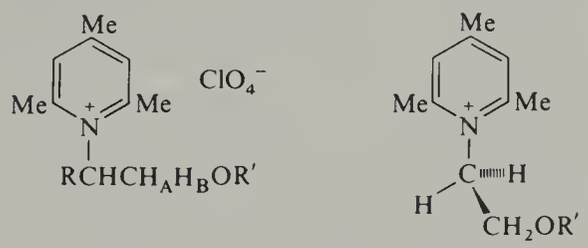
2-Formylpyridine exists largely in the planar *trans* form (**266**; R = H) (see also ⟨75BCJ2009⟩, Section 2.04.2.1), as does 2-acetylpyridine (**266**; R = Me). 2-Benzoylpyridine also has a strong preference for the *trans* arrangement (**266**; R = Ph), but here the molecule is again twisted and both forms ($\theta = \phi = 155°$) and ($\theta = 155°$, $\phi = 25°$) are observed. These observations, together with PPP MO calculations, have allowed the interpretation of the UV spectra of these acylpyridines ⟨81JST(73)49, 81JST(75)141⟩.



cis (**265**) *trans* (**266**)

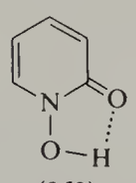
The barrier to methyl rotation in 4-methylpyridine has been measured by means of proton spin lattice relaxation time ⟨74MI20405⟩, and found to be very low, about 0.06 kJ mol^{-1}. This is in line with *ab initio* calculations using a minimal STO-3G basis set ⟨76JST(32)67⟩, and MINDO/3 MO calculations ⟨79JST(57)209⟩, the second of which also show that the equilibrium position for the methyl group is with one hydrogen atom in the plane of the pyridine ring.

Rotation barriers have also been looked at ⟨80TL1553⟩ in *N*-substituted 2,4,6-trimethylpyridinium cations (**267**). In addition to diastereotopic protons H_A and H_B, the α-Me and β-protons are anisochronous as shown by ^{1}H NMR, as are the α-Me, α-ring and β-ring carbons, as shown by ^{13}C NMR. This anisochronism appears to be due to hindered rotation about the pyridinium N—C bond (**268**), the stable conformation being that in which the hydrogen atom on the sp^3 C is in the plane of the pyridine ring. Observation of coalescence temperatures in deuterated acetone or pyridine solvent allows calculation of energy barriers to this rotation, and these are as follows: (**267**; R = Me, R′ = H), 7.1; (**267**; R = Me, R′ = COMe); (**267**; R = Et, R′ = H), 8.1 kJ mol^{-1}.



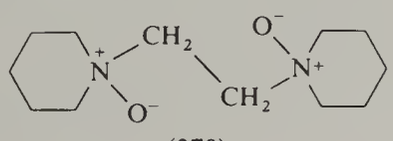
(**267**) (**268**)

It has already been noted (Section 2.04.4.2) that 1-hydroxypyridin-2-one exists in that tautomeric form in both ground and excited states. Strong intramolecular hydrogen bonding of the monomer in nonpolar solvents shows the *syn* conformer (**269**) is the preferred one in the ground state ⟨49JCS2091⟩. In the excited singlet state, dual fluorescence is observed ⟨81TL1515⟩; in C_6H_{12} with a maximum of 3700 Å, and in MeOH with a maximum of 4000 Å. The shorter wavelength is ascribed to the *syn* conformer, and the latter to the *anti* conformer. Solvent induced rotational isomerism thus appears to occur in the excited state.

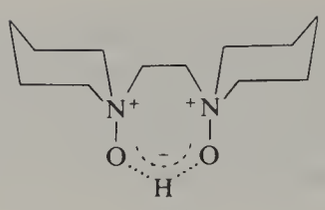


(**269**)

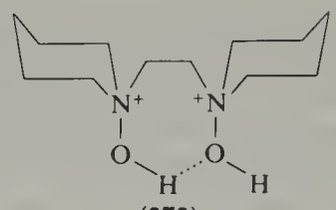
IR studies together with ^{1}H NMR have been of importance in deciding the conformations of 1,2-di(*N*-piperidyl)ethane bis-*N*-oxide (**270**) in its mono- and diprotonated forms ⟨79JST(52)77⟩. In aqueous methylcellosolve solutions the *cis* isomers (**271**) and (**272**) predominate, while in water the equilibrium shifts in favor of the *trans* isomers (**273**) and (**274**).



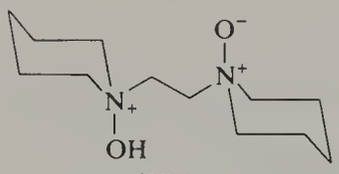
(**270**)



(271)



(272)



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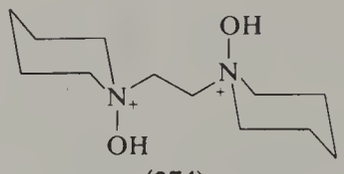

(274)

In the crystal, where the molecule exists with four molecules of water, X-ray measurements reveal a precise *trans* orientation. These measurements provide a final example to illustrate the fine details of structure and conformation which are available from the use of modern physical techniques.

2.04.6 SUMMARY

In these discussions, we have focused attention on details of the physical measurements which confer understanding of structure in pyridine based compounds: bond lengths, bond angles, electronic levels in both ground and excited states, and the involvement of solvation, complexation and other environmental features. In the latter, we have, out of necessity, restricted ourselves generally to complexes in which the role of the pyridine structure is of paramount interest, for the whole of the available space could have been filled with lists of complexes incorporating these structures, but where they were of subordinate interest to some other feature, typically the mode of coordination of metallic ions.

Listing of spectral data has also been eschewed; such compilations are conveniently available elsewhere. Here we have been more concerned with the light such measurements throw on structural detail than on the value of the measurements for their own sake. We therefore conclude with a bibliography of where these and other relevant details are available. Many have already been referred to in appropriate parts of the chapter, but this will enable us to finish with an acknowledgement of the great assistance such previous reviews have been in the preparation of the present text: 'Physical Methods in Heterocyclic Chemistry', edited by A. R. Katritzky; 'The Chemistry of Heterocyclic Compounds', edited by A. Weissberger and E. C. Taylor; 'Advances in Heterocyclic Chemistry', particularly Supplement 1, 'The Tautomerism of Heterocycles', by J. Elguero, C. Marzin, A. R. Katritzky and P. Linda; 'Hetero-aromatic Nitrogen Compounds. Pyrroles and Pyridines', by K. Schofield; 'NMR Spectra of Simple Heterocycles', by T. J. Batterham; 'Mass Spectrometry of Heterocyclic Compounds', by Q. N. Porter and J. Baldas.

2.05

Pyridines and their Benzo Derivatives: (ii) Reactivity at Ring Atoms

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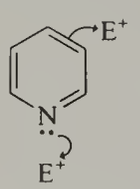
2.05.1 GENERAL SURVEY OF REACTIVITY

2.05.1.1 Neutral Molecules

Replacing a CH group of benzene, naphthalene and anthracene with a nitrogen atom gives, among others, the heterocycles (**1**)–(**4**). These all undergo electrophilic attack readily at nitrogen, but attack at a pyridine ring carbon (C-3) is considerably slower than in benzene. The pyridine nitrogen may have a deactivating effect upon electrophilic attack at position 3 comparable with that of a nitro group on the *meta* position of nitrobenzene. However, pyridines exist mainly in the protonated form under the strongly acidic conditions required for, say, nitration or hydrogen isotope exchange. Therefore, if the free base is the reacting species, very little of it is available for reaction. Nitration of pyridine can be achieved in only very low yield under extreme conditions, and hydrogen isotope exchange with pyridine itself has yet to be reported. The benzo derivatives of pyridine of course react with electrophiles much more readily at the benzene ring, but again protonation at nitrogen slows the observed rate of reaction. Substitution at C-3 in quinoline (during bromination, or nitration in acetic anhydride) occurs by an addition–elimination mechanism rather than an S_EAr process.



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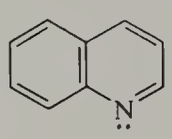

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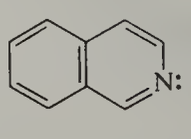

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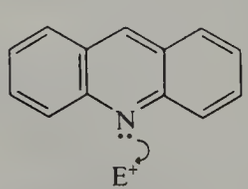
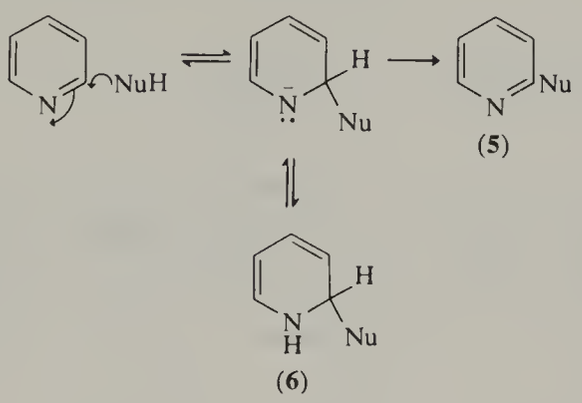
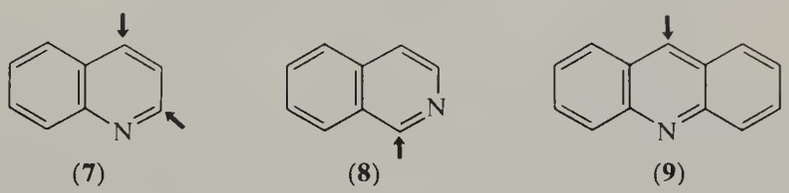


(4)

Nucleophilic reagents attack pyridine at the α-position to form an adduct that rearomatizes by dissociation (Scheme 1). Only very strong nucleophiles, *e.g.* NH_2^-, RLi, LAH, $Na–NH_3$, react, and for the second step to afford a substitution product (**5**), conditions that favour hydride loss are required. Adducts formed with hydride ions (from LAH) or carbanions (from lithium alkyls) are relatively more stable than the others at low temperature, and dihydropyridines (**6**) can be obtained by careful neutralization. Fusion of a benzene ring to pyridine increases reactivity towards nucleophiles, and attack is now found at both α- and γ-positions in quinoline (**7**) and at C-1 in isoquinoline (**8**). This may be attributed to a smaller loss of aromaticity in forming the initial adduct than in pyridine, and thus a correspondingly decreased tendency to rearomatize is also observed. Acridine reacts even more easily, but nucleophilic attack is now limited to the γ-position (**9**), as attachment of nucleophiles at ring junctions is very rare.



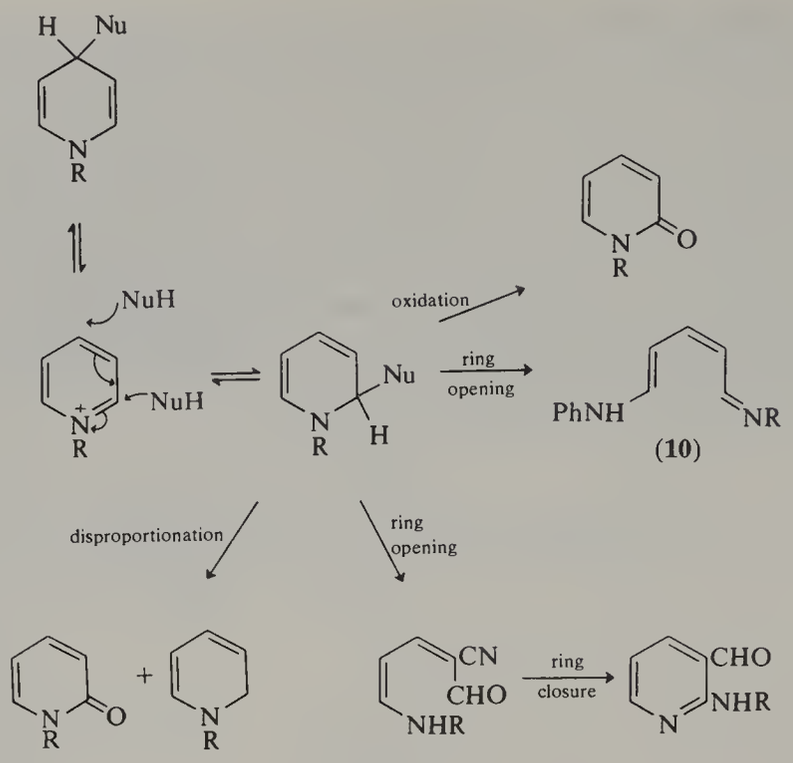
Scheme 1



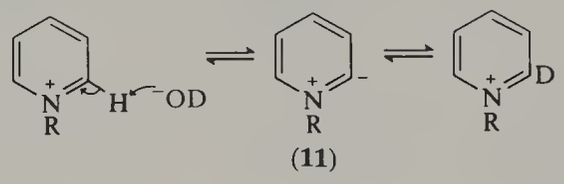
Free radical attack at the pyridine ring is noted for its low selectivity and substituents have little effect. Arylation takes place at all three positions, but halogen atoms preferentially attack the α-, and alkyl radicals the α- and γ-positions. Metals such as sodium and zinc transfer a single electron to pyridine to form anion radicals. These can dimerize by reaction at the α- or γ-position to yield dipyridyls by loss of hydride ion. Thus, reduction of pyridine by chemical and catalytic means is easier than reduction of benzene.

2.05.1.2 Pyridinium Cations

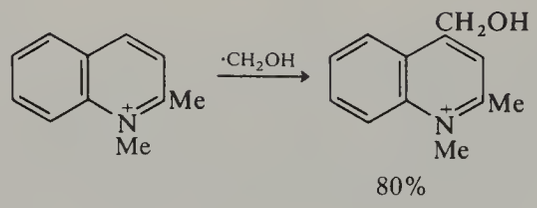
N-Substituted pyridinium salts and conjugate acids are very deactivated indeed towards electrophilic attack by the positive charge they bear. Only those with one or more activating substituents attached give significant reaction, usually at C-3. The deactivating effect of the positive pole directs electrophilic reactions to the benzo substituent in acridine and the quinolines. Conversely, the positive charge in pyridinium ions favours attack by nucleophiles at the α- (usually) or γ-positions under mild conditions to give adducts (Scheme 2). Examples of such nucleophiles are hydroxide, alkoxide, sulfide, cyanide, amines, carbanions and organometallic compounds. Sometimes these adducts can be isolated, but they normally undergo further reaction very rapidly (Scheme 2). Three pathways are followed on treatment with sodium hydroxide: oxidation, disproportionation, and ring opening followed by ring closure on to a suitable 3-substituent (*e.g.* 3-CN), overall an ANRORC reaction. Heating a pyridinium salt bearing an electron withdrawing R-group with aniline at 100 °C yields a stable ring-open product (**10**) (the Zincke reaction). Nucleophilic attack at a hydrogen atom attached at C-2 can also occur under mild conditions to give an ylide (**11**) which is the intermediate in base catalyzed hydrogen–deuterium exchange (equation 1). Pyridinium salts undergo electron transfer reactions with free radicals and these provide some high-yielding selective ring substitution reactions (equation 2).



Scheme 2



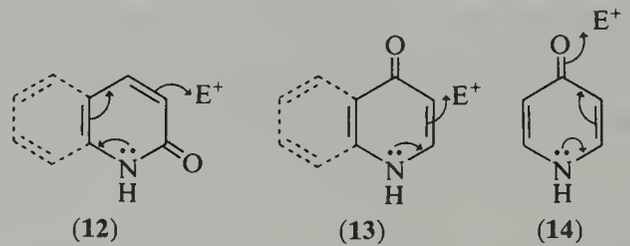
(1)



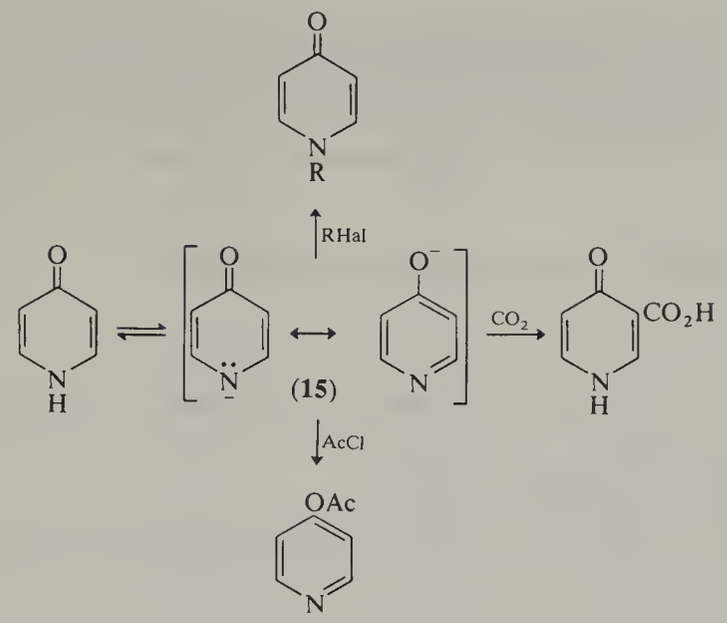
(2)

2.05.1.3 Pyridinones

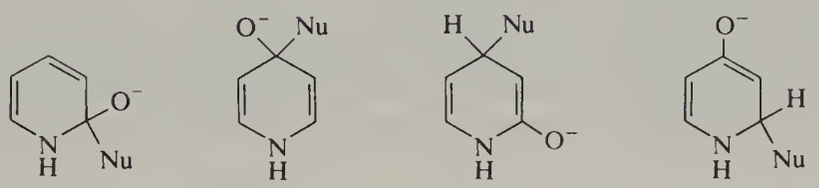
Pyridinones and quinolinones undergo electrophilic attack at the β-position (**12, 13**) fairly easily and disubstitution is well known in the pyridine series. Pyridinones are more easily halogenated than benzene, but the highly acidic conditions used for nitration and sulfonation makes these less easy reactions. Electrophiles also attack at the oxygen (**14**), but this is considered as a substituent reaction and therefore will be dealt with in Chapter 2.06.



Nucleophilic reagents can attack the N—H hydrogen to yield an anion (**15**) which reacts readily with electrophiles at the nitrogen, oxygen and β-carbon atoms (Scheme 3). Strong nucleophiles may attack directly at the carbonyl groups to afford (**16, 17**) or in conjugate fashion to produce (**18, 19**); these intermediates usually rearomatize to pyridines (see Chapter 2.06). Reactions of free radicals with pyridinones are not very numerous.



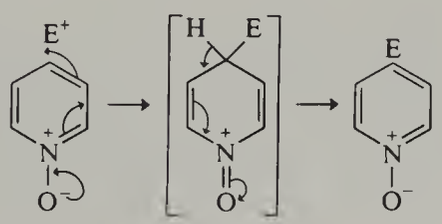
Scheme 3



(16) **(17)** **(18)** **(19)**

2.05.1.4 *N*-Oxides

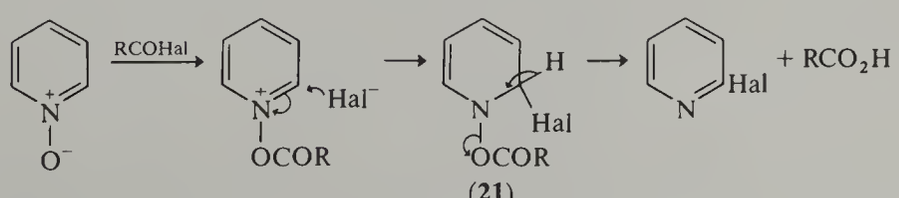
Pyridine 1-oxide is remarkable in that it reacts easily with both electrophiles (as its free base) and nucleophiles. Activation toward electrophilic attack (at C-4) derives from donation of a pair of electrons by the *N*-oxide oxygen and the involvement of a relatively stable Wheland intermediate (**20**) (equation 3).



(3)

(20)

Nitration, by the relatively hard electrophile NO_2^+, is a classic example of 4-substitution, but some softer electrophiles (*e.g.* mercury(II) acetate) favour attack at C-2. The *N*-hydroxypyridinium cation undergoes electrophilic attack (*e.g.* sulfonation in oleum) at the 3-position, which is analogous to the behaviour of other pyridinium ions. *N*-Oxides react with electrophiles like alkyl halides at oxygen to give *N*-alkoxy quaternary salts. Acyl halides also react in the same way with *N*-oxides, but the quaternary salt formed rapidly undergoes attack by the counter-ion before it can be isolated (Scheme 4). Strong nucleophiles (*e.g.* Grignard reagents) attack at the α-carbon atom to form an adduct which rearomatizes with loss of the *N*-oxide oxygen. They can also, as with quaternary salts, abstract an α-hydrogen to give an ylide intermediate. Weaker nucleophiles (*e.g.* cyanide or chloride) require coordination of the *N*-oxide function before they are able to attack the α- or γ-carbons in the ring, as in the second step of Scheme 4. The intermediate (**21**) eliminates an acid to ultimately give overall α-substitution.



(21)

Scheme 4

The main principles of pyridine reactivity and how they influence attack at ring atoms have been stated briefly. The most important examples of these reaction types will now be examined in some detail. It will be seen that the principles provide an invaluable, though not infallible, guide to understanding and classification. However, each reaction will have nuances of its own, and some will provide occasional surprises.

2.05.2 ELECTROPHILIC ATTACK AT NITROGEN

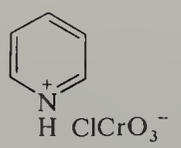
2.05.2.1 Introduction

The lone pair on a pyridine nitrogen reacts with electrophiles under mild conditions.
Protonic acids give salts.
Lewis acids form coordination compounds.
Transition metal ions form complex ions.
Reactive halogen compounds and alkyl halides give quaternary salts.
Activated alkenes (and alkynes) give quaternary salts (Michael reaction).
Halogens form adducts.
Certain oxidizing agents yield amine oxides.

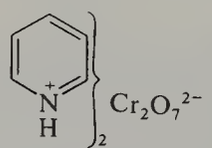
The ease of the above reactions is controlled by the electronic effect of substituents and, as one might expect, electron-releasing groups usually promote and electron-withdrawing groups suppress reaction. In the case of an α-substituent the crucial factor usually proves to be its size; one or two large α-groups can prevent quaternization by all except protons.

2.05.2.2 Salt Formation and Protonation

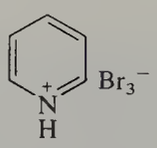
Pyridine ($pK_a = 5.20$) is considerably less basic than an aliphatic amine ($pK_a \sim 10$) but it and its derivatives readily form pyridinium salts with acids. These have been used to characterize pyridines and their benzo analogues (*e.g.* hydrochlorides, platinichlorides and picrates). A salt that has gained prominence of late is pyridinium chlorochromate (Corey's reagent) (**22**) which has proved to be a mild oxidizing agent for effecting the conversion of alcohols to carbonyl compounds ⟨75TL2647, B-80MI20500⟩. Two other pyridinium salts are notable oxidizing agents, py_2CrO_3 (Collins reagent) and pyridinium dichromate (**23**). Pyridinium chlorochromate and dichromate have been made in polymeric form by oxidation of crosslinked poly-4-vinylpyridine ⟨81JOC1728⟩. These polymers are as effective oxidizing agents as the pyridinium salts (**22**) and (**23**), with the added advantages derived from being polymer-supported reagents. Pyridine hydrobromide dibromide (**24**) is a well-known brominating agent and it too has been made in polymeric form ⟨77MI20500, B-80MI20501⟩.



(**22**)



(**23**)



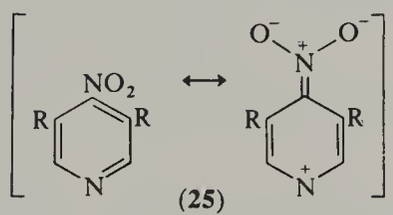
(**24**)

Protonation is the most studied reaction of pyridine nitrogen. It has attracted so much attention because of its practical importance and as a testing ground for quantitative theories of substituent effects ⟨76AHC(20)1⟩. A list of the pK_a values of some of the more common pyridines and their *N*-oxides appears in Table 1. Almost all simple alkylpyridines are more basic than pyridine itself, but electron withdrawing substituents attached to ring carbons reduce the basicity relative to pyridine. That electronic effects outweigh steric ones is exemplified by the pK_a of 2,6-lutidine (6.69) being higher than that of 2-picoline (5.97). Successive increase in the size of α-alkyl substituents leads to slightly less than the estimated additive enhancement of base strength, but steric effects do not predominate until very large groups are introduced at both the 2- and 6-positions. Only in the case of 2,6-di-*t*-butylpyridine (3.58) does the pK_a fall below that of pyridine. Changing the size of a 4-alkyl substituent has little effect on pK_a. The influence of potential resonance donors and acceptors (attached at β- or γ-positions in pyridine) on the nitrogen basicity are of long standing interest ⟨B-67MI20500⟩. Some time ago it was shown ⟨63JCS2225⟩ that a 4-nitro substituent reduces the basic strength of a pyridine nitrogen by its inductive effect alone. Ionization

Table 1 pK_a Values for the Dissociation of some Monosubstituted Pyridinium Ions and their *N*-Oxides

	pK_a *Pyridine* (N-*oxide*)	pK_a *Pyridine*	pK_1, pK_2 *Pyridine*	pK_1, pK_2 (N-*oxide*)
Position substituent	Me	Pr^n	OH	
2-	5.97 (1.02)	5.97	0.75, 11.62	(−0.8, 5.99)
3-	5.60 (1.08)	—	4.68, 8.72	(6.4)
4-	6.03 (1.29)	6.05	3.27, 11.09	(2.45, 5.9)
	Et	Pr^i	NH_2	
2-	5.93 (1.19)	5.83	−7.6, 6.86	(2.67)
3-	5.63 (0.97)	5.72	−1.5, 5.98	(1.47)
4-	5.95	6.02	−6.3, 9.17	(3.69)
	Bu^t	$CHCH_2$	NMe_2	
2-	5.76	4.98	−10.21, 6.94	(2.27)
3-	5.82 (0.84)	5.54	−2.11, 6.37	—
4-	5.99 (1.16)	5.64	−9.28, 9.71	(3.88)
	Ph	CH_2Ph	CO_2H	
2-	4.48 (0.77)	5.13	1.01, 5.32	—
3-	4.80 (0.74)	—	2.07, 4.81	(0.09, 2.7)
4-	5.55 (0.83)	5.59	1.84, 4.86	(−0.48, 2.9)
	OMe	F	CHO	
2-	3.28 (1.23)	−0.44	3.80, 12.80	—
3-	4.88	2.97	3.80, 13.10	—
4-	6.62 (2.05)	—	4.77, 12.20	—
	NO_2	Br	SH	
2-	−2.63 (−2.13)	0.79	−1.07, 9.97	(−1.95)
3-	0.81	2.84	2.28, 7.01	—
4-	1.61 (−1.7)	3.78	1.43, 8.83	(1.53)
	Cl	SO_3H		
2-	0.72 (−0.83)	1.75	— —	—
3-	2.81 (1.34)	3.22	— —	—
4-	3.83	3.44	— —	—

constants were measured for a series of 4-nitropyridines bearing 3- (and 5-) alkyl substitutents of increasing size to twist the nitro group out of the plane of the ring and suppress any resonance contribution (**25**). Values of ΔpK_a (obtained by comparison with the pK_a of the parent alkylpyridine) were virtually invariant for the substituents 3-H, 3-Et, 3-Pr^i, 3,5-Me_2, 2,3,5,6-Me_4, indicating an insignificant resonance contribution. Consistent with this, a good correlation has been found between pK_a values for a series of pyridines bearing resonance acceptors at the 4-position and σ_I values ⟨64JCS3591⟩. A recent comprehensive study ⟨81JOC891⟩ has confirmed that resonance acceptors make a negligible contribution to pyridinium ion acidities and that their effects are small or even reversed in the gas phase.



(**25**)

Quite the contrary is true for strong resonance donors in the 4-position of the pyridine ring; they raise pK_a values by exerting a considerable resonance effect. This was first detected by introducing 3- and 5-alkyl groups into 4-dimethylaminopyridine and measuring the variation of pK_a with temperature for the resultant base (Table 2) ⟨61JCS3939⟩. As the steric effect of the substituent is increased the 4-dimethylamino group exerts progressively less influence as a base-strengthening substituent, because coplanarity with the ring can no longer be achieved. That this is due to the steric inhibition of resonance was confirmed by the progressive drop in ΔpK_a and ΔH whilst $T\Delta S$ remains steady ($T\Delta S$ for the 3,5-dimethyl derivative appears lower, but the error in this case is high). So in this series basicity is determined by an intrinsic effect, steric inhibition of resonance, rather than by external factors such as solvation. This is as one might expect because the 3- and 5-substituents are remote from the site of protonation.

Table 2 Ionization Constants in Aqueous Solution at 20 °C and Arrhenius Parameters for 4-Dimethylaminopyridines

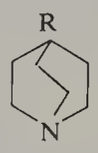
Substituent	pK_a	ΔpK_a	ΔG^a	ΔH^a	$T\Delta S^a$
3-H	9.71	4.44	13.01	10.75	2.26 ± 0.31
3-Me	8.68	2.89	11.64	9.02	2.62 ± 0.19
3-Et	8.66	2.86	11.62	9.15	2.47 ± 0.38
3-Pr^i	8.27	2.39	11.09	8.76	2.33 ± 0.27
3,5-Me_2	8.15	1.92	10.93	9.83	1.10 ± 0.71

[a] Expressed in kcal mol^{-1} (kJ $mol^{-1} \equiv$ kcal $mol^{-1} \times 4.18$).

Lately it has been established ⟨81JCS(P2)409⟩ that effects (for β- or γ-substituents) on nitrogen reactivity are an intrinsic property of the system and they are independent of reaction type and solvent. Furthermore, a convincing argument is made against the use of the dual substituent parameter equation (equation 4) which has been employed to try to

$$\log (K/K_0) = \rho_I \sigma_I + \rho_R \sigma_{R^+} = 5.15\sigma_I + 2.69\sigma_{R^+} \quad (4)$$

accommodate the effect of 4-substituents on pyridine protonation. Another approach has employed the effect of a substituent R on the protonation of a series of quinuclidines (**26**) as a model for inductive effects in pyridines. A plot of pK_a values for protonation of 4-substituted pyridines against the pK_a values of the corresponding 4-substituted quinuclidines is linear.



(**26**)

The strong base-weakening effect that halogens have on pyridines and their *N*-oxides (Table 1) makes available a series of Hammett indicators of decreasing pK_a. This has facilitated the investigation of the effect of temperature on the H_0 (protonation of pyridines) and H_A (protonation of amides and pyridine 1-oxides) acidity functions. Pyridinones are weak bases which undergo protonation on oxygen and, as might be expected for cyclic amides, those that protonate outside the pH region usually follow the amide acidity function H_A. Acid–base behaviour of this class is discussed in more detail in Chapter 2.04, which is concerned with tautomerism. Monoprotonation of aminopyridines and their mono- and di-alkyl derivatives occurs at the pyridine nitrogen in the pH region. The pyridinium cations so formed are strongly deactivated towards further protonation at the amino nitrogen. Ionization constants for benzo analogues of pyridine appear in Table 3. Quinoline is less basic than pyridine, and so is isoquinoline, but only marginally so.

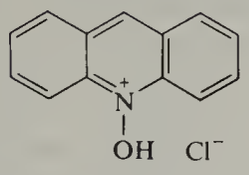
Table 3 pK_a Values for the Dissociation of some Benzopyridinium Ions

System / *Substituent*	*Substituent position*							
	None	*2-*	*3-*	*4-*	*5-*	*6-*	*7-*	*8-*
Quinoline	4.87	—	—	—	—	—	—	—
Methyl	—	5.41	5.14	5.20	4.62	4.92	5.08	4.60
Nitro	—	—	1.03	—	2.73	2.76	2.44	2.59
Isoquinoline	5.14	—	—	—	—	—	—	—
Nitro	—	—	—	1.35	3.53	3.47	3.61	3.59
Acridine	5.60		Benzo[*f*]quinoline		5.13	Benzo[*h*]quinoline		4.25
Phenanthridine	4.52		Benzo[*g*]quinoline		5.05			

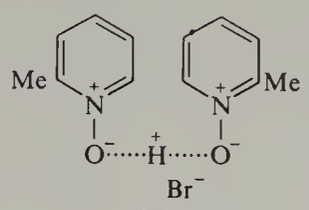
Values of pK_a for some selected derivatives are also listed to give some idea of how the position and nature of a substituent affects basicity. In quinoline 2- and 4-methyl groups have the greatest base-strengthening effect. Attachment of nitro groups at any position in either system has a strong base-weakening effect.

Pyridine, the quinoline and acridine *N*-oxides readily form salts (*e.g.* hydrochlorides (**27**) and picrates) which have been used for their characterization. Basic salts of the type $(ArNO)_2HX$ are also known; the structure (**28**) is indicated for 2-picoline 1-oxide hemihydrobromide based on IR evidence. A list of these salts has been compiled ⟨B-71MI20500⟩.

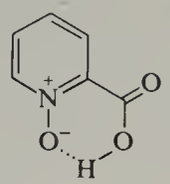
2-Carboxypyridine 1-oxide has been found to assume the hydrogen bonded form (**29**) in the solid state.



(**27**)



(**28**)



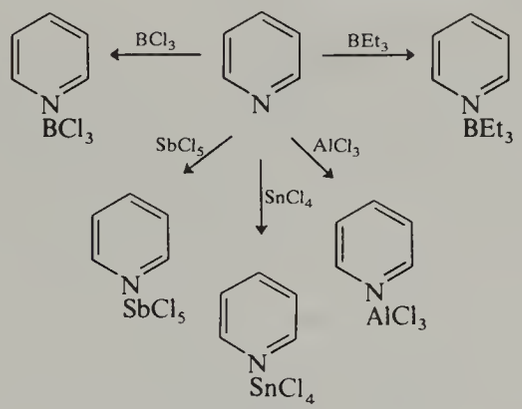
(**29**)

The pK_a values for pyridine 1-oxides are lower than those for the corresponding pyridines (Table 1). Electronic effects of substituents on pK_a values of *N*-oxides are in the same direction as in the pyridines but smaller in magnitude. This has been quantified by a Hammett correlation for the pK_a values of 3- and 4-substituted pyridine 1-oxides that yields a ρ value of 2.09, which compares with one of 5.71 for a series of similarly substituted pyridines.

A good correlation has been found between pK_a values for a series of pyridine 1-oxides and the corresponding pyridines. Weakly basic pyridine 1-oxides that protonate in the H_0 region have been shown to follow the H_A acidity function. Some of these have been used to extend the H_A scale and to determine its variation with temperature.

2.05.2.3 Lewis Acids

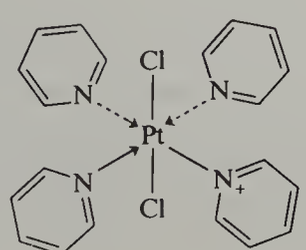
Pyridine gives adducts with halides of boron, aluminum, gallium, tin and antimony, and with various metal alkyls (Scheme 5). Both 2- and 6-substituents on pyridine exert a very much larger steric hindrance to addition of alkylboranes than to addition of a proton. Triethylaluminum forms pyridine complexes with greater facility than does the boron analogue, which at first sight appears rather unexpected. The explanation lies in the fact that the larger covalent radius of aluminum allows the Al—N bond to be formed at a greater distance, which reduces unfavourable steric requirements. Quinoline, isoquinoline and acridine also form adducts with many Lewis acids ⟨77HC(32-1)1⟩.



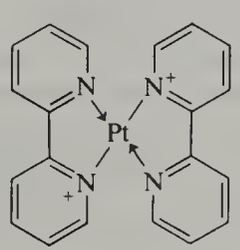
Scheme 5

2.05.2.4 Metal Ions

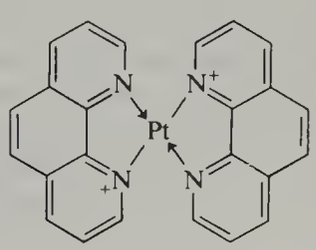
Examples of coordination complexes of pyridine with metals are legion and only a few can be mentioned here. Pyridine is a ligand in square complexes of gold ($AuEt_2Br{\cdot}py$) and copper ($Cupy_2{\cdot}Cl_2$). The cobalt complex $CoCl_4{\cdot}py_2$ has an octahedral structure. Nickel and platinum can coordinate with four pyridine molecules (**30**).



(**30**)

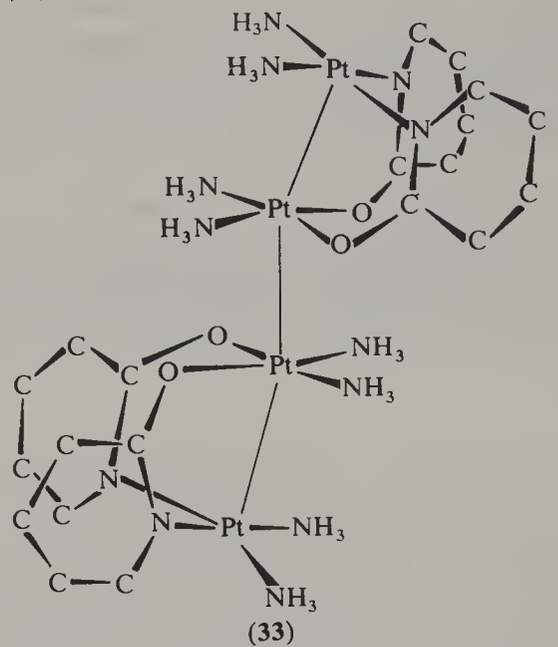


(**31**)



(**32**)

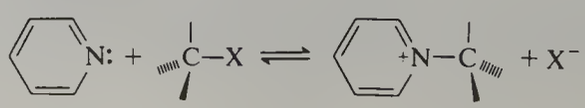
2,2′-Bipyridyl and its derivatives have many applications in analytical chemistry, for instance in the ferrioxalate actinometer ⟨64JCP(40)519⟩. They are bidentate chelating agents for many metal ions, amongst them iron, ruthenium, copper and platinum (**31**). A similar reagent is 1,10-phenanthroline, which complexes many metals, *e.g.* platinum in (**32**). A 6-substituent decreases the chelating ability of 2,2′-bipyridyls by a steric interaction, whilst 6,6′-disubstitution totally inhibits it. 3,3′-Disubstitution also reduces complexing ability. Efforts to find an alternative for the potent, but very toxic, antitumor agent *cis*-diammineplatinum has led to the preparation of *cis*-diammineplatinum-α-pyridone blue, $[Pt_2(NH_3)_4(C_5H_4NO)_2](NO_3)_5 \cdot H_2O$, which has the mixed valency oligomeric structure illustrated schematically in (**33**) ⟨79JA7269⟩.



(**33**)

2.05.2.5 Alkyl Halides and Related Compounds

The reaction of pyridines with alkyl halides to give quaternary salts is an example of the Menschutkin reaction ⟨1890MI20500⟩. Mechanistically pyridine quaternization has been regarded as usually involving an S_N2 process, namely nucleophilic attack by the pyridine on the alkyl halide (equation 5) ⟨74MI20502⟩, but recently this has been questioned ⟨80JA5892⟩ and defended ⟨81CC421⟩. For the purposes of this chapter quaternization is classified in the reverse sense as an electrophilic attack by an alkyl halide at a pyridine nitrogen. Examples of this reaction abound and many are to be found in pertinent reviews ⟨74HC(14-S1)309, 78AHC(22)71⟩. Pyridine reacts vigorously with methyl iodide, and benzyl and diphenylmethyl halides also react readily (Scheme 6) by the S_N1 mechanism. Tertiary alkyl halides undergo elimination in the presence of pyridines, but although quaternary pyridinium salts give alkenes on pyrolysis they are not involved in these reactions. In cases where isomeric alkenic products are possible, the proportions formed depend upon the steric requirements of the pyridine. For example, pyridine and pentyl bromide give 2-methylbut-1-ene (25%) (least substituted alkenic product, Hofmann's rule), but use of 2,6-lutidine gives the same alkene in 45% yield ⟨56JA2197⟩. Triphenylmethyl chloride (no β-hydrogens) reacts with pyridine under high pressure to yield triphenylmethylpyridinium chloride ⟨70JOC3752⟩. Primary halides are usually more reactive than secondary, and for a particular alkyl group attached to halogen the reactivity falls off in the order iodide > bromide > chloride. Electron donors attached at position 3 or 4 facilitate the reaction but 2-substituents hinder it. The effect of 3- and 4-substituents in pyridines on the rate of quaternization with ethyl iodide has been measured recently in several solvents ⟨81JCS(P2)409⟩. As expected, the rate of quaternization in dichloromethane drops with increasing electron demand by the 4-substituent (Table 4). This behaviour is typical in all solvents used (nitromethane, DMF, acetone, acetonitrile and nitrobenzene) except methanol. In methanol quite a different picture emerges; now the rate is virtually independent of the 4-substituent. It was suggested that this is due to

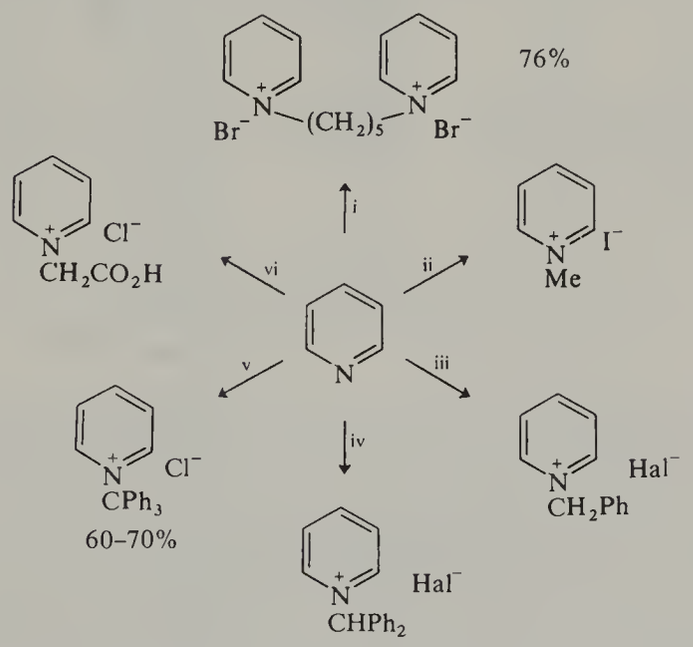


(5)

Table 4 Second Order Rate Coefficients for Reaction of Pyridines with Ethyl Iodide at 25 °C

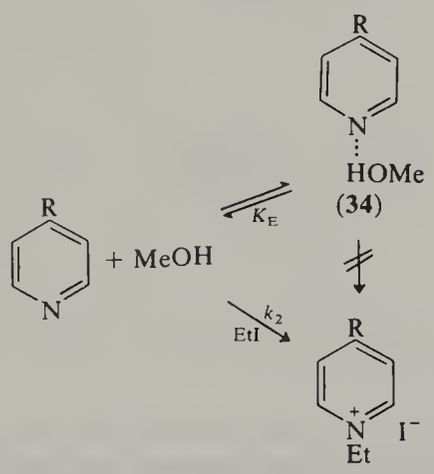
Substituent	*Rate coefficient* $\times 10^6$ (CH_2Cl_2)	*Rate coefficient* $\times 10^6$ (*MeOH*)
4-NMe_2	787	1.47
4-OEt	117	1.15
4-Me	89.1	1.21
H	32.9	1.12
4-COMe	9.44	1.07
4-COEt	9.17	—
4-CN	2.36	—

the free pyridine molecule being in equilibrium with a hydrogen bonded form (**34**) which is strongly favoured (Scheme 7). Therefore, the observed rate of quaternization is equilibrium controlled and depends upon $K_E \cdot k_2$.



i, $Br(CH_2)_5Br$; ii, MeI; iii, $PhCH_2Hal$; iv, Ph_2CHHal; v, Ph_3CCl, 60–70 °C, 4–5 kbar; vi, $ClCH_2CO_2H$

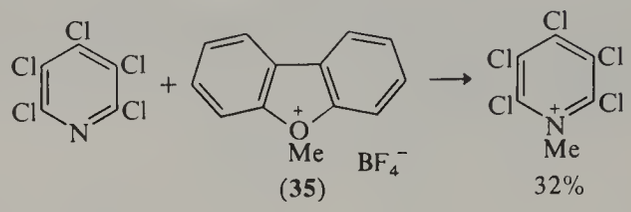
Scheme 6



Scheme 7

Very high deactivation is encountered in the alkylation of polyhalopyridines, but pentachloropyridine may be quaternized readily (83% yield) by the super-methylating agent methyl fluorosulfonate. This compound may also be methylated by the Meerwein reagent (**35**; equation 6) ⟨72CC315⟩. *N*-(4-Pyridyl)pyridinium chloride hydrochloride, which has a positive pole at position 4, defies methylation with methyl chloride but it succumbs to dimethyl sulfate (equation 7) ⟨70AJC1495⟩. Steric hindrance to alkylation by α and *peri* substituents presents the ultimate test of alkylating ability. Use of methyl iodide or methyl

fluorosulfonate at high pressures (known to promote quaternization reactions ⟨78CRV407⟩) enables the quaternization of the highly hindered acridine (**36**) (equation 8). Quaternization of 2,6-di-*t*-butylpyridine with methyl iodide under pressure gives the methyl derivative in only 20% yield. However, treatment of 2,4,6-tri-*t*-butylpyridine with methyl fluorosulfonate is more successful giving (**37**) in 60% yield (equation 9). Surprisingly, these salts are very stable even at 250 °C, at which point they sublime. It is felt that the *t*-butyl groups might hold the methyl on the nitrogen 'like the claws of a crab' ⟨75JA4015⟩. The same alkylating agent has been used to diquaternize di-2-pyridyl ether (equation 10). Quinoline and isoquinoline react with alkyl halides and dimethyl sulfate to form quaternary salts. The steric effect of a *peri* hydrogen in quinoline is greater than that of a 2-methyl group in pyridine towards alkylating agents and the effect is greatest for the largest alkyl halide (Table 5).



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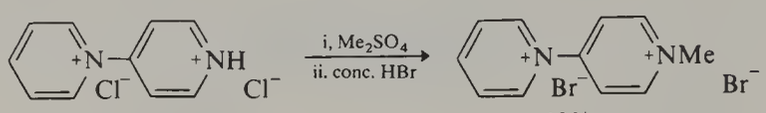

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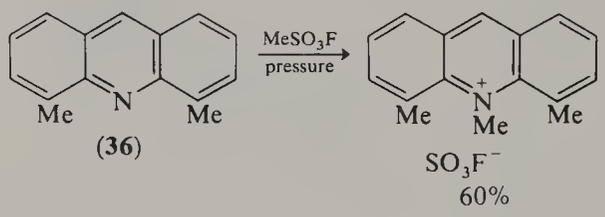

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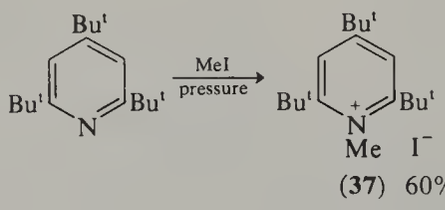

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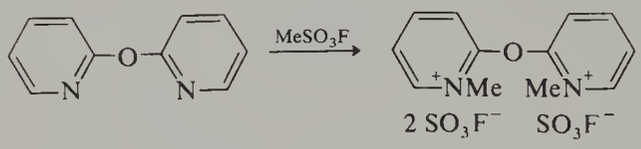


(10)

Table 5 Relative Rates of Alkylation of Pyridine Compared with Quinoline and 2-Methylpyridine

	MeI	*EtI*	*Pr^{i}I*	*Ref.*
Pyridine/quinoline	10	15	55	76AJC1745
Pyridine/2-methylpyridine	2.1	4.1	12	55JA1715

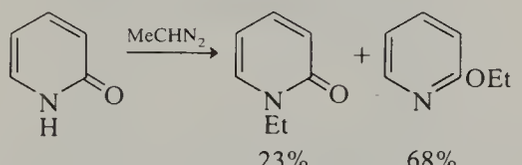
Pyridinones, 3-hydroxypyridine and their derivatives have presented a problem as they can undergo alkylation at either nitrogen or oxygen. The question of which isomer is formed, the yield and the quantitative separation of mixtures of *O*- and *N*-alkyl products in even simple cases has caused a lot of confusion until quite recently. For instance, it was widely believed until about 1966 ⟨62HC(14-3)509⟩ that treatment of pyridin-2-one with diazomethane gave exclusively 2-methoxypyridine, but in fact *N*-methylpyridin-2-one (55%) is the major product rather than the methoxypyridine (35%). These yields do not seem to vary much on changing the reaction solvent from diethyl ether–methanol to an aprotic solvent. However, changing the alkylating agent to diazoethane, under the same reaction conditions, gives predominant *O*-ethylation (equation 11).

More commonly, alkylation is performed by treating metal salts of pyridin-2-one with an alkyl halide; usually in a solvent ⟨74HC(14-S3)597⟩. Under these conditions the outcome depends upon the following factors: the nature of the metal, the alkyl halide (both the alkyl group and the halide ion), the substituents in the pyridinone, and the solvent. Perhaps the most striking example of the operation of some of these factors is seen in the benzylation of pyridin-2-one. Pyridin-2-one (silver salt) undergoes quantitative benzylation to 2-benzyloxypyridine with benzyl bromide in benzene, whilst treatment of its sodium salt with benzyl iodide in DMF gives virtually a quantitative yield of *N*-benzylpyridin-2-one ⟨67JOC4040⟩ (Table 6).

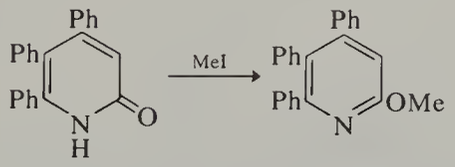
Table 6 Alkylation of Pyridin-2-one Salts

Alkylating agent	*Salt cation*	*Solvent*	*Overall conversion* (%)	N-*Alkyl* (%)	O-*Alkyl* (%)	*Pyridin-2-one* (%)
MeI	Ag	DMF	81	74	12	21
MeI	Ag	benzene	99	3	97	—
MeI	Na	DMF	93	95	5	—
EtI	Na	DMF	87	69	31	—
Pr^iI	Na	DMF	90	30	61	9
$PhCH_2I$	Na	DMF	99	98	2	—
$PhCH_2Br$	Na	DMF	95	97	3	—
$PhCH_2Br$	Ag	DMF	85	54	46	—
$PhCH_2Br$	Ag	benzene	100	—	100	—
$PhCH_2Cl$	Na	DMF	100	94	6	—
EtBr	Na	DMF	94	77	23	—
Pr^iBr	Na	DMF	84	29	68	3

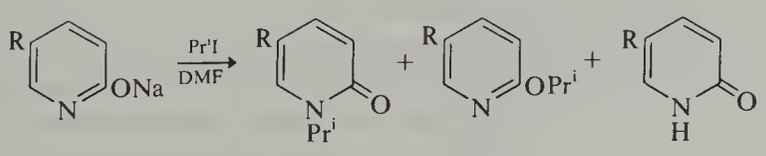
Predominant *N*-alkylation is found in the reaction of pyridin-2-one (sodium salt) with methyl iodide, but an increase in the size of the attacking alkyl group increasingly favours *O*-alkylation. This has been attributed to the greater steric hindrance toward *N*- compared with *O*-alkylation. This effect is seen to be at work again in the methylation of 4,5,6-triphenylpyridin-2-one with methyl iodide in methanol, which yields mainly the *O*-methyl product (equation 12). Electron withdrawing groups attached at the 5-position of pyridin-2-one favour an increase in *N*-alkylation (Scheme 8). The effect is more pronounced for silver salts ⟨70JOC2517⟩. The same study also revealed that silver salts undergo homogeneous reactions in DMF (mainly *N*-alkylation) and heterogeneous reactions in hexane and benzene (almost exclusive *O*-alkylation). Use of the phase transfer agent tetrabutylammonium bromide leads mainly to *N*-alkylation (~4 : 1) when 2- and 4-pyridinone anions are treated with alkyl (Bu^n, Pr^i, $PhCH_2$, allyl) bromides ⟨77JHC321⟩.



23% 68% (11)



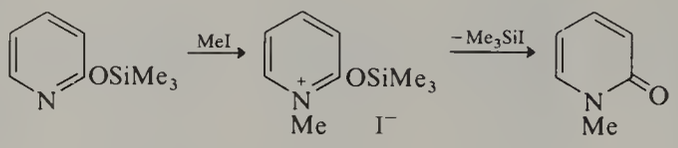
(12)



R = H	30%	61%	9%
R = CO_2Et	42%	51%	7%
R = NO_2	54%	46%	

Scheme 8

Specific *N*-methylation of pyridin-2-one has been achieved by conversion of the 2-oxo group to the trimethylsilyl ether before methylation (equation 13) ⟨64CB934⟩. Alkylation of pyridin-4-ones has been less well studied than that of the 2-isomer although the same problems have been encountered. Orientation is largely determined by '*ortho*' effects and again *N*- is more susceptible to these than *O*-alkylation. Thus, 3-nitropyridin-4-one undergoes *N*-methylation with methyl iodide (equation 14) ⟨59YZ1123⟩ whilst the pyridinone (**38**) undergoes exclusive attack at oxygen (equation 15), as does (**39**) (equation 16). A superior method ⟨77BCJ1510⟩ of achieving specific *N*-alkylation of 2- (and 4-) pyridinones in good yields utilizes dialkyl phosphates (equation 17). Methylation of pyridin-2-one proceeds smoothly to give *N*-methylpyridin-2-one at 171 °C. Only when the reaction is carried out at lower temperature is any *O*-methyl product formed. This product is rapidly converted into the *N*-methyl isomer at 171 °C. The relative ease of alkylation of pyridinones and quinolinones (sodium salts) has been determined and comparison of pyridinone:quinolinone pairs indicates that there is little steric hindrance to *N*-ethylation (ethyl iodide) for quinolin-4-one compared with pyridin-4-one, and none for the 2-isomer. However, 6-methylpyridin-2-one is considerably less reactive than pyridin-2-one. These apparent anomalies have been accounted for by tautomerism studies which indicate a greater aromaticity for quinolin-2-one relative to quinoline than for pyridin-2-one relative to pyridine.



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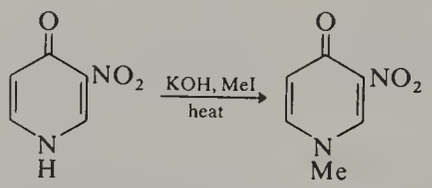

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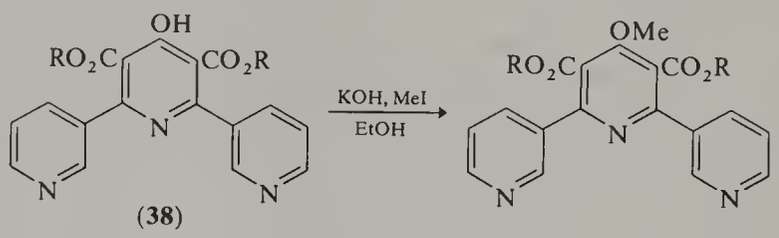
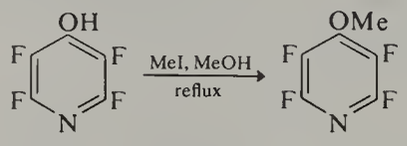


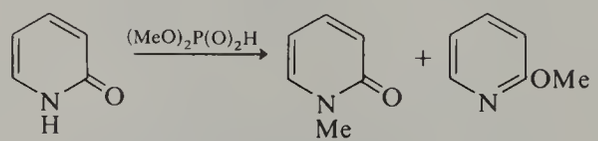
(38)

(15)



(**39**) 34%

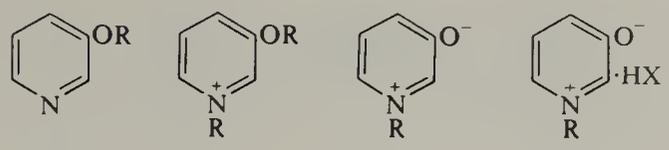
(16)



6 h, 171 °C	81%	—
11.5 h, 100 °C	52%	5%

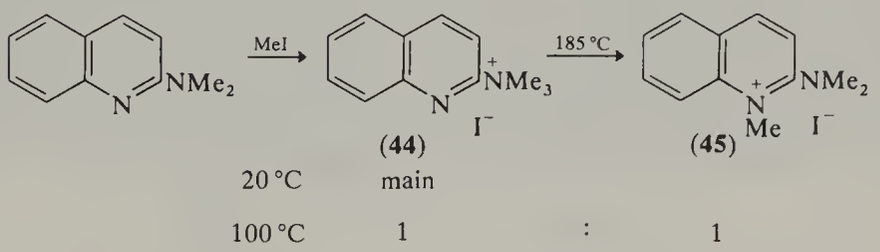
(17)

This results in a higher charge density on the nitrogen in quinolin-2-one compared with quinoline, and so alkylation of the former is favoured. This electronic effect outweighs the unfavourable steric effect when quinolin-2-one is compared with pyridin-2-one ⟨77AJC1349⟩. 3-Hydroxypyridine of course also shows ambident behaviour with alkylating agents, and products with the structures (**40**)–(**43**) have been claimed ⟨74HC(14-3)745⟩. *N*-Alkylation tends to be favoured ⟨59JA5140⟩ over attack at the substituent under most conditions, although as with pyridinones diazomethane gives mixtures ⟨57RTC58⟩. The best methods for *N*- (3-pyridinol, alkyl halide, *N*-propanol) ⟨59JA5140⟩ and *O*- (3-pyridinol sodium salt, alkyl halide in DMSO) ⟨69ACS(B)1791⟩ alkylation have been described.



(40) (41) (42) (43)

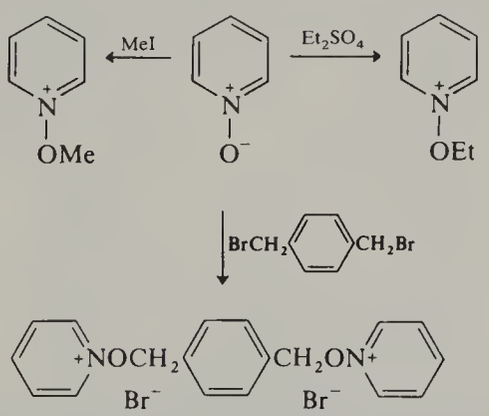
Alkylation of aminopyridines and their benzo analogues has presented many puzzles, the causes of which have been the availability of two sites for attack, dealkylation and rearrangement. The three aminopyridines react with methyl iodide at the nuclear nitrogen atom, but 2-aminopyridine gives small amounts of 2-methylaminopyridine. The latter process becomes more important with long chain alkyl halides. 2-Trimethylammoniopyridine is the principal product on treatment of 2-dimethylaminopyridine with methyl iodide, but the 3- and 4-isomers give ring methylation under these conditions. 2-Dimethylaminoquinoline yields the trimethylammonio derivative with methyl iodide at 20 °C. The sterically less hindered nitrogen undergoes attack at 20 °C, but when the reaction is carried out at 100 °C (**44**) and (**45**) are formed in roughly equal amounts (equation 18). Rather strangely, 1-dimethylaminoisoquinoline undergoes methylation at the annular nitrogen, which is the more sterically hindered of the two. Recently, 8-aminoquinoline was shown to undergo alkylation at the 8-substituent rather than at the ring nitrogen as previously reported.



(18)

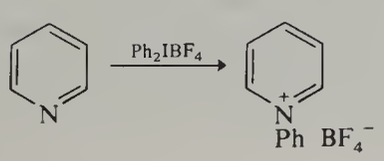
	(44)		(45)
20 °C	main		
100 °C	1	:	1

Pyridine 1-oxide and its benzo analogues undergo *O*-alkylation to form quaternary salts on treatment with alkyl iodides, bromides, sulfates or sulfonates (Scheme 9). The reaction is slowed down by bulky α-substituents and by electron-withdrawing groups attached to the β- or γ-positions. These reactions have been surveyed by several authors ⟨B-67MI20501, B-71MI20500, 74HC(14-S2)1⟩.

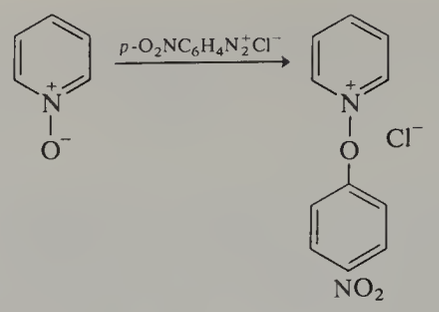


Scheme 9

Only activated aryl halides (*e.g.* 2,4-dinitrochlorobenzene and picryl chloride) react with pyridine, and the facility of these reactions is subject to much the same steric and electronic controls as alkylation. Picryl chloride forms characteristic yellow *N*-picryl derivatives with pyridines. These have been used to help separate, purify and characterize particular liquid pyridines. Pyridine also undergoes quaternization with diphenyliodonium fluoroborate (equation 19). Treatment of pyridine 1-oxides with arenediazonium salts yields aryloxy quaternary salts (equation 20).



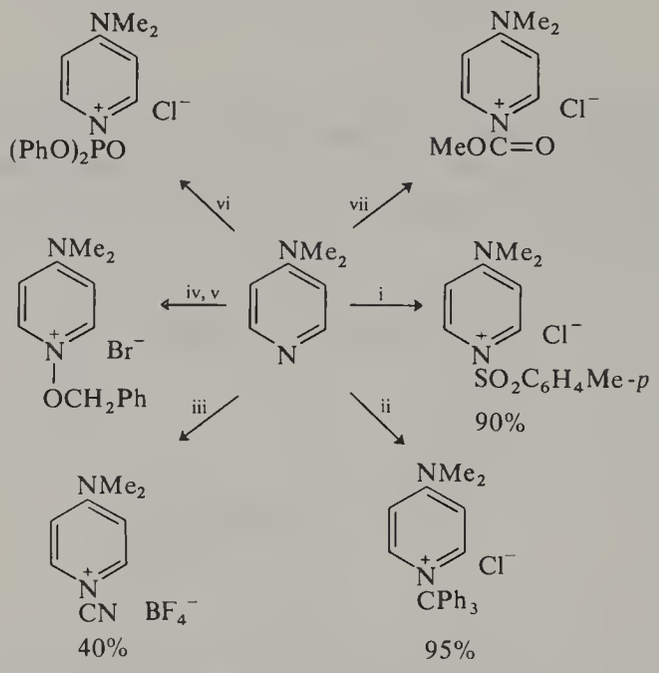
(19)



(20)

2.05.2.6 Acyl Halides and Related Compounds

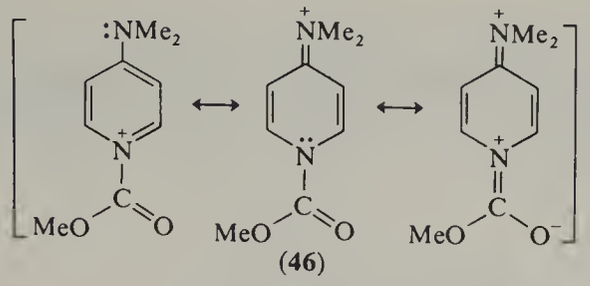
Pyridine reacts instantly with acyl and sulfonyl halides and anhydrides to give quaternary salts ⟨73RCR642⟩. These have rarely been isolated as they are so readily hydrolyzed. This property of course makes them good acylating and sulfonylating agents, which is the reason that pyridine is so often the solvent of choice for these reactions. They have been confirmed as intermediates in the pyridine-catalyzed acylation of water (or hydrolysis of acetic anhydride) ⟨70JA5432⟩ and postulated in the pyridine solution acylations of acyl chlorides (to anhydrides), diacyl sulfides and β-keto esters. *N*-Acetylpyridinium chloride has been isolated but it is of limited use as an acylating agent as it is insoluble in aprotic solvents. The so-called 'super nucleophiles' 4-dimethylaminopyridine (DMAP) and 4-*N*-pyrrolidinopyridine (PPY) are 10 000 fold more effective than pyridine in catalyzing acylation and related reactions ⟨78AG(E)569, B-82MI20500⟩. Examples of some of the highly reactive acyl and alkyl salts of DMAP that have actually been isolated are illustrated in Scheme 10.



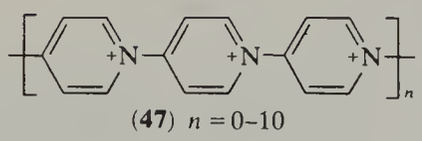
i, *p*-$MeC_6H_4SO_2Cl$, EtOAc, 0 °C; ii, Ph_3CCl, CH_2Cl_2, 25 °C; iii, $AgBF_4$, then BrCN, MeCN, 20 °C; iv, MCPBA; v, $PhCH_2Br$, MeCN; vi, $(PhO)_2POCl$, CH_2Cl_2, r.t.; vii, MeOCOCl, EtOAc, 0 °C.

Scheme 10

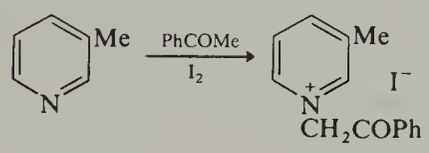
The remarkable stabilizing effect of the *p*-dimethylamino group on acyl- and sulfonylpyridinium derivatives is believed to be due to resonance stabilization of (**46**). Halopyridines may be viewed as being analogous to acid halides and they can undergo 'autoquaternization' to give a polymer (**47**) if not thoroughly purified before storage. Heating active methyl and methylene compounds with pyridine in the presence of iodine yields pyridinium salts (equation 21). This, the Ortoleva–King reaction ⟨63AG(E)225⟩ (see Chapter 2.04) has been employed in approaches towards Ipecacuanha alkaloids (Scheme 11) ⟨60JCS717⟩. Treatment of pyridine with thionyl chloride yields ultimately a pyridylpyridinium salt (**48**) but yields have proven to be variable ⟨B-64MI20500⟩. The mechanism of this reaction is also something of an enigma. That presented in Scheme 12, whilst plausible, has yet to be subjected to close scrutiny.



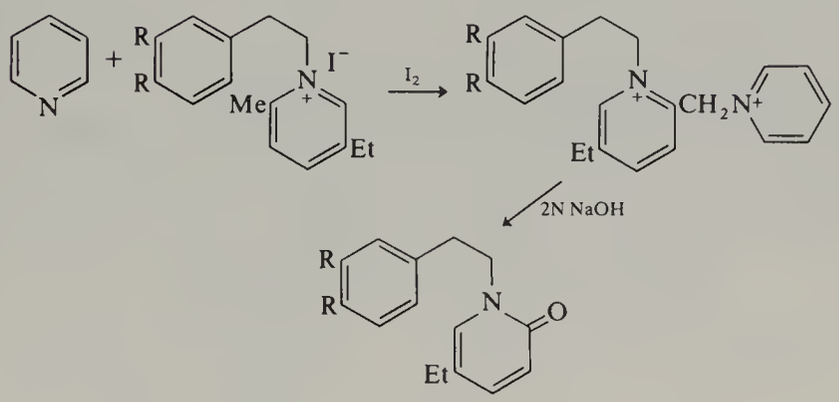
(46)



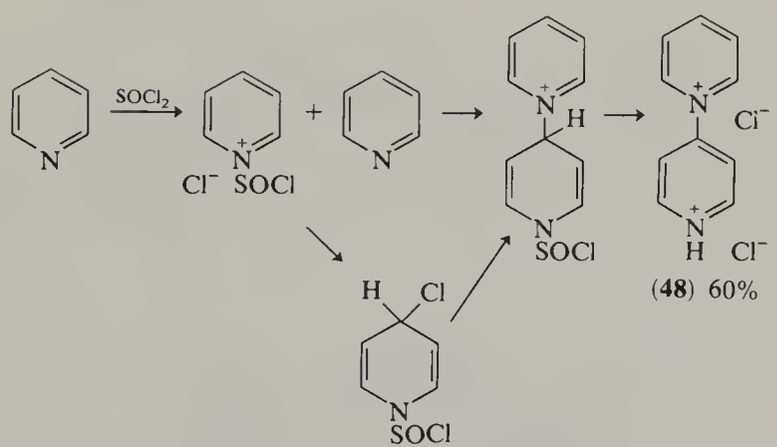
(47) $n = 0$–10



(21)

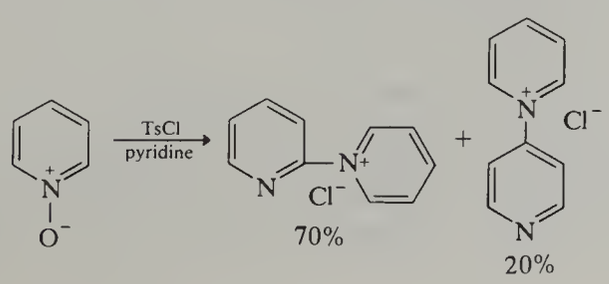


Scheme 11

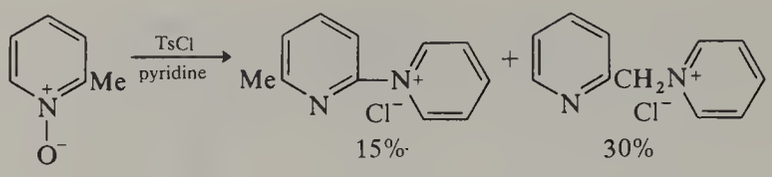


Scheme 12

Benzoylation constitutes the first step of the Reissert and Reissert–Henze reactions of quinoline and quinoline 1-oxides respectively, but as the benzoyl intermediates are rarely isolated this topic will be dealt with in Section 2.05.4.7. Pyridine and quinoline *N*-oxides react easily with *p*-toluenesulfonyl chloride in pyridine solution to give a variety of products which closely resemble those from the last two reactions discussed (equations 22 and 23). These belong to a family of reactions that have considerable synthetic potential and much mechanistic interest ⟨B-67MI20501⟩ which will be discussed collectively in Section 2.05.4.5.



(22)

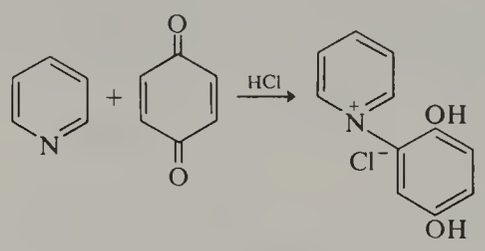


(23)

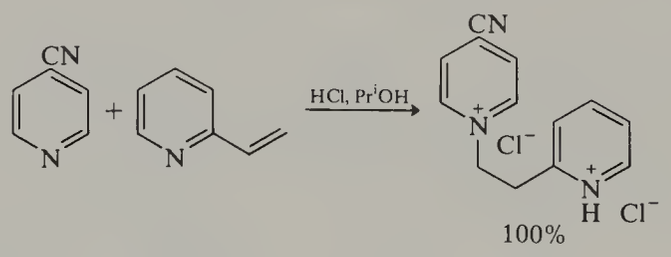
2.05.2.7 Activated Alkenes: Michael Type Reactions

Pyridines, quinolines and isoquinolines add to various Michael acceptors under acid catalysis (equations 24–27). Even pyridines bearing electron-withdrawing substituents undergo this reaction, but large α-substituents severely retard it. These reactions can be reversed by addition of base, but when this is slow and heating is necessary, nucleophilic ring opening often accompanies reversal. The addition of pyridines and several other heterocyclic bases to ethyl acrylate and related alkenes is often best carried out using the pyridinium chloride and Michael acceptor in an organic solvent. A special mechanism has been suggested to explain this (equation 28). 2-Vinylpyridine hydrobromide dimerizes at 160 °C, and the reaction may be partially or fully reversed (Scheme 13). The 2- and 4-vinylpyridines can undergo spontaneous polymerization on quaternization or protonation to give either ionene (**49**) or pendant polymers (**50**) ⟨71MI20501⟩.

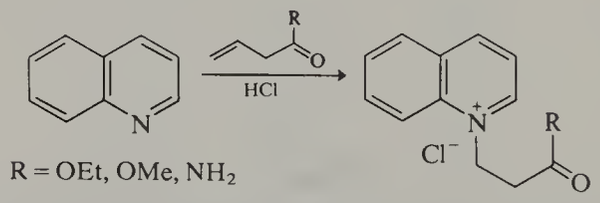
Cycloadditions of alkenes to pyridines will be considered later in Section 2.05.7.



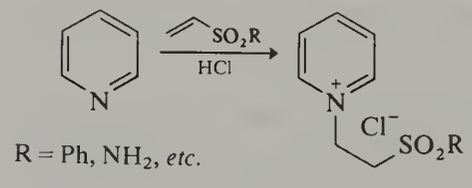
(24)



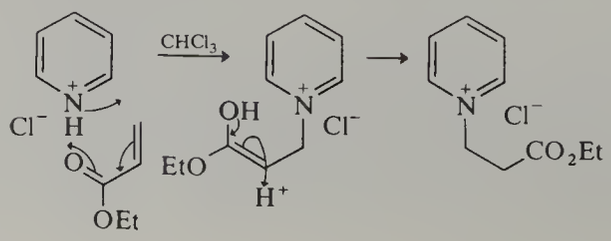
(25)



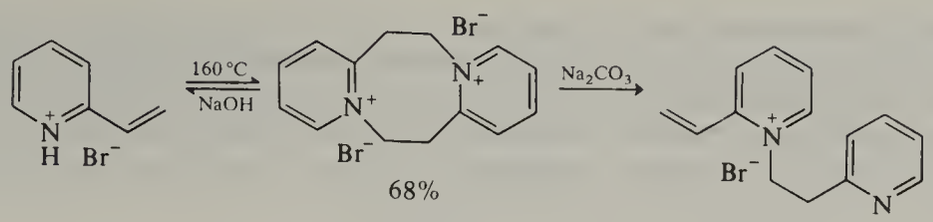
(26)



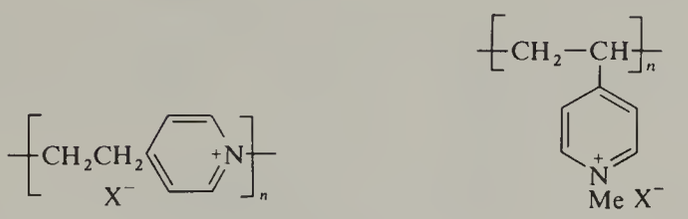
(27)



(28)



Scheme 13

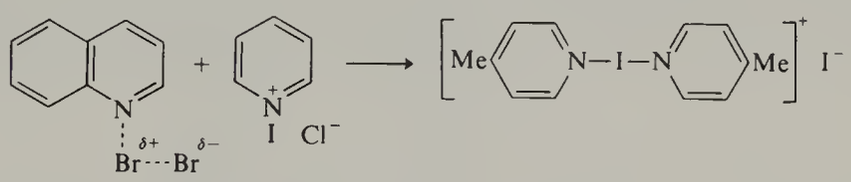


$X^- = CF_3CO_2^-, I^-, Cl^-$, *etc.*
(**49**)

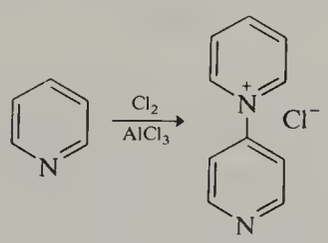
$X^- = MeSO_4^-, I$
(**50**)

2.05.2.8 Halogens

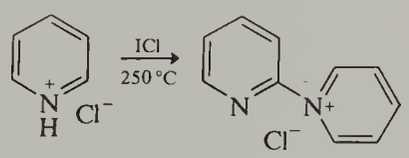
A very large number of complexes of pyridines and quinolines with all the halogens and interhalogen compounds are known, and as they have been enumerated elsewhere ⟨74HC(14-S2)407, 77HC(32-1)319⟩ just a few examples are illustrated (Scheme 14). Treatment of pyridine with chlorine or bromine in the presence of aluminum chloride yields 4-pyridylpyridinium salts (equation 29), but rather curiously the action of iodine chloride on pyridinium hydrochloride at 250 °C produces the 2-isomer (**51**; equation 30).



Scheme 14



(29)



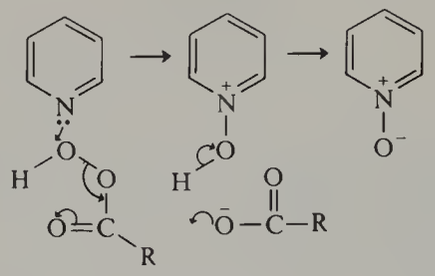
(30)

(**51**)

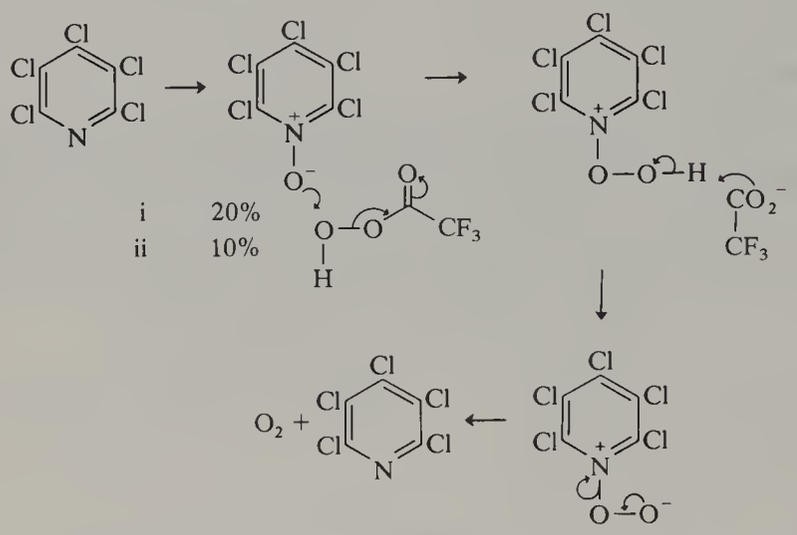
2.05.2.9 Peracids

Pyridine 1-oxide was first prepared by Meisenheimer ⟨26CB1848⟩, who oxidized pyridine with perbenzoic acid. Since that time many different peracids have been employed to achieve *N*-oxidation and the mechanism of the process follows the course shown (Scheme 15). A kinetic study has demonstrated that the oxidation of pyridine with perbenzoic acid in aqueous dioxane is second order and involves pyridine (free base) and the peracid. The rate falls off at low pH due to pyridinium ion formation, and at high pH it drops because of peracid anion formation. Like all the other reactions of electrophiles at pyridine-nitrogen the rate is enhanced by electron donating substituents, and slowed by acceptors and by large groups situated in the α-positions. Heating a deactivated pyridine with trichloroperacetic acid for a long period of time at a high temperature can lead to a drop in

yield owing to deoxygenation (Scheme 16) ⟨67CC893⟩. The preparative aspects of *N*-oxidation with peracids have been comprehensively surveyed by Katritzky and Lagowski ⟨B-71MI20500⟩, Ochiai ⟨B-67MI20501⟩ and Abramovitch and Smith ⟨74HC(14-S2)1⟩. The reagent of choice is usually peracetic acid which is prepared *in situ* from glacial acetic acid and 30% aqueous hydrogen peroxide. Temperature (20–90 °C) and time (3–24 h) of reaction are varied according to the reactivity of the heterocycle.



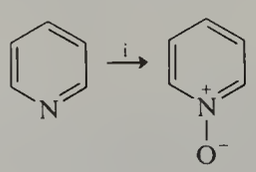
Scheme 15



i, CF_3CO_2H, 90% H_2O_2, 50 °C, 5 h; ii, CF_3CO_2H, 90% H_2O_2, 50 °C, prolonged heating

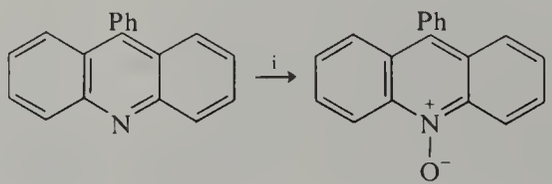
Scheme 16

The preparative procedure is typified by that for pyridine 1-oxide (equation 31) ⟨63OS(4)828⟩. Some of these reactions have been claimed to proceed faster and in better yield when inorganic peracids are present; pertungstic acid is worthy of note in this connection ⟨62USP3047579⟩. Aromatic peracids have found favour when less severe conditions are required for oxidation of sensitive heterocycles and they are usually carried out in organic solvents at room temperature. Perbenzoic acid is the favoured reagent for the oxidation of acridines (equation 32). Currently, *m*-chloroperbenzoic acid is very popular for *N*-oxidation of substrates bearing oxidizable substituents. For instance, 2-aminopyridine and 1-aminoisoquinoline can be converted to their *N*-oxides with the amino group left intact, thus avoiding the normal protection–deprotection sequence ⟨77SC509⟩. A new application of *N*-oxidation by a peracid has appeared recently in a study of the pathways of oxidation of polycyclic azaarenes. 3,4-Dihydrobenz[*a*]acridine-3,4-diol, which is not mutagenic in the Ames test ⟨76PNA950⟩, is oxidized by excess of *m*-chloroperbenzoic acid



(31)

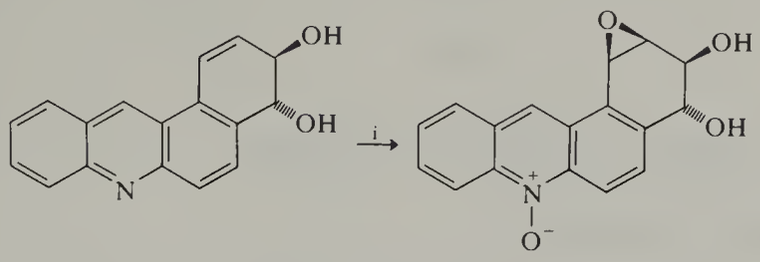
i, 40% $MeCO_3H$, 85 °C, 50–60 min



(32)

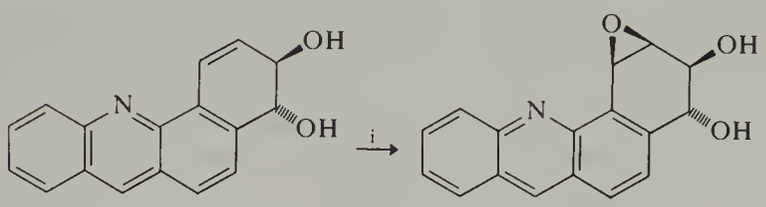
i, $PhCO_3H$, Et_2O, 0 °C, 2.5 h 61%

to an acridine *N*-oxide (equation 33). In contrast, 3,4-dihydrobenz[*c*]acridine-3,4-diol, found to be a mutagen in the Ames test, does not form an *N*-oxide under identical conditions, presumably due to a steric effect (equation 34). It is speculated that the ability of benz[*a*]acridines to form water soluble *N*-oxides provides a detoxification pathway for them ⟨81TL4687⟩.



(33)

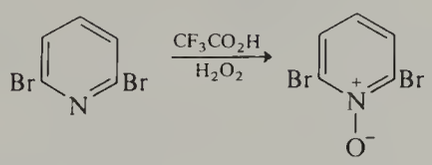
i, MCPBA(10 molar excess), dry THF



(34)

i, MCPBA (10 molar excess), dry THF

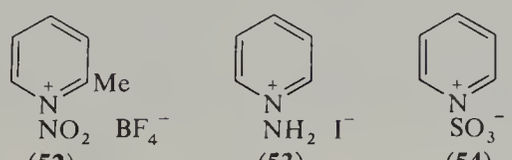
Perphthalic acid ⟨55OSC(3)619⟩ is an even milder reagent that works even at −20 to 20 °C. Performic, permaleic and pertrifluoroacetic acids are strong oxidizing agents and they are recommended for *N*-oxidation of the least reactive substrates. The last of the three is the most commonly used, especially for the oxidation of highly deactivated substrates (Scheme 16) such as perchloropyridine (electronic deactivation) ⟨74MI20501⟩ and 2,6-dibromopyridine (electronic and steric deactivation) (equation 35).



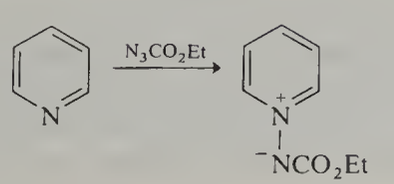
(35)

2.05.2.10 Miscellaneous Electrophiles

2-Picoline forms an *N*-nitronium salt (**52**) with nitronium fluoroborate in toluene; these salts can act as 'transfer' nitrating agents. Reaction with cyanogen bromide has been mentioned already (Scheme 10). Pyridines react with potassium hydroxylamine-*O*-sulfonate to give 1-aminopyridinium salts (**53**) ⟨59CB2521⟩. Treatment of pyridine with sulfur trioxide yields pyridinium 1-sulfonate (**54**), which is a good sulfonating agent. Azides that can afford highly electrophilic nitrenes, when decomposed thermally or photolytically in the presence of pyridines (preferably lacking α-substituents), give *N*-iminopyridinium ylides (equation 36) ⟨69BSF948⟩. The corresponding reaction by carbenes is not so well documented, but an ylide (**56**) has been obtained by heating (**55**) in pyridine under reflux (equation 37) ⟨71JCS(C)2939⟩.



(**52**) (**53**) (**54**)



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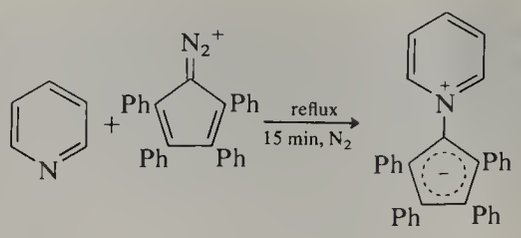
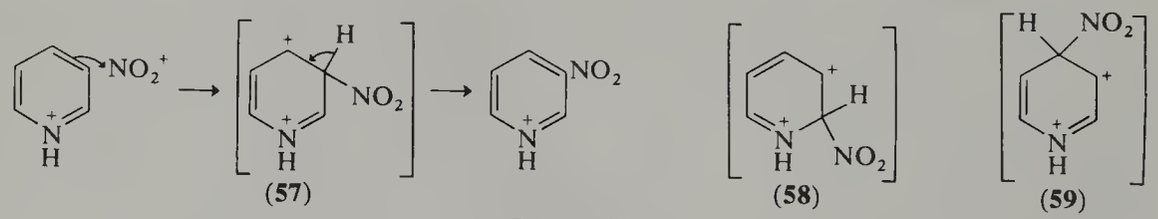


(55) (56)

2.05.3 ELECTROPHILIC ATTACK AT CARBON

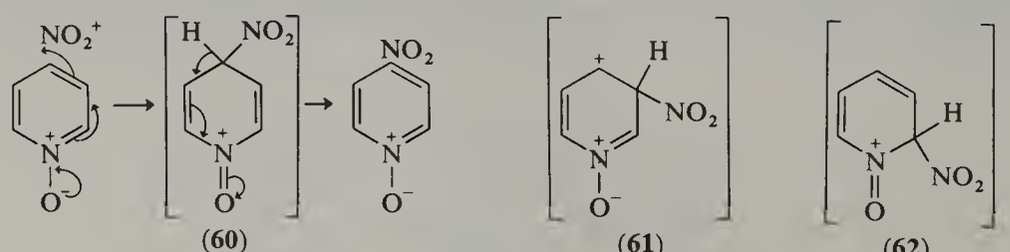
2.05.3.1 Reactivity and Orientation

Electrophilic substitution at carbon is by its nature an intrinsically unfavoured reaction for aromatics containing a pyridine-like nitrogen. This fact is exacerbated in that many of these reactions are of necessity carried out at high acidity where the reacting species is either the very small amount of free base or the even more unreactive conjugate acid. This aspect will be developed quantitatively in the discussion of nitration and hydrogen isotope exchange which will concentrate on methods of determining the nature of the reacting species and relative rates of substitution. Preparative work, some of industrial importance, will be highlighted for halogenations. It is interesting to compare the orientation of substitution from attack on pyridine, pyridine 1-oxide and 3-hydroxypyridine by a set of electrophiles. Pyridine undergoes electrophilic attack at position 3, usually as its cation, and the orientation may be rationalized by considering the rate determining step to involve a transition state that resembles the Wheland intermediate (**57**, Scheme 17). The Wheland intermediates for 2- or 4-substitution, (**58**) or (**59**) respectively, are clearly less stable. The close proximity of the two positive charges is a main cause of the deactivation. This may partially be alleviated by carrying out the reaction (especially halogenation and sulfonation) in the presence of a metal ion (*e.g.* aluminum or mercury) that can coordinate at nitrogen and suppress protonation. Nitration of pyridine 1-oxide at position 4 takes place on the free base. It is a high yield reaction that is very much easier than the nitration of pyridine itself. The orientation may be explained by inspection of the Wheland intermediates (**60**)–(**62**), bearing in mind the aforementioned assumptions. Attack at position 4 is also favoured by electron release by the *N*-oxide oxygen (Scheme 18) to give a Wheland intermediate (**60**) that is more stable than that for 3-attack (**61**). It might be argued that the intermediate (**62**), formed by C-2 attack, is almost as stable as (**60**). Indeed, a little 2-nitropyridine (deoxygenation is a common side reaction under nitrating conditions) accompanies the main product 4-nitropyridine 1-oxide in most nitrations.



(57) (58) (59)

Scheme 17



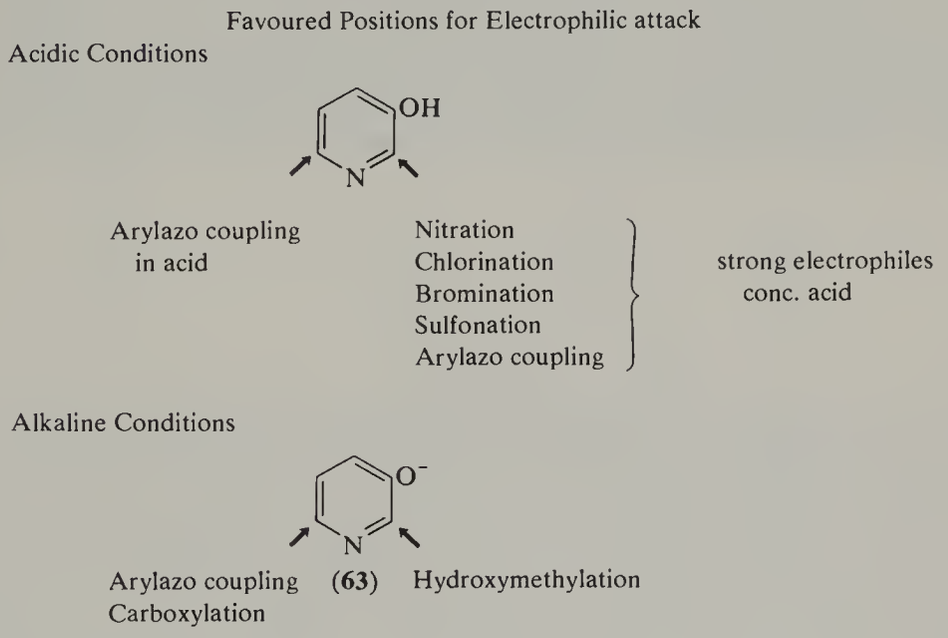
(60) (61) (62)

Scheme 18

In the case of mercuration (soft electrophile), attack at the 2-position is favoured. These observations accord with predictions based on molecular orbital calculations, that hard electrophiles (nitronium ions) should attack at C-4 and soft electrophiles (*e.g.* $HgSO_4$) at C-2 ⟨68JA223⟩. Furthermore, very hard electrophiles (*e.g.* SO_3) are predicted to attack at C-3. This is hard to verify because pyridine 1-oxide reacts at C-3 as its conjugate acid (or

SO_3 complex) with sulfur trioxide–oleum (*cf.* pyridine), and weak electrophiles will only react with pyridines bearing at least one activating substituent. Therefore, 3-hydroxypyridine was chosen as the third example because it contains an *ortho–para* directing substituent and three vacant positions activated towards electrophilic attack. Attack by strong electrophiles under acidic conditions overwhelmingly favours position 2 (Scheme 19) ⟨75RCR823⟩. Only a very small amount of 6-substitution is found except with a weak electrophile, the benzenediazonium ion in dilute acid. This gives an equal amount of the 2- and 6-phenylazo compounds. The anion (**63**) is the reacting species that undergoes attack by weak electrophiles in mildly alkaline conditions. Substitution at C-6 is favoured over that at C-2, but both the 2- and the 6-positions have to be blocked before 4-substitution is found to occur in significant yield; electrophilic substitution at position 4 is an uncommon reaction in pyridines, but it is the preferred orientation for electrophilic attack on *N*-oxide free bases.

This short summary has aimed to highlight a few of the more important aspects of the orientation of electrophilic substitution of pyridines and their benzo analogues. Strictly, reactions that involve metallation could be treated under this heading but they will be considered as involving a nucleophilic attack at a ring hydrogen (see Section 2.05.5). Electrophilic cyclizations of a substituent on to a pyridine will be mentioned briefly, but Chapter 2.06 should be consulted for those reactions.



Scheme 19

2.05.3.2 Nitration

It has long been known that pyridine is difficult to nitrate. Only a 15% yield of 3-nitropyridine was obtained on treating pyridine with potassium nitrate in fuming sulfuric acid at 330 °C ⟨12CB428⟩. Pyridines bearing alkyl substituents can be nitrated more easily and in better yields, whilst nitration of pyridinones is quite easy. Older work was reviewed and the stage set for future developments in the study of heterocyclic nitration in a fascinating article by Schofield ⟨50QR382⟩. Recently the same author has produced the most comprehensive account yet of aromatic nitration which contains the discussion of developments in heterocyclic nitration in the intervening 30 years ⟨B-80MI20502⟩. Nitration is usually carried out under acidic conditions. Therefore, when nitrating pyridine and its analogues which are basic, a problem arises as to whether the free base or its conjugate acid is undergoing reaction, or if both of these species are reacting. Four criteria have been used to identify the reacting species:

slopes of rate profiles;
comparison of the rate of nitration with that of 'fixed forms';
comparison of the observed rate of nitration with the calculated diffusion controlled rate;
determination of Arrhenius parameters.

Experience has shown that more than one criterion should be applied to each case if possible, as application of just one has sometimes led to erroneous conclusions. Most

mechanistic nitration studies have been carried out in sulfuric acid; preparative work in other media will be considered later. Occasionally some nitration at substituents will be mentioned (*e.g.* at positions 5 and 8 in quinoline) for comparative purposes but Chapter 2.06 should be consulted for substituent nitration.

A plot of the logarithm of the observed second order rate coefficient (k_2 obs) at 25 °C for nitration, with nitric acid in fairly concentrated sulfuric acid (60–85%), against weight percent sulfuric acid, $d(\log_{10} k_2 \text{ obs})/d(\%H_2SO_4)$, is linear with a slope of 0.3–0.4 for nitration of a cationic species, or a base as its conjugate acid. For example, the rate profile for quinolinium has a slope of 0.36, 1-methylquinolinium 0.38. A plot of the logarithm of the observed rate coefficient against $-(H_R + \log a_w)$ gives a slope of unity for majority (*i.e.* protonated) species nitration (*e.g.* slopes for quinolinium and 1-methylquinolinium are 0.95 and 1.00 respectively).

Nitration of less reactive substrates has to be studied in concentrated sulfuric acid. Originally, the shape of the rate profile in the 85–98% sulfuric acid region for the compound under study was compared with those for compounds known to react as either the free base or conjugate acid. Maximum rates of nitration occur in *ca.* 90% H_2SO_4, when nitric acid is completely ionized, and then the rates fall off sharply for reaction on free base species (*e.g.* 2,6-dimethoxy-3-nitropyridine, Figure 1). A fall-off in nitration rate in H_2SO_4 above 90% is also observed for reaction on majority species, due to a medium effect, but this is much less sharp than in the free base case (*e.g.* 2,6-dimethoxypyridine, Figure 1). Sufficient reliable data are now available so that comparison may be made directly with rate profile slopes from nitrations of known species in the region above 90% H_2SO_4. The slope $d(\log k_2 \text{ obs})/d(\%H_2SO_4) \approx 0.2$–$0.6$ for the majority and 0.8–1.5 for free bases.

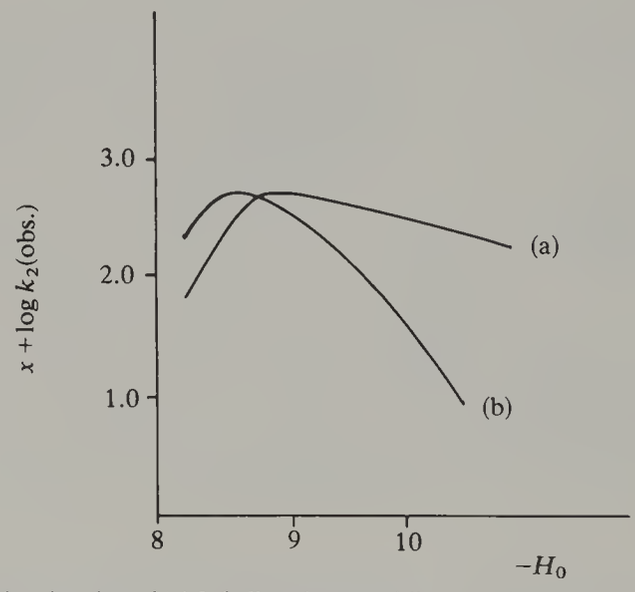


Figure 1 Rate profiles for the nitration of (a) 2,6-dimethoxypyridine ($x = 3$) and (b) 2,6-dimethoxy-3-nitropyridine ($x = 5.5$)

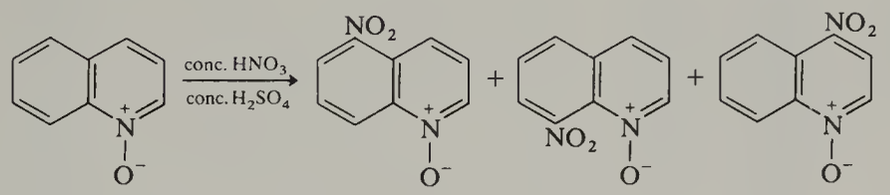
Having tentatively established the identity of the reacting species from the rate profiles, the second criterion may be applied. This involves comparison of the rate (and rate profile if possible) for the compound under study and a fixed form of its conjugate acid.

An example of the application of this test to a compound that nitrates as its free base is provided by pyridine 1-oxide. Under an identical set of conditions, nitration of this *N*-oxide had a half life of 20 min, whilst 1-methoxypyridinium gave no nitro compound in 144 h. Two further criteria have been used to provide confirmatory evidence, namely comparison of the rate of nitration for the reactive species with the encounter controlled rate, and by determination of the Arrhenius parameters.

The rate coefficient (k_2 enc) for the collision of two species is given by $8RT/3Z$ (where Z is the viscosity of the medium at the reaction temperature), the Smoluchowski equation. This is the maximum possible rate of reaction, which is controlled by the rate at which the two reacting species diffuse together. For nitration in >90% H_2SO_4, where nitric acid is completely ionized, if exclusively the free base nitrates the rate coefficient (k_2 fb) would equal $k_2 \text{ obs} \cdot K_a/h_x$ (where K_a is the ionization constant of the base, and h_x the acidity function that it follows). Thus, if $k_2 \text{ fb} > k_2 \text{ enc}$ free base nitration is precluded, but if

k_2 fb $< k_2$ enc nitration of either or both species is possible. Application of this criterion to the nitration of quinoline excludes reaction on the free base, but it is ambiguous with regard to the nitration of pyridin-4-one, quinolin-4-one and 1-methylquinolin-4-one. Nitration of 2-dimethylamino-3- and 2-dimethylamino-5-nitropyridine occurs at or near the encounter rate but a special mechanism is believed to be operative in these cases. It may be predicted by electrostatic theory that the electrostatic contribution to the entropy of activation $\Delta S_{el}^{\ddagger}$ should be less for a reaction between two cations than between a cation and neutral molecule. A value of $\Delta S_{el}^{\ddagger} = -40$ kJ K^{-1} mol^{-1} has been calculated for the former case. A comprehensive survey of the Arrhenius parameters for many examples of nitration of pyridines, other bases and aromatics reveals that no clear-cut distinction can be made in practice between conjugate acid and free base nitrations on the basis of entropies of activation. This might in part be due to the large error inherent in the determination of this parameter.

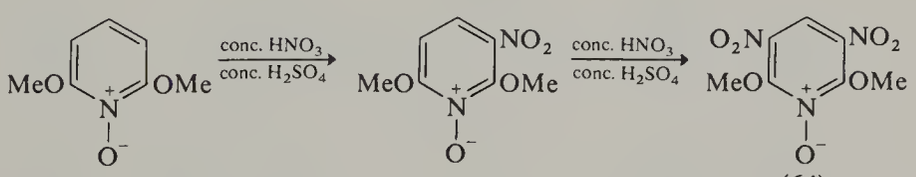
In addition to the four criteria based on kinetic analysis, the orientation of nitration can give a rough guide as to reacting species. Quinoline 1-oxide, for instance, undergoes 5- and 8-nitration as its conjugate acid whilst 4-nitration takes place concurrently on the free base. Carrying out this nitration at higher acidity leads to an increase in 5- and 8-nitro products with concomitant decrease in 4-nitration (Scheme 20) ⟨68JCS(B)316⟩.



% H_2SO_4		% *Yield*	
82	24.2	31.5	44.4
83.4	31.7	41.1	27.3
85	35.4	48.9	15.7

Scheme 20

Orientation also provides a valuable guide in the pyridine 1-oxide series. Nitration of pyridine 1-oxide is well known to yield the 4-nitro derivative in good yield and it has been found to involve the free base. On the other hand, 2,6-dimethoxypyridine 1-oxide ⟨67JCS(B)1213⟩, which is nitrated as the conjugate acid, yields the 3-nitro derivative, but subsequent nitration takes place on the free base to give (**64**; equation 38). The mono- and di-nitration of 3,5-dimethoxypyridine and its 1-oxide follow the same course. These observations may be explained by considering the former case. 3,5-Dimethoxypyridine forms a mononitro derivative ($pK_a = -2.52$) which although further deactivated compared with the starting pyridine ($pK_a = 4.44$) is able to undergo reaction as the free base rather than the conjugate acid as more of it is available. 2,6-Dichloropyridine ($pK_a = -2.57$) undergoes mononitration as the free base in good yield under relatively mild conditions ⟨67JCS(B)1204⟩.



(38)

(**64**)

On the basis of the above and other information a rule (which has few exceptions) has been adumbrated for the pyridines themselves relating the nature of the reacting species in nitration to the magnitude of the pK_a. It states that pyridines with a $pK_a > +1$ will nitrate as the conjugate acids at the α- or β-positions depending upon the orientating effect of attached substituents, whilst derivatives with $pK_a < -2.5$ will nitrate as the free bases. In the region between +1 and −2.5 a mechanistic changeover takes place. A knowledge of the nature of the reacting species and the availability of the rates of nitration in sulfuric acid for many pyridines and quinolines has allowed the estimation of their relative rates of nitration ⟨75JCS(P2)1600⟩. The great variation in rate of nitration means that data are only available at different temperatures and acidities. Consequently, an intermediate set of standard conditions, 25 °C and $H_0 = -6.6$ (75% w/w H_2SO_4), were used for evaluation of standard nitration rates ($k_2°$). Accuracy of the calculations suffers particularly in cases where

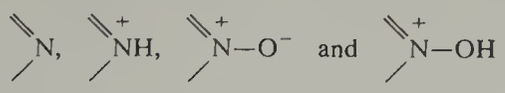
free base nitrations are carried out at high temperatures in acidities well removed from $H_0 - 6.6$, when long extrapolations involving variation of log k_2 obs, pK_a (of substrate) and H_0 with temperature are required. However, these standard rates (Table 7) give the best measure yet of the relative reactivity of pyridines with electrophiles.

Table 7 Standard Rates of Nitration for Pyridines and Quinolines

Substituent	*Range* $\%H_2SO_4$	*T* (°C)	*Reacting species*	*For free base* pK_a	*m*	*Position (Yield %)*	$-\log k_2°$ *(calc.)*	$-\log k_2°$ *(corr.)*[a]
Benzene								
None	63–71	25	0[b]	—	—	Any	−1.23	−0.45
Pyridines								
4-OMe	90–96	110	+[c]	—	—	3,5	9.90	10.20
3-OMe	90–96	60	+	—	—	2	8.09	8.09
3-OH	90–96	40	+	—	—	2	7.66	7.66
2-NMe_2	76–86	30	+	—	—	3 (11)	1.72	2.68
						5 (89)	—	1.77
4-NMe_2	72–86	50	+	—	—	3,5	2.68	2.98
2-NMe_2-5-NO_2	77–84	30	0	3.11	1	3	−4.86	−4.86
2-NMe_2-3-NO_2	79–86	30	0	2.50	1	5	−3.71	−3.71
4-NMe_2-3-NO_2	82–89	50	0	5.23	1	5	−5.05	−5.05
3,5-$(OMe)_2$-2-NO_2	82–85	51	0	−2.52	1.10	6	2.26	2.26
2,4,6-Me_3	92–98	101	+	—	—	3,5	9.73	10.03
2,6-$(OMe)_2$	74–81	58.5	+	—	—	3,5	4.43	4.73
3,5-$(OMe)_2$	82–88	25	+	—	—	2,6	4.45	4.75
2-OMe-3-Me	91–96	25	+	—	—	5	7.98	7.98
2-Ph	77–81	25	+	—	—	2′,6′ (9)	3.80	5.15
						3′,5′ (45)	—	4.45
						4′ (46)	—	4.14
Pyridones								
Pyridin-2-one	75–87	25	0	0.77	0.65	3	0.39	0.37
		40	0	—	—	3	0.34	—
		25	0	—	—	5	0.85	0.85
		40	0	—	—	5	0.85	—
Pyridin-4-one	85–89	86	0	3.27	0.65	3,5	1.45	—
	85–89	110	0	—	—	3,5	1.35	1.69
	79–85	133.5	0	—	—	3,5	1.28	—
	73–81	157.5	0	—	—	3,5	1.49	—
	93–98	86	+	—	—	3,5	9.50	9.76
	92–98	110	+	—	—	3,5	9.42	—
Pyridinium Salts								
1-Me-2-NHMe	78–89	25	+	—	—	3 (31)	5.44	5.95
						5 (69)	—	5.60
	76–80	25	+	—	—	3,5	1.88	2.18
Pyridine 1-oxides								
2,6-Me_2	78–88	80	0[d]	—	—	4	2.38	2.38
2,6-$(OMe)_2$	80–86	25	+	—	—	3,5	7.18	7.48
2,4,6-$(OMe)_3$	80–85	25	+	—	—	3,5	5.81	6.11
Quinolines								
None	77–87	25	+	—	—	5 (50)	5.98	6.28
						8 (42)	—	6.36
4-OMe	81–85	25	+	—	—	6 (72)	4.96	5.10
						8 (28)	—	5.51
Quinolones								
None	81–85	25	+	—	—	6 (81)	4.60	4.69
						8 (19)	—	5.32
1-Me	77–86	25	+	—	—	3 (14)	4.81	5.67
						6 (86)	—	4.88

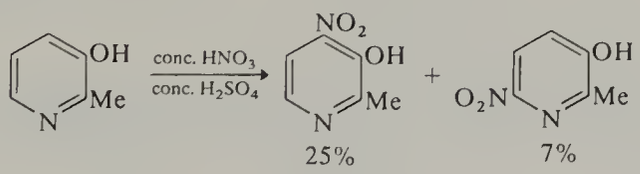
[a] Corrected for isomer distribution and statistical factor.
[b] 0, free base is reacting species.
[c] +, conjugate acid is reacting species.
[d] Free base nitration is assumed.

From a knowledge of the standard rates it had originally been hoped that the Hammett σ–ρ treatment could be applied to calculate the deactivating effect of



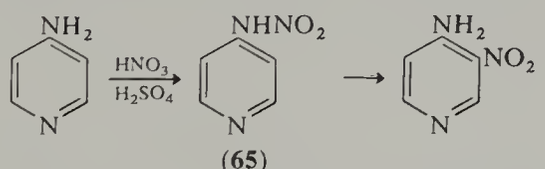
towards electrophilic substitution at ring positions. It has not proved possible to do this with any certainty for a number of reasons. Chief amongst these is incursion of diffusion control into the rate of nitration of corresponding aromatics at the acidities required for comparison. On the pyridine side, substituents have been found to exert widely different effects in different situations, making the application of σ values derived from aromatic reactivity unreliable. The establishment of a unique value of the reaction constant, ρ, also has not been possible. The standard rate coefficient for 3-nitration of 2,4,6-trimethylpyridinium relative to benzene is 3.3×10^{-11} ⟨75JCS(P2)1600⟩. This compares with a partial rate factor 3.5×10^{-12} relative to benzene using an 'overlap' technique ⟨67JCS(B)1204⟩. These values are both underestimates of the effect of $\overset{+}{N}$—H in pyridine itself. The true figure is probably $<10^{-(12-13)}$ for pyridine relative to benzene, which compares with 10^{-8} for the effect of a trimethylammonio group.

Having discussed the overall reactivity pattern and relative rates, some examples of interest will be considered individually. Pyridin-2-one, which undergoes nitration as the free base in the 75–97% H_2SO_4 region, is subject to a large medium effect which is probably due to hydrogen bonding to hydronium ions. The effect results in predominant 3-nitration at low acidity and high temperature, and mainly 5-nitration at high acidity and low temperature. Pyridin-4-one also exhibits unusual behaviour, reacting as the conjugate acid at high acidity and as the free base in H_2SO_4 below 85%. 3-Hydroxy- and 3-methoxypyridine are both nitrated at the 2-position in good yield as the conjugate acids in 85–96% H_2SO_4 ⟨70JCS(B)114⟩. When the 2-position is blocked, as in 2-methyl-3-hydroxypyridine, nitration takes place mainly at the 4-position (equation 39), providing the only confirmed instance of this orientation in the nitration of a pyridine ⟨68JOC478⟩. Nitration of 6-hydroxy- and 6-methoxy-pyridin-2-one in 70–77% H_2SO_4 takes place at the 3-position on the free bases which react at near the encounter rate.



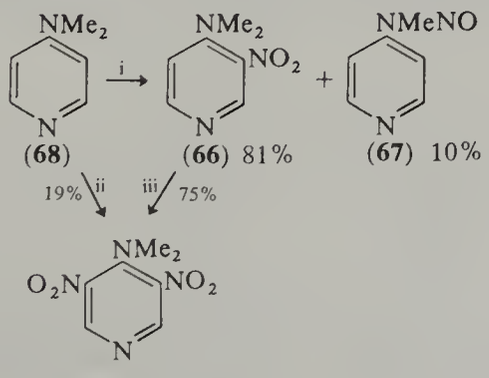
(39)

Nitration of the aminopyridines and their methyl derivatives reveals some interesting facets. The amino group strongly activates the positions *ortho* and *para* to itself towards nitration, but reaction proceeds *via* the *N*-nitroamines. 4-Aminopyridine undergoes nitration *via* the *N*-nitroamine (**65**) to yield 4-amino-3-nitropyridine (equation 40). Nitration



(40)

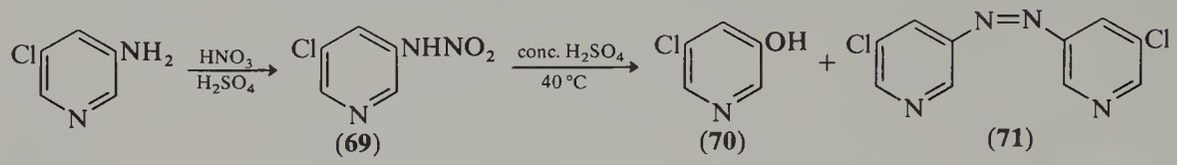
(**65**)



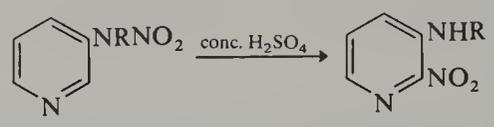
i, 70% HNO_3, 90% H_2SO_4, 20 °C, 3 h; ii, conc. HNO_3, conc. H_2SO_4, 24 h; iii, 70% HNO_3, 90% H_2SO_4, 20 °C, 24 h

Scheme 21

of 4-dimethylaminopyridine does not involve the intermediacy of a nitramine and takes place on the first conjugate acid to give a good yield of the 3-nitro product (**66**) and a by-product (**67**) that arises by nitrosodemethylation (Scheme 21). Dinitration is achieved in better yield by further nitration of (**66**) rather than nitration of (**68**) under more forceful conditions. Nitration of 3-aminopyridine and some of its ring-substituted derivatives yields the nitramine (**69**) which on rearrangement does not produce aminonitropyridines, but instead, for example (**69**), yields a 3-hydroxypyridine (**70**) and an azo compound (**71**) (equation 41) ⟨60BAP281⟩. On the other hand, when the 3-amino group is monosubstituted, rearrangement takes place in the usual fashion (equation 42).



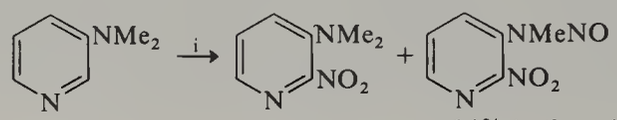
(41)



(42)

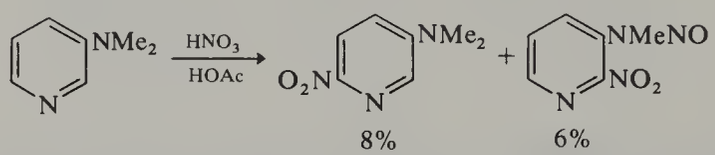
R = Me or CO_2Et

Note again that a strong resonance donating group at position 3 directs nitration to position 2 rather than 4 (*cf.* OH, OMe, NMe_2). The factors involved in directing this orientation have been discussed ⟨66AHC(6)229⟩. Nitration of 3-dimethylaminopyridine with nitric and sulfuric acids in the presence of urea (which is usually a poor nitrosonium ion trap) is still complicated by nitrosodealkylation (equation 43) and only low yields of *C*-nitro products are obtained. Use of acetic acid as solvent (equation 44) also did not lead to very successful *C*-nitration.



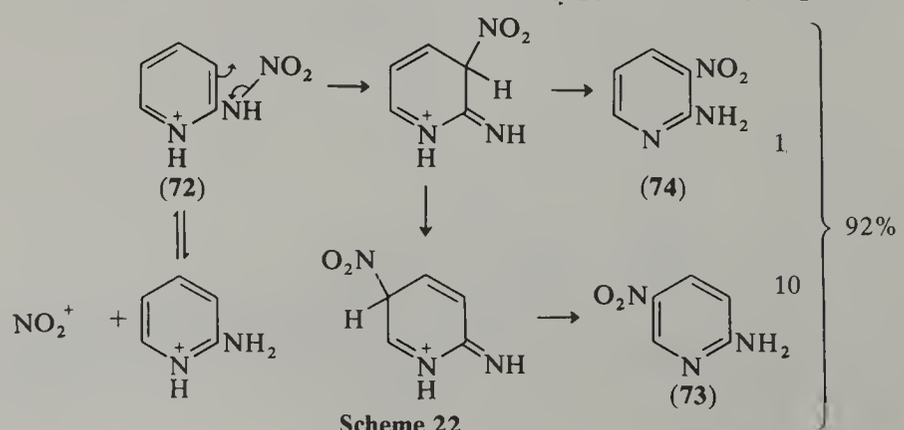
(43)

i, 70% HNO_3, 86% H_2SO_4, urea



(44)

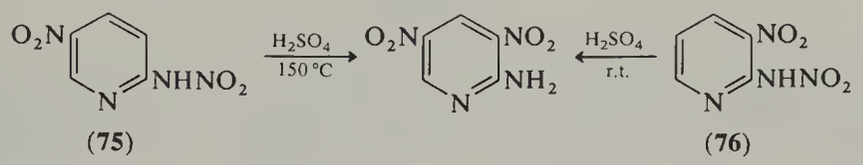
In the search for a rare example of 4-nitration, 3-dimethylamino-2,6-dimethylpyridine was nitrated but only 3-nitrosomethylamino-2,6-dimethylpyridine was characterized in 76% (HNO_3/HOAc) or 56% (HNO_3/H_2SO_4) yield and no products of 4-nitration were detected. Nitration of 2-aminopyridine first gives the nitramine (**72**) which on warming rearranges exothermically to the aminonitropyridines (**73**) and (**74**), the former being favoured. Alternatively, the nitramine may be isolated and then rearranged to (**73**) and (**74**) by adding it slowly to cold 92% sulfuric acid. Use of 70% sulfuric acid results in an 80% yield of pyridin-2-one ⟨79T2895⟩. It has been suggested that the favoured 5-nitro product arises *via* the 3-isomer (Scheme 22). If this indeed proves to be so, then the formation of 2-amino-3-methyl-5-nitropyridine by nitration of 2-amino-3-methylpyridine might provide the first



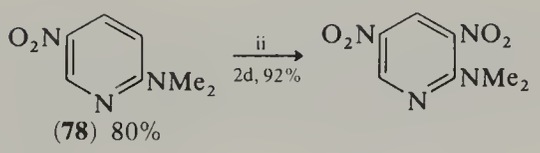
Scheme 22

example of *ipso* nitration in the pyridine series. Such a possibility is also suspected in the nitration of substituted methylpyridin-2-ones ⟨B-80MI20502⟩.

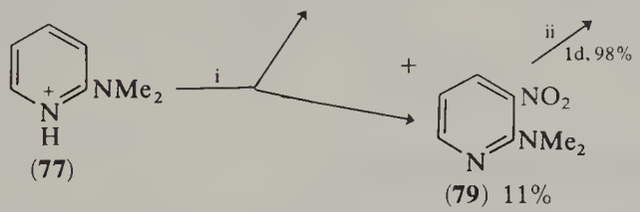
Further nitration of (**73**) and (**74**) gives the nitramines (**75**) and (**76**) respectively, of which the former is difficult to rearrange, the latter easy (equation 45) as one might expect. Nitration of 2-dimethylaminopyridine takes place at the 3- and 5-positions (Scheme 23) in similar proportions as for the 2-amino compound. This particular reaction has come in for close scrutiny ⟨72JCS(P2)1940, 72JCS(P2)1950⟩ as it has been used as a model with which to study the 'proton loss' mechanism in nitration ⟨68JCS(B)1068⟩. The first nitration involves the monocation (**77**), but the nature of the reacting species in the second nitration is more complicated. The low acidity nitration of both (**78**) and (**79**) apparently takes place on the free bases at the encounter rate. At high acidity this is probably still true for the 5-nitro isomer, but the other isomer reacts as its conjugate acid. It is now considered more probable that for apparent free base nitrations taking place at the encounter rate, pre-association mechanisms operate. These are believed to involve reversible pre-equilibrium proton loss in the encounter pairs that contain the monoconjugate acid (Scheme 24) ⟨80MI20503⟩.



(75) (76) (45)



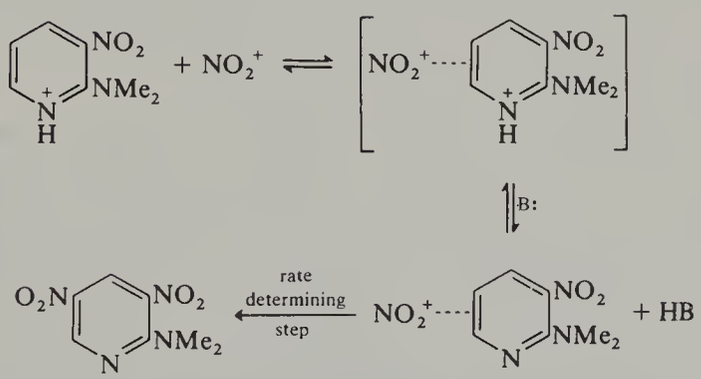
(78) 80%



(77) (79) 11%

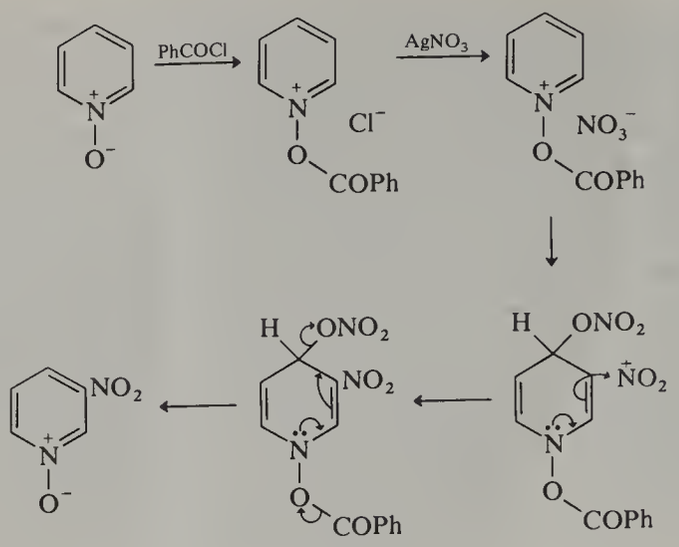
i, conc. HNO_3, conc. H_2SO_4, 0 °C; ii, 70% HNO_3, conc. H_2SO_4, 20 °C

Scheme 23

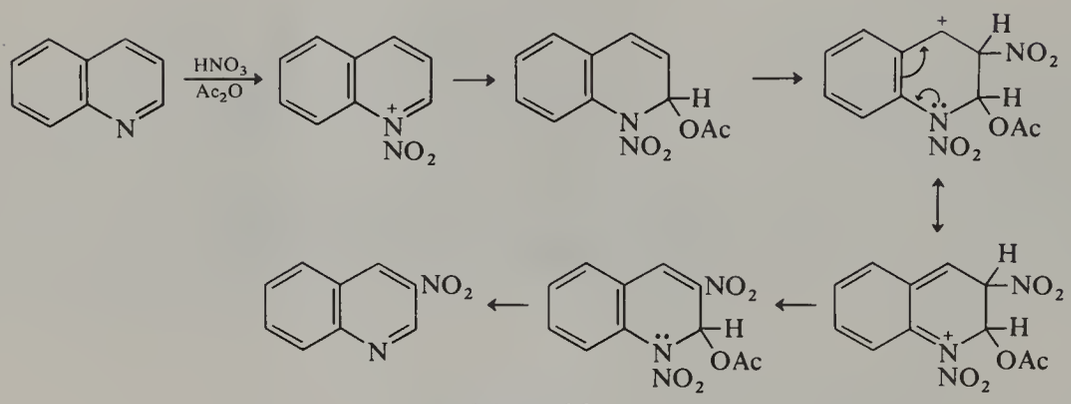


Scheme 24

Nitration of pyridines in other than nitric or sulfuric acids is of little interest here because either no reaction or *N*-nitration takes place (see Section 2.05.2.10). However, pyridine 1-oxide is considerably more reactive and treatment with benzoyl nitrate ultimately leads to the 3-nitro derivative (Scheme 25) ⟨60CPB28⟩. Annelation of a benzene ring bestows greater reactivity on the 3-position in quinoline, compared with pyridine, and reaction with nitric acid in acetic anhydride furnishes the 3-nitro derivative (*ca.* 6%) (Scheme 26). This isomer has also been obtained, again at low yield (6–10%), by treatment of quinoline with tetranitratotitanium(IV) in carbon tetrachloride ⟨74JCS(P1)1751⟩. Nitration of benzo analogues of pyridine occurs much more readily in the benzene ring, and Chapter 2.06 should be consulted for these reactions.



Scheme 25



Scheme 26

2.05.3.3 Acid-catalyzed Hydrogen Isotope Exchange

Early studies of acid-catalyzed hydrogen isotope exchanges utilized tritium as a tracer. By this means pyridine and 4-methylpyridine were found to be unreactive even under the most vigorous conditions, but exchange proceeded smoothly (at the β-positions) with 2,6-di- and 2,4,6-tri-methylpyridine ⟨63JCS3753⟩. The availability of NMR spectroscopy made it more convenient to study hydrogen–deuterium isotope exchange. A large body of H–D exchange data was obtained for heterocycles by Katritzky and coworkers and this has been compared with results from nitration studies (*vide infra*).

Before relative exchange rates could be obtained, criteria for determining the reacting species had to be established. As with nitration, comparison of the rate profile for a substrate with that for a fixed form of its conjugate acid provides the best criterion. 2,4,6-Trimethylpyridine was examined by heating with aliquots of sulfuric acid and tritiated water at a certain temperature in sealed tubes for a known time. After heating, the base was isolated as its picrate. This was burned and the water produced was monitored. A first-order kinetic form was found and exchange rates (k) were obtained at 182 °C and various acidities to give the rate profile (a) (Figure 2). A rate profile (b) with a similar slope was obtained for bis-1,2,4,6-tetramethylpyridinium sulfate in the same manner. The methyl quaternary salt reacts faster than 2,4,6-trimethylpyridine, ruling out involvement of the free base of the latter. *N*-Methylation usually results in a slight enhancement of the rate of hydrogen isotope exchange (and nitration, *vide supra*) compared with the rate for the corresponding protonated species, which is similar to the effect of a methyl group on benzenoid reactivity.

Rates of hydrogen–deuterium exchange are measured by observing the disappearance of signals due to exchanging protons in the NMR spectrum of reaction mixtures. The slope of a rate profile for H–D exchange on a species, the concentration of which is not changing rapidly with acidity, is given by $\delta \log k/\delta H_0 = \delta H_x/\delta H_0$ where H_x is the acidity function for kinetic *C*-protonation ⟨67AG(E)608⟩. For exchange on a substrate mainly present as its conjugate acid, $\delta \log k/\delta H_0 = (\delta H_x/\delta H_0) - (\delta H_y/\delta H_0)$, where H_y is the acidity function followed by the substrate.

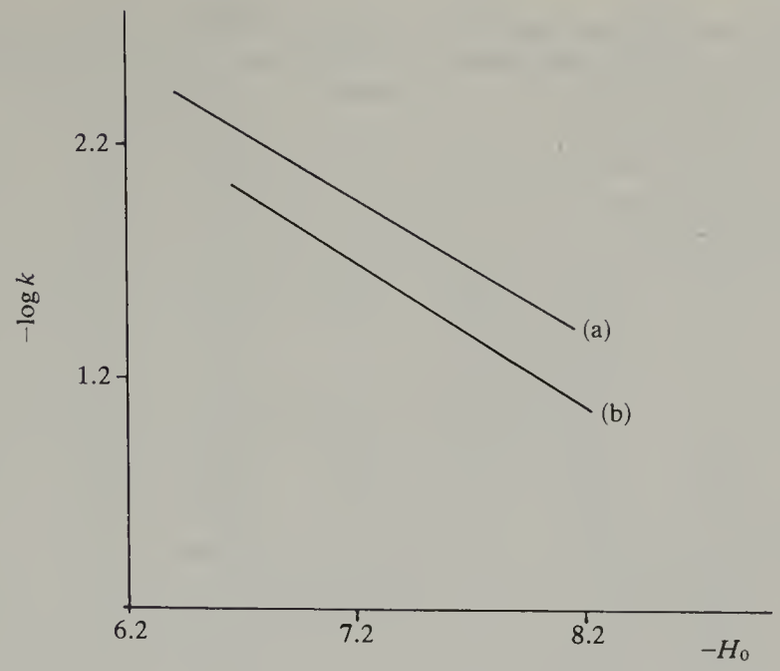


Figure 2 Rate profiles for acid-catalyzed hydrogen–tritium exchange of (a) 2,4,6-trimethylpyridine and (b) its *N*-methyl salt

For exchange in dibasic compounds, such as aminopyridines, ideally if both equilibrium and kinetic protonations follow H_0, a rate profile of the type in Figure 3 should be expected ⟨67JCS(B)1219⟩. Rate profiles obtained for 4-amino, 4-amino-2,6-dichloro- and 2-amino-5-methyl-pyridine correspond to the portions b–c, c–d and d–e respectively of Figure 3.

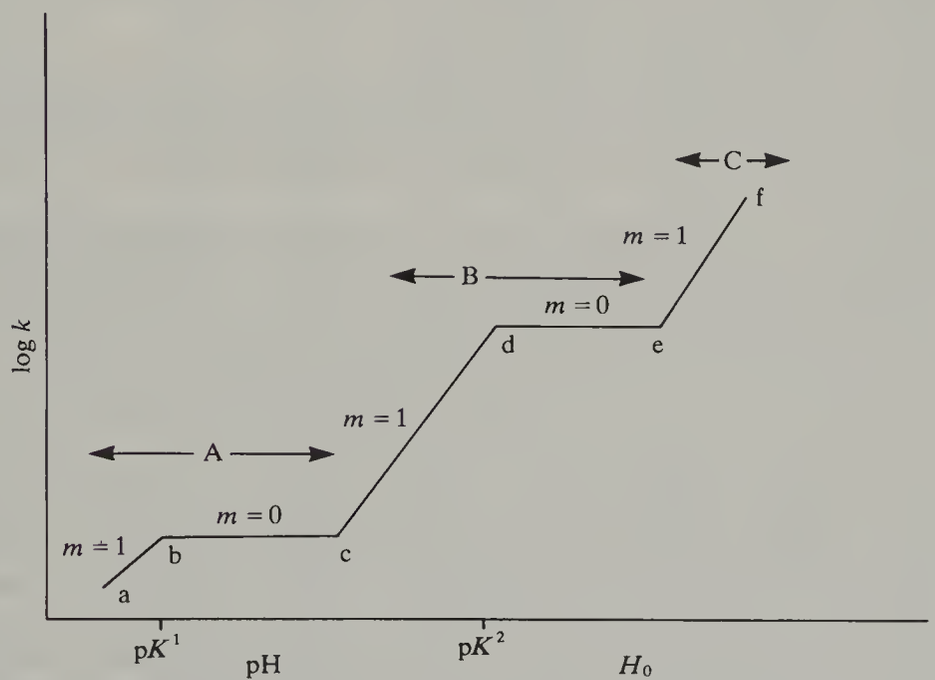


Figure 3 Ideal rate profile for H–D exchange in aminopyridines: A = exchange on free base; B = exchange on first conjugate acid; C = exchange on second conjugate acid

Comparison of the observed rate of exchange with the calculated encounter rate provides another method of determining the reacting species. It is applied as described for nitrations and is subject to similar limitations. Determination of Arrhenius parameters typically yields a value of $\Delta H^{\ddagger} \approx 125 \pm 25\ \text{kJ mol}^{-1}$, but $\Delta S^{\ddagger}$ varies considerably. $\Delta S^{\ddagger}$ values of $-80\ \text{J K}^{-1}\ \text{mol}^{-1}$ or less ⟨B-53MI20500⟩ were originally considered to indicate exchange at a cationic species, but subsequent work has demonstrated this to be a rather fallible criterion and at best only a rough guide. The problem is that most Arrhenius parameters have been determined in a medium the acidity of which was known only at 25 °C, whereas kinetic measurements were often, of necessity, carried out at high temperatures (*e.g.* 180–220 °C).

A pH of zero and a temperature of 100 °C were selected to compare rate coefficients for hydrogen exchange. The temperature of 100 °C was chosen to minimize temperature extrapolation as most rates have been measured in the range 20–180 °C. Measuring at pH = 0 is the best available means of correcting to unit activity of hydrogen ions, and so converting pseudo first-order rate coefficients into second-order ones. The determination of k (100 °C), and ultimately $-\log k$ (average) (Table 8), is rather complicated and the following procedure was used. (*a*) The stoichiometric rate coefficient (k_{stoic}) is determined at a temperature (T °C). This involves a knowledge of the acidity function followed by the substrate, the effect of dissolved substrate on the acidity function and the effect of D_2SO_4 instead of H_2SO_4. (*b*) Determination of k_{stoic} (T °C) at pH = 0, which requires the construction of a rate profile and extrapolation to pH = 0. (*c*) Determination of k_{stoic} (100 °C) at pH = 0, which usually involves an Arrhenius extrapolation. (*d*) Determination of k_0 (100 °C) at pH = 0, which requires a knowledge of variation of substrate pK_a with temperature so that a correction for minority species can be made if needed. (*e*) When comparing exchange rates involving different hydrogen isotopes, an isotope effect correction has to be made.

Application of this procedure has provided the relative rates of hydrogen exchange (Table 8), and details of calculations have been given ⟨73JCS(P2)1065⟩. A few comments on this table are necessary. Rates of hydrogen isotope exchange on 2,4,6-trimethylpyridinium are very similar when measured by H–T ($-\log k_0 = 12.4$) or H–D ($-\log k_0 = 11.6$) exchange. Methylpyridines react as conjugate acids, and the amino- and aminomethyl-pyridines generally react as their cations except at low acidities. Both 2- and 4-pyridinone and their *N*-methyl derivatives undergo exchange as free bases, but some derivatives of pyridin-4-one show mechanism changeover to reaction on the conjugate acid at higher acidities. 3,5-Dimethylpyridine 1-oxide is noteworthy as it undergoes H–D exchange not only at the 2- and 6-positions (on the free base) but also at the 4-position (on the free base). In contrast, 3,5-dimethoxypyridine 1-oxide does not undergo exchange at position 4; only the 2- and 6-protons are exchanged on the free base at low acidity and the conjugate acid at high acidity. Hydrogen exchange on 2,4,6-trimethyl- and 2,6-dimethyl-pyridine 1-oxides proceeds at positions 3 and 5 on the conjugate acids.

1-Hydroxy-2,6-dimethylpyridin-4-one is remarkable in that it can undergo exchange with deuterium as three species; that which is favoured depends upon the acidity used. It reacts as its conjugate acid in high acidity (73–93% H_2SO_4); in 25–51% H_2SO_4 exchange takes place on the free base, but in <2% H_2SO_4 the conjugate base is the principal reacting species ⟨68JCS(B)866⟩.

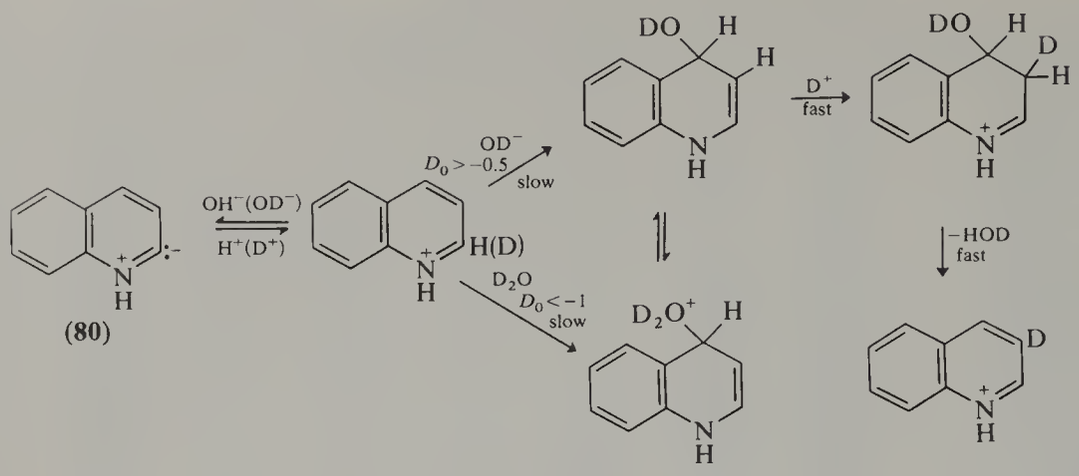
Quinoline undergoes H–D exchange as its conjugate acid principally in the benzene ring and the hydrogens are substituted in the order 8 > 5, 6 > 7 > 3 using 46–96% H_2SO_4 at 180 °C. Isoquinoline undergoes exchange at positions 5 then 8 in high acidity at 180 °C ⟨71JCS(B)4⟩. Our concern here is ease of substitution in the pyridine ring (see Chapter 2.06 for substitutuent reactions). This is observed at higher temperature (245 °C) and lower acidity (pH +0.5 to $H_0 - 3$) first rather surprisingly at position 2 followed by 3, then 8 and 5, and finally H-6 and H-7 exchange. As the acidity is increased, rates of exchange at positions 2 and 3 decrease whilst those at 8, 5 and 6 increase; no exchange is ever observed at position 4. At 245 °C, in the acidity range pD +0.5 to $H_0 - 3$, isoquinoline undergoes rapid exchange at positions 1 and 4, and as the acidity is increased the 5, 8 and 6 (or 7) protons are exchanged. This dichotomy was resolved in favour of the electrophilic substitution mechanism for positions 5, 6, 7 and 8. Rate profiles point to exchange at position 3 in quinoline (4 in isoquinoline) occurring *via* rate determining covalent hydration by water at higher, and OD^- at lower, acidities (Scheme 27). Exchange at position 2 probably involves the ylide (**80**); such species are well established as intermediates in exchange reactions under neutral and basic conditions. A similar argument holds for exchange at the 1-position in isoquinoline. On the other hand, exchange at the 3-position of quinolin-4-one (as the free base in low, and conjugate acid in high acidity) is a true electrophilic substitution.

The standard rate coefficients (Table 8) have been used to try to establish structure–reactivity relationships for hydrogen exchange on pyridines, but difficulties similar to those with nitration have been encountered ⟨74JCS(P2)1294⟩. Standard rates of hydrogen–deuterium exchange when plotted against nitration rates give a 'scattergram' ⟨78JCS(P2)613⟩, but the use of identical standard conditions does give a good linear correlation for substrates of closely related structure. Part of the reason for nonlinearity may be due to the different steric demands of the two electrophiles, which would be most evident for *ortho* substitutions. What is perhaps more serious is that some reactivity inversions occur; for instance, pyridin-4-one is more reactive than benzene towards deuteriation, but less reactive towards nitration.

Table 8 Standardized Rates of Hydrogen Isotope Exchange

Substituents	*Range* $\%H_2SO_4$	*Exchange T* (°C)	*Reacting species*	*Position(s) of exchange*	pK_a 25 °C	pK_a 100 °C	$-\log k_0$ *(calc.)*	$-\log k_0$ *(average)*
Pyridines								
2-NH_2,3-Me	4–78	158	+	5	—	—	7.95	8.0
2-NH_2,5-Me	14–61	107	+	3	—	—	8.05	8.1
2-NH_2,4-Me	17–43	148	+	3	—	—	7.84	7.8
2-NH_2,4-Me	2–10	148	0	3	7.88	6.56	0.81	0.8
2-NH_2,4-Me	17–43	148	+	5	—	—	7.62	7.6
2-NH_2,4-Me	2–10	148	0	5	7.88	6.56	0.54	0.5
2-NH_2,6-Me	19–36	158	+	3	—	—	7.40	7.4
2-NH_2,6-Me	2–8	158	0	3	7.81	6.50	0.48	0.5
2-NH_2,6-Me	8–36	158	+	5	—	—	6.90	6.9
2-NH_2,6-Me	2–8	158	0	5	7.81	6.50	0.28	0.3
2-NH_2,5-Cl	71–96	158	+	3	—	—	9.86	9.7
2-NH_2,5-Cl	71–90	179	+	3	—	—	9.46	
2-NH_2,5-Cl	19–33	158	0	3	5.11	4.38	3.87	3.8
2-NH_2,5-Cl	14–28	179	0	3	5.11	4.38	3.78	
2-NMe_2,5-Cl	66–88	158	+	3	—	—	9.22	9.2
2-NMe_2,5-Cl	54–66	158	0	3	5.51	4.72	2.16	2.2
3-NH_2	20–40	176	+ (min.)	2	−1.03	−1.18	8.95	8.7
3-NH_2	9–20	176	+ (maj.)	2	—	—	8.54	
3-NH_2	1–4	176	0	2	6.38	5.33	3.08	3.1
4-NH_2	3–69	107	+	3,5	—	—	7.28	7.6
4-NH_2	4–51	146	+	3,5	—	—	7.76	
4-NH_2	4–51	170	+	3,5	—	—	7.66	
4-NH_2,2,6-Cl_2	62–68	107	+	3,5	—	—	9.05	9.1
4-NH_2,2,6-Cl_2	65–69	122	+	3,5	—	—	9.18	
4-NH_2,2,6-Cl_2	17–58	107	0	3,5	1.57	1.39	2.88	3.0
4-NH_2,2,6-Cl_2	2–57	122	0	3,5	—	—	3.04	
2,6-Me_2	89–95	204	+	3,5	—	—	15.59[a]	15.6
2,4,6-Me_3	73–86	204	+	3,5	—	—	12.40[a]	12.4
2,4,6-Me_3	71–91	180	+	3,5	—	—	11.80	11.6
2,4,6-Me_3	66–91	209	+	3,5	—	—	11.37	
4-OMe,2,6-Me_2	60–91	100	+	3,5	—	—	9.80	9.8
4-OMe,2,6-Me_2	22–42	100	0	3,5	8.26	6.87	0.96	1.0
Pyridin-2-one	40–93	128	0	3,5	1.10	0.84	4.75	4.8
1-Me-pyridin-2-one	32–89	103	0	5	0.65	0.50	4.26	4.3
1-Me-pyridin-2-one	32–89	120	0	3	1.52	1.15	4.73	4.7
Pyridin-4-one	<98	170	0	3,5	3.67	2.76	4.85	4.8
Pyridin-4-one	<98	187	0	3,5	3.67	2.76	4.80	
1-Me-pyridin-4-one	<98	170	0	3,5	3.73	2.81	4.77	4.8
2,6-Me_2-pyridin-4-one	68–99	108	+	3,5	—	—	8.46	8.5
2,6-Me_2-pyridin-4-one	<40	108	0	3,5	4.53	3.41	2.81	2.8
1,2,6-Me_3-pyridin-4-one	52–96	100	+	3,5	—	—	8.64	8.6
1,2,6-Me_3-pyridin-4-one	22–41	100	0	3,5	4.52	3.40	3.22	3.2
Pyridine 1-oxides								
4-OH,2,6-Me_2	73–93	100	+	3,5	—	—	8.74	8.7
4-OH,2,6-Me_2	25–51	100	0	3,5	3.40	2.59	3.96	4.0
4-OH,2,6-Me_2	<2	100	—	3,5	10.44	7.94	−0.87	−0.7
4-OH,2,6-Me_2	—	100	—	3,5	7.04	5.36	−0.54	
4-NH_2	13–67	107	+	3,5	—	—	7.92	7.9
2-NH_2,5-Br	50–79	158	+	3	—	—	9.81	9.8
2-NH_2,5-Br	48–80	182	+	3	—	—	9.71	
2-NH_2,5-Br	4–17	158	0	3	2.35	1.80	7.12	7.1
2-NH_2,5-Br	16–28	182	0	3	2.35	1.80	7.08	
3,5-Me_2	8–85	230	0	2,6	1.56	1.18	8.13	8.1
3,5-Me_2	8–85	230	0	4	1.56	1.18	8.38	8.4
2,4,6-Me_3	85–97	185	+	3,5	—	—	11.43	11.8
2,4,6-Me_3	55–82	202	+	3,5	—	—	12.08	
2,4,6-Me_3	71–97	216	+	3,5	—	—	11.87	
3,5-$(OMe)_2$	39–78	119	+	2,6	—	—	6.48	6.5
3,5-$(OMe)_2$	<39	119	0	2,6	—	—	4.09	4.1
4-OMe,2,6-Me_2	61–99	100	+	3,5	—	—	9.68	9.7
Quinoline	48–66	245	+	3	—	—	13.06	13.1
4-OMe	73–99	90	+	3	—	—	9.52	9.5
Quinolin-2-one	71–86	110	+	3	—	—	8.90	8.9
Quinolin-4-one	77–99	90	+	3	—	—	7.61	7.6
Quinolin-4-one	5–64	90	0	3	2.67	2.01	2.09	2.4
Quinolin-4-one	16–67	124	0	3	2.67	2.01	2.75	

[a] Determined from hydrogen–tritium exchange.



Scheme 27

Other examples of these inversions are known and they may to some extent be a consequence of the different dependence of standard rates of proton exchange and nitration on acidity. A note of caution is appropriate here. What this great body of data on H–D exchange and nitration does seem to show is that no one reaction will ever provide a universal probe for quantitatively measuring the order of reactivity of a large set of heterocycles with any electrophile. The idea of a general electrophile is best used as a means for classifying reagents (as in this monograph) and as a means of comparing reactivity and positional selectivity among related compounds. It should be remembered that each electrophile will exert its own 'character' on reactions in which it is involved, as we shall see in the rest of Section 2.05.3.

2.05.3.4 Halogenation

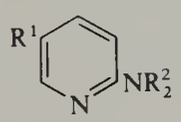
Some 16 or so years ago, Schofield ⟨B-67MI20500⟩ was able to state of halogenation: 'this is the most studied of electrophilic substitutions in the pyridine series'. In the intervening years, although mechanistic studies of nitration and hydrogen isotope exchange have claimed the limelight in the journals, inspection particularly of the patent literature reaffirms the truth of the above statement today ⟨B-74MI20500⟩. The study of halogenation presents some particularly difficult problems. Firstly, the nature of the halogenating agent changes with conditions, and so it is often more difficult to discern the precise nature of the reacting species compared with nitration. Coupled with this, most pyridines, apart from amino and hydroxy derivatives, are very resistant to halogenation except under rather extreme conditions. However, the rates of bromination at the 3- and 5-position of several methylpyridines with hypobromous acid have been measured in aqueous perchloric acid at 25 °C ⟨74JOC3481⟩. By use of the rate profile criterion (*vide supra*) and comparison with corresponding *N*-methylpyridinium salts, the bromination of these compounds by positive bromine was shown to involve the conjugate acids as reacting species. The relative rates and partial rate factors for these pyridinium salts appear in Table 9. Although it was not possible to measure

Table 9 Relative Rates and Partial Rate Factors for the Bromination of some Pyridinium Perchlorates with Hypobromous Acid in Perchloric Acid at 25 °C

Substituents	*Relative rate*	f_3	f_5
2,4,6-Me_3	3.0×10^{-7}	9.0×10^{-7}	—
1,2,4,6-Me_4	2.3×10^{-7}	6.9×10^{-7}	—
2,6-Me_2	2.8×10^{-9}	8.4×10^{-9}	—
1,2,6-Me_3	2.8×10^{-9}	8.4×10^{-9}	—
2,4-Me_2	4.1×10^{-9}	1.5×10^{-8}	9.8×10^{-9}
1,2,4-Me_3	3.6×10^{-9}	—	—
4-Me	3.1×10^{-11}	9.3×10^{-11}	—
1,4-Me_2	4.6×10^{-11}	1.4×10^{-10}	—
2-Me	3.1×10^{-11}	1.0×10^{-10}	8.6×10^{-11}
1,2-Me_2	3.4×10^{-11}	—	—
1-Me-2,6-$(OMe)_2$	7.8×10^{-3}	2.3×10^{-2}	—
1-Me-2-OMe	1.8×10^{-7}	—	—

directly the rate of bromination of the pyridinium cation by this method (no bromination was detected in up to 77.5% $HClO_4$ ($H_0 = -10$) at 25 °C), the data (Table 9) allowed the estimation (by an 'overlap' method) of the partial rate factor, f_3, for electrophilic bromination of the pyridinium ion by positive bromine to be 6×10^{-13} at 25 °C. A Hammett σ–ρ treatment of the same data arrived at a similar value, *viz.* 2×10^{-13}. Thus, bromination by positive bromine provides a method of determining the deactivation towards electrophilic substitution at position 3 in a pyridine ring caused by $=\overset{+}{N}H-$ that avoids certain problems inherent in nitration and hydrogen isotope exchange studies (see Sections 2.05.4.2 and 2.05.4.3). Nevertheless, the deactivating effect of $-\overset{+}{N}H=$ for nitration is comparable, but deactivation is much greater in acid-catalyzed hydrogen exchange reactions ($\sim 10^{-18}$).

The kinetics of 3-bromination of a series of 5-substituted 2-amino and 2-dimethylamino-pyridines (**81**) were determined potentiometrically using the H_2SO_4–H_2O–KBr–Br_2 system and a comparison was made with the corresponding anilines ⟨70JCS(B)117⟩. In contrast to the hypobromous acid work, the electrophile here is molecular bromine and reaction takes place on the minority free base species (rate profile evidence). The precise estimation of the deactivating effect of —N= was however complicated by several factors. Rates were affected by variation in bromide ion concentration, and also the amino and dimethylamino substituents exerted different effects in the pyridine and benzene series. In the benzene series the dimethylamino compounds have approximately the same reactivity as their amino analogues, but dimethylaminopyridines are brominated considerably faster than their amino counterparts. Several reasons were advanced to account for this. The buttressing effect is important in bromination *ortho* to a dimethylamino group, but substitution of N for CH should have a negative buttressing effect and relieve steric hindrance to bromination at position 3. Hydrogen bonding between the ring N and solvent will exert a deactivating effect on 3-bromination, but this will be sterically hindered in the dimethylamino case. The incursion of rate determining C—H bond breaking has been noted, particularly for *ortho* bromination of 5-substituted aromatic amines; however, hydrogen–deuterium isotope effects are small for the bromination of the amino- and dimethylamino-pyridines ⟨78APO(16)1⟩.



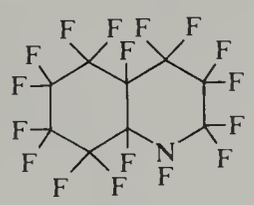
(**81**)

R^1 = Me, Cl, Br, NO_2
R^2 = H, Me

By contrast to the paucity of kinetic results available, preparative chlorination and bromination of pyridines and quinolines have been carried out under many conditions varying from mild (for hydroxy and amino derivatives) to drastic. Various aspects of this work have appeared in reviews on the halogenation of pyridines ⟨61HC(14-2)299, 74HC(14-S2)407, 66AHC(7)1, 66AHC(6)229, B-67MI20500⟩, pyridine 1-oxides ⟨B-71MI20500, B-67MI20501⟩ and the quinolines ⟨77HC(32-1)319⟩. The lack of mechanistic studies of many of the reactions involving ring halogenation makes classification somewhat difficult and some of them may eventually be shown to belong to other sections, *viz.* nucleophilic or free radical substitution.

Pyridine is converted into perfluoropiperidine (**82**) in low yield by reaction with fluorine in the presence of cobalt trifluoride ⟨50JCS1966⟩; quinoline affords (**83**) under similar conditions ⟨56JCS783⟩. Perfluoropiperidine can be obtained electrochemically. This is useful, as it may be readily aromatized to perfluoropyridine by passing it over iron or nickel at *ca.* 600 °C ⟨74HC(14-S2)407⟩. Recently, pyridine has been treated with xenon difluoride to yield 2-fluoropyridine (35%), 3-fluoropyridine (20%) and 2,6-difluoropyridine (11%), but it is not likely that this is simply an electrophilic substitution reaction ⟨76MI20500⟩.

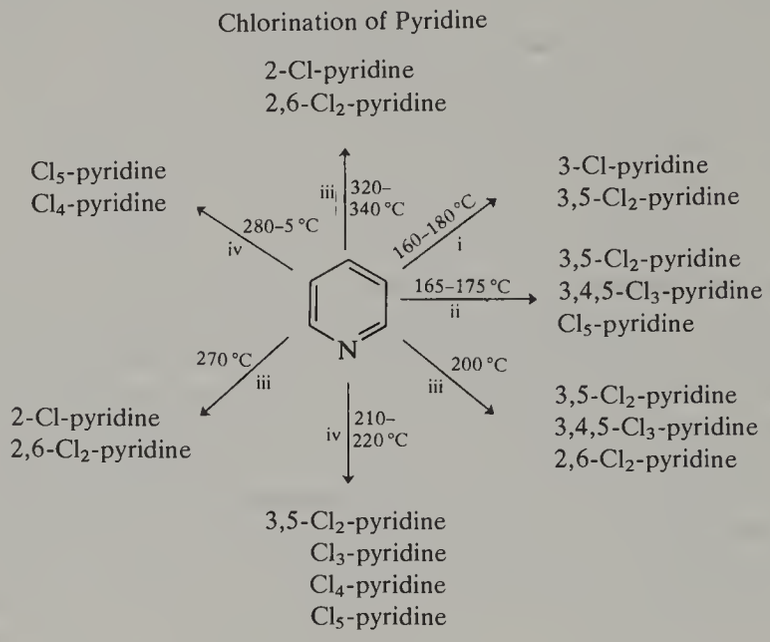
(**82**)



(**83**)

The direct chlorination of pyridine is not easy, as may be seen by consideration of the reaction conditions and complex product mixtures obtained (Scheme 28). As the temperature is raised (proceeding clockwise round the Scheme) predominant β-substitution

(electrophilic attack) gives way to preferred α- or poly-substitution (free radical attack) at higher temperatures. Description of the precise course of some of these reactions is further complicated by detection of an aminotrichloropyridine in (i) and 2-aminopyridine (after hydrolysis) in (v). Such products may well emanate from the corresponding 2- and 4-pyridylpyridinium salts which are known to give aminopyridines by nucleophilic ring opening (Section 2.05.4.5).

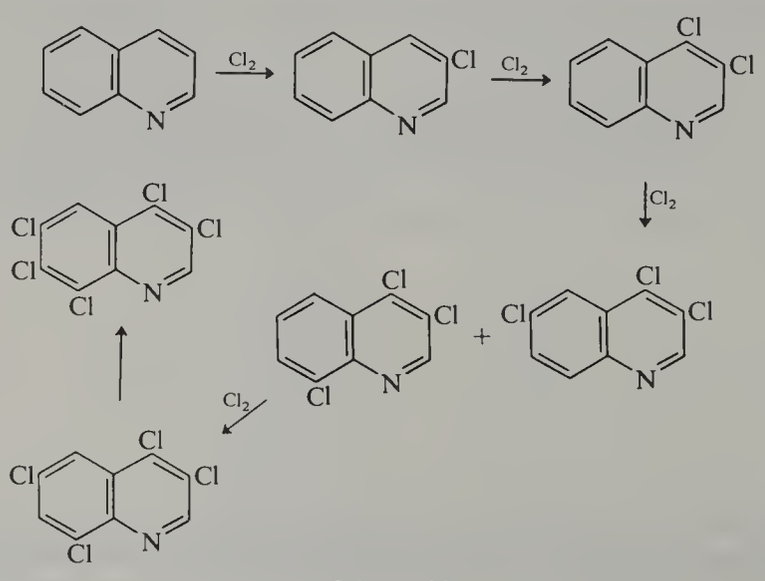


i, rapid heating of preformed chlorine–pyridine hydrochloride complex
ii, heating pyridine hydrochloride in presence of chlorine
iii, vapour phase chlorination with Cl_2
iv, PCl_5

Scheme 28

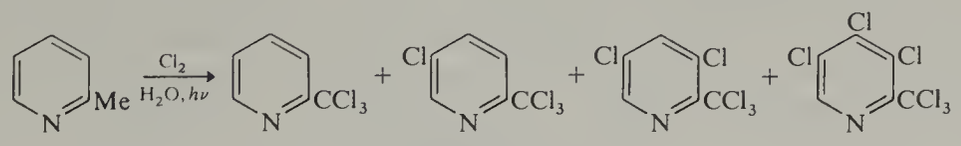
The development of industrial processes for the selective chlorination of pyridine has prompted intense study of vapour phase chlorination. Vapour phase chlorination of pyridine at *ca.* 500 °C has been carried out using either fluidized bed or turbulent flow methods to ensure good mixing of reactants, which is essential for control. The rate coefficients for each chlorination step in the pentachlorination of pyridine have been calculated ⟨B-74MI20500⟩.

Exhaustive chlorination of quinoline over antimony pentachloride leads to fragmentation into perchlorobenzene and hexachloroethane ⟨1882JCS412⟩. Direct uncatalyzed chlorination of quinoline at 160–190 °C gives at least five chloroquinolines (Scheme 29) among the ten products of reaction detected by gas chromatography ⟨70JHC171⟩. Substitution at position



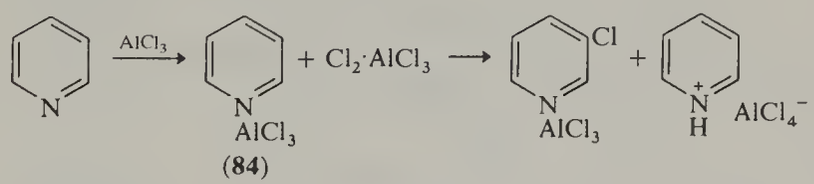
Scheme 29

4 probably arises by an addition–elimination mechanism rather than electrophilic substitution. When carried out at a lower temperature (100 °C), this process affords a small yield of 3-chloroquinoline.



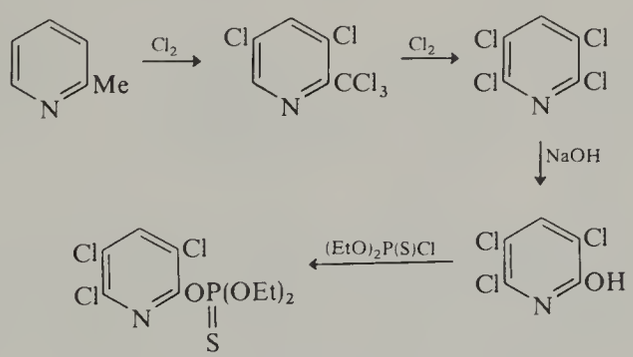
Scheme 30

Irradiation of 2-methylpyridine in chlorine water yields an array of chlorinated products (Scheme 30) ⟨47MI20500⟩. Attack at the methyl group probably occurs by a homolytic process, and β-ring substitution by electrophilic attack. Curiously, no chloro products are obtained when 3- and 4-methylpyridines are treated in the same way. Another direct method (Scheme 31) for chlorination of pyridine involves passing chlorine through a molten complex of pyridine (1 equiv.) and aluminum chloride (2 equiv.) at 80–115 °C ⟨61JOC789⟩. A 30–35% yield of 3-chloropyridine is obtained. The excess aluminum chloride acts as a 'support' for the electrophile 'Cl^+' that attacks the Lewis acid–pyridine salt (**84**), which is not as deactivated as a pyridinium ion. This so-called 'swamping catalyst effect' is said to work best for $AlCl_3$, but $FeCl_3$, BF_3 and $SnCl_4$ among others have been claimed to be effective ⟨70USP3538100⟩. Under these conditions, 4-methylpyridine gives the 3-chloro (40%) and 3,5-dichloro (15%) derivatives.



Scheme 31

Chlorination of quinoline in the presence of aluminum chloride results in substitution in the benzene ring; no evidence was found of attack at positions 2, 3 or 4. A route to the important wide-spectrum insecticide chloropyriphos from 2-methylpyridine involves two chlorination steps (Scheme 32) ⟨B-74MI20500⟩.

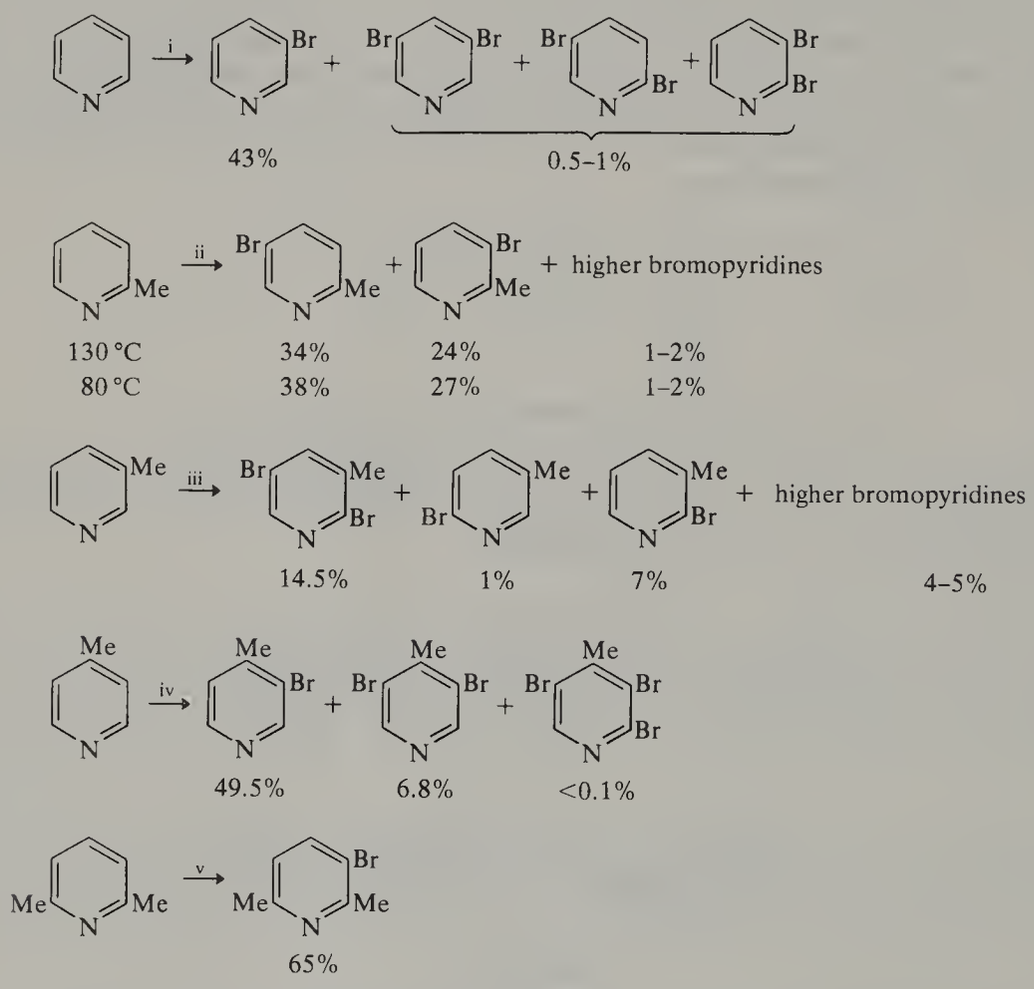


Scheme 32

Bromination of pyridine is much easier than chlorination. Vapour phase bromination over pumice or charcoal has been studied extensively ⟨B-67MI20500⟩ and, as with chlorination, orientation varies with change in temperature. At 300 °C, pyridine yields chiefly 3-bromo- and 3,5-dibromo-pyridine (electrophilic attack), whilst at 500 °C 2-bromo- and 2,6-dibromo-pyridine predominate (free radical attack). At intermediate temperatures, mixtures of these products are found. Similarly, bromination of quinoline over pumice at 300 °C affords the 3-bromo product, but at higher temperatures (450 °C) the 2-bromo isomer is obtained ⟨77HC(32-1)319⟩. Mixtures of 3-bromo- and 3,5-dibromo-pyridine may be produced by heating a pyridine–bromine complex at 200 °C, by addition of bromine to pyridine hydrochloride under reflux, and by heating pyridine hydrochloride perbromide at 160–170 °C ⟨B-67MI20500⟩.

A superior method for the bromination of pyridine and its methyl analogues consists of heating them with bromine in oleum ⟨62RTC864, 65RTC951⟩. Monosubstitution at the β-position is favoured (Scheme 33), providing a useful synthetic method for all except 3-bromo-5-methylpyridine. Note how this reaction becomes more facile with introduction of methyl groups into the pyridine ring (shorter reaction time, lower temperature, higher

yield). Bromination by this procedure, which is thought to involve attack by Br^+ on a neutral pyridine–sulfur trioxide complex, benefits from the same factors that promote halogenation by the 'swamping catalyst effect'. Indeed, a spectacular yield of 5-bromo-3-methylpyridine (85%) has been obtained from 3-methylpyridine by the bromine–aluminum chloride method ⟨66CJC1765⟩. The 2-methyl isomer yields the 5-bromo product (40%) mixed with some of the 3-bromo analogue, whilst 4-methylpyridine brominates at the 3-position (32%), utilizing the aluminum chloride method ⟨61JOC789⟩. As with chlorination, quinoline undergoes bromination in the benzene ring when the aluminum chloride procedure is used and perhaps also with bromine in oleum ⟨02JPR(174)209⟩. Further, it should be mentioned that treatment with concentrated sulfuric acid and silver sulfate, the Derbyshire–Waters procedure, does give substitution in the benzene ring ⟨58CI(L)361⟩. 3-Substitution in the quinoline ring is easily accomplished using bromine in hot carbon tetrachloride and pyridine ⟨66AHC(7)1⟩. Pyridine undergoes 3,5-dibromination, in unspecified yield, surprisingly easily with *N*-bromosuccinimide in carbon tetrachloride, but it is possible that a radical mechanism is operative here.



i, Br_2, fuming H_2SO_4 containing 65% SO_3, 7.5 h, 130 °C; ii, Br_2, fuming H_2SO_4 containing 65% SO_3, 7 h, 80 °C; iii, Br_2, fuming H_2SO_4 containing 65% SO_3, 7 h, 80 °C; iv, Br_2, fuming H_2SO_4 containing 65% SO_3, 7 h, 80 °C; v, Br_2, fuming H_2SO_4 containing 65% SO_3, 5 h, 55 °C

Scheme 33

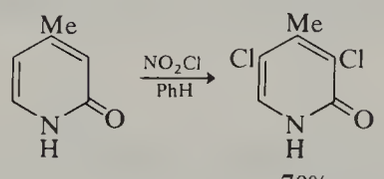
Only a little 3,5-di- and penta-iodopyridine is obtained when pyridine reacts with iodine in the vapour phase. Treatment of pyridine with iodine in 50% oleum furnishes 3-iodo- (18%) and some 3,5-di-iodo-pyridine. This is probably the result of electrophilic substitution by I^+, with oleum performing in the rôle already discussed ⟨57JCS387⟩. The products of iodination of quinoline are not well defined; however, a reviewer ⟨77HC(32-1)319⟩ has pointed out that one such product (formed by heating quinoline with iodine and potassium iodide at 160–170 °C in the presence of mercury(II) chloride) has a melting point identical with that of 3-iodoquinoline.

Oxo-, hydroxy and amino groups activate *ortho* and *para* positions toward attack by halogens and this far outweighs the deactivating effect of the pyridine nitrogen. Consequently, these compounds are much more reactive than the foregoing examples and this

Table 10 Halogenation of Amino-, Oxo- and Hydroxy-pyridines and -quinolines

Substituent	*Reaction*	*Conditions*	*Yield of Products (%)* *Major*		*Minor*	
Pyridine						
2-OH	Chlorination	Cl_2, $CHCl_3$	3,5-Cl_2	major	5-Cl	minor
	Bromination	Br_2, H_2O	3,5-Br_2	low	—	—
	Iodination	I_2/KI, aq. Na_2CO_3, 100 °C, 1 h	5-I	33.5	3,5-I_2	26.5
3-OH	Chlorination	—	2-Cl	major	--	—
	Bromination	—	2-Br	major	2,6-Br_2	minor
					2,4,6-Br_3	minor
	Iodination	I_2/KI, aq. Na_2CO_3, 35–40 °C, overnight	2-I	65	—	—
4-OH	Bromination	—	3,5-Br_2	major	—	—
	Iodination	I_2/KI, aq. Na_2CO_3, 100 °C, 1 h	3-I	50	3,5-I_2	29
Quinoline						
2-OH	Chlorination	Cl_2, HOAc	3,6-Cl_2	major	—	—
2-OH-4-Me	Bromination	Br_2, HOAc	3-Br	major	—	—
3-OH	Chlorination	Cl_2, EtOH, 20 °C	4-Cl	65	—	—
	Bromination	Br_2, HOAc	4-Br	78	—	—
	Iodination	I_2/KI, 10% NaOH, 20 °C	4-I	88	—	—
4-OH-8-OMe	Chlorination	Cl_2, HOAc, r.t.	3-Cl	25	—	—
4-OH	Bromination	Br_2, hot glacial HOAc	3-Br	~100	—	—
Pyridine						
2-NH_2	Chlorination	Cl_2, 20% H_2SO_4, 25 °C	5-Cl	54	3,5-Cl_2	minor
	Bromination	—	5-Br	major	—	—
	Iodination	I_2, pumice	5-I	major	—	—
3-NH_2	Chlorination	HCl, H_2O_2, 70–80 °C	2-Cl	88	2,6-Cl_2	—
	Bromination	2,4,4,6-Tetrabromocyclohexa-2,5-dienone, CH_2Cl_2	2-Br	67	2,6-Br_2	14
	Iodination	—	2,6-I_2	major	—	—
4-NH_2	Chlorination	HCl, H_2O_2	3-Cl	major	—	—
	Bromination	Br_2, HOAc	3-Br	major	—	—
	Iodination	ICl, HCl, 100 °C	3-I	78	—	—
		ICl, HOAc, 120 °C	3,5-I_2	79	—	—

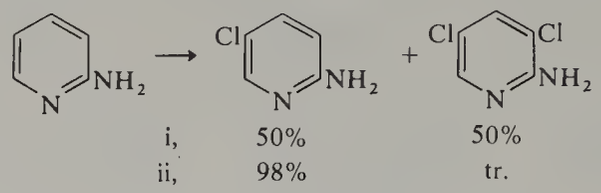
is manifest in the reaction conditions used for halogenations of oxo- and hydroxy-pyridines and -quinolines, and aminopyridines (Table 10). The reviews mentioned at the beginning of this section should be consulted for further examples of halogenation of the compounds in Table 10 and their analogues. A few new methods have appeared in addition to these. Pyridin-2-ones may be chlorinated easily with nitryl chloride; note that no nitration or substituent chlorination takes place under these conditions (equation 45) ⟨76MI20501⟩.



70% (45)

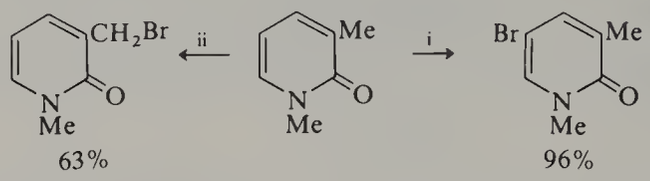
A synthetically useful method has been devised for the selective 5-chlorination of 2-aminopyridine in sulfuric acid (Scheme 34) ⟨76JOC93⟩. This exploits the fact that the initially formed 5-chloropyridine is protonated at the high acidity used and so is resistant to further chlorination. Conditions have been established for the use of NBS such that bromination of 3-methylpyridin-2-ones can be directed either to the substituent or the ring (Scheme 35) ⟨76JOC2065⟩. Bromination of 4-hydroxypyridin-2-one gives the 3-bromo derivative (**85**); surprisingly, no evidence for any attack at position 5 was found. Subsequent chlorination of (**85**) with chlorine in aqueous hydrochloric acid yields 5-bromo-3-chloro-4-hydroxypyridin-2-one (equation 46). This is just one example from an interesting series

of acid-catalyzed rearrangements undergone by 3-bromo-4-hydroxypyridin-2-one ⟨66AHC(6)229, B-67MI20500⟩.



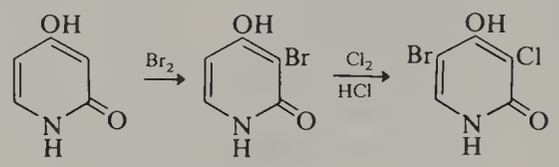
i, Cl_2, 17% H_2SO_4; ii, Cl_2, 72% H_2SO_4, −33 °C

Scheme 34



i, NBS, CCl_4, reflux, 30 min; ii, NBS, $(PhCOO)_2$, CCl_4, reflux, 1 h

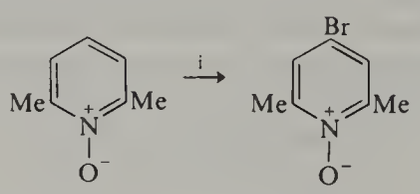
Scheme 35



(46)

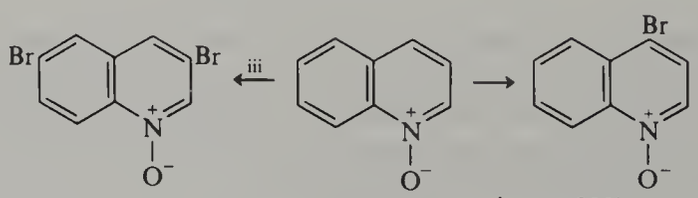
(85)

Bromination of *N*-oxides is not as easy as nitration. Only 3% of the 2-, and 7% of the 4-monobromo products (2,4- and 2,6-dibromopyridine 1-oxides are also found) are formed on treatment of pyridine 1-oxide with bromine, 90% sulfuric acid and silver sulfate. When bromine in 65% oleum is employed, pyridine 1-oxide gives mainly 3-bromopyridine 1-oxide ⟨62T227⟩. These results have been interpreted as the bromination in the first case involving the free base and in the second either the conjugate acid or *N*-oxide–sulfur trioxide complex. This contrasts with the nitration of pyridine 1-oxide, which takes place relatively easily on the free base. Recently, 4-bromination of 2,6-dimethylpyridine 1-oxide was achieved in fairly good yield using bromine in the presence of thallium(III) acetate (equation 47), but even under these conditions no bromination was detected with pyridine 1-oxide and its 2-methyl derivative ⟨79H(12)475⟩. Hydroxy- and amino-pyridine 1-oxides are readily halogenated like the parent systems ⟨B-71MI20500⟩. Quinoline 1-oxide has been brominated under various conditions (Scheme 36). 3-Bromination in acetic anhydride probably occurs by an addition–elimination mechanism similar to that for nitration, but the 4-substituted product almost certainly arises by electrophilic attack. Bromination of acridine 10-oxide affords the 9-bromo derivative in good yield when the reaction is carried out in acetic acid ⟨60JCS3367⟩.



(47)

i, Br_2, $Tl(OAc)_3$, AcOH, 70 °C, 24 h

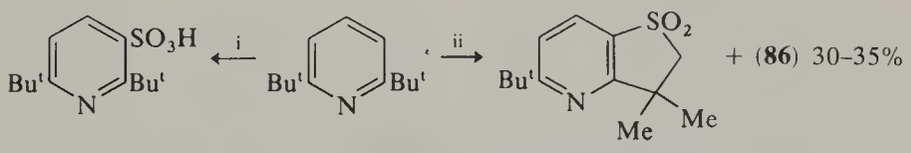


i, Br_2, H_2O; ii, Br_2, $Tl(OAc)_3$, AcOH; iii, Br_2, Ac_2O, $CHCl_3$

Scheme 36

2.05.3.5 Sulfonation

Pyridine undergoes sulfonation to produce 3-pyridinesulfonic acid in good yield on heating with oleum at *ca.* 250 °C in the presence of mercury(II) sulfate, aluminum or vanadium catalysts ⟨B-67MI20500⟩. As with halogenation, coordination of pyridine by a metal ion rather than protonation favours reaction. It should be added that reaction time, temperature and the concentration of the oleum used are critical factors in determining yield. When the reaction is carried out at 330 °C, the products are the 3- and 4-sulfonic acids (25%) and pyridin-4-one (15–20%), and 35–40% of the pyridine is recovered. Heating pyridine-3-sulfonic acid under similar conditions leads to the 4-sulfonic acid, pyridin-4-one and *ca.* 50% pyridine. Presumably the 4-substituted products from high temperature sulfonations arise by desulfonation and rearrangement. The three methylpyridines are also sulfonated under similar conditions to pyridine. The 2- and 3-isomers furnish the respective 5-sulfonic acids and 4-methylpyridine gives 4-methylpyridine-3-sulfonic acid. 2,6-Dimethylpyridine does not undergo β-sulfonation but merely yields a sulfur trioxide complex. In contrast, 2,6-di-*t*-butylpyridine is sulfonated very easily to give the 3-sulfonic acid (**86**) ⟨53JA3865⟩. This surprising behaviour has been attributed to attack on the free pyridine as sulfur trioxide complex formation is prevented by the steric effect of the large α *t*-butyl groups. When the reaction is carried out at higher temperature a cyclic compound (**87**) is also obtained (Scheme 37) ⟨61JOC2611⟩.

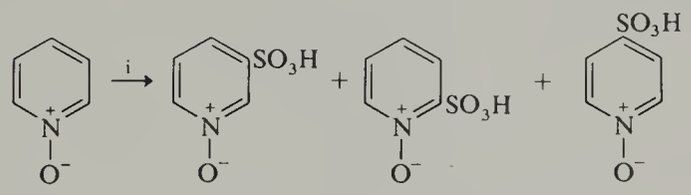


(**86**) (**87**) 15–20%

i, SO_3, liq. SO_2, −10 °C, 4 h; ii, SO_3, 240–250 °C, 15 h, sealed tube

Scheme 37

Quinoline and isoquinoline both undergo sulfonation in the benzene ring ⟨77HC(32-1)1⟩. Oxo-, hydroxy- and amino-pyridines are activated towards sulfonation, which takes place *ortho* or *para* to the activating group. Thus, 2-aminopyridine is sulfonated at the 5-position, 3-amino- and 3-hydroxy-pyridine at C-2; 4-aminopyridine and pyridin-4-one are sulfonated at the 3-position. The sulfonation of pyridin-2-one has not been reported; however, 1-alkylpyridin-2-ones are substituted at the 5-position ⟨B-76MI20502⟩. Unlike nitration, sulfonation of pyridine 1-oxide is very difficult and only under vigorous conditions is the 3-sulfonic acid formed by reaction on the conjugate acid (equation 48) ⟨B-71MI20500⟩. 2,6-Dimethylpyridine 1-oxide also undergoes sulfonation at position 3.



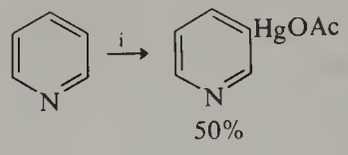
(48)

i, 20% oleum, $HgSO_4$, 230 °C, 22 h in an open vessel

2.05.3.6 Mercuration

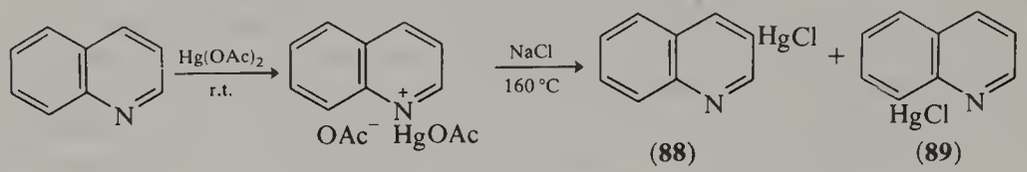
3-Pyridylmercury(II) acetate is formed by heating pyridine and aqueous mercury(II) acetate in a sealed glass vessel (equation 49) ⟨55JA4658⟩. 4-Methylpyridine is mercurated at the 3-position but the yield is poor (3%) ⟨48JCS198⟩. Quinoline undergoes mercuration on nitrogen at room temperature and substitution at C-3 and C-8 at 160 °C. Further reaction with sodium chloride yields the mercuriochlorides (**88**) and (**89**) (equation 50). Chloromercuration of pyridin-2-one is effected at C-5 using mercury(II) acetate–acetic acid followed by hydrochloric acid; treatment with aqueous mercury(II) acetate yields the 3,5-dimercurioacetate. Mercury(II) acetate mercuration of pyridin-4-one takes place at position 3, and that of 3-hydroxypyridine at C-2 ⟨74HC(14-S2)489⟩. 4-Aminopyridine is also readily mercurated at C-3 and C-5. Mercuration of pyridine 1-oxide has been studied with several reagents (Scheme 38) ⟨62RTC124⟩. Substitution at the 2-position predominates, but formation

of the 3-isomer becomes more significant under acidic conditions, probably due to reaction on the protonated *N*-oxide. Quinoline 1-oxide undergoes mercuration at C-8.

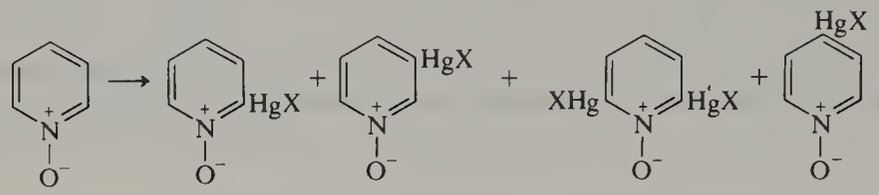


50% (49)

i, $Hg(OAc)_2$ aq., 155 °C, 2.5 h



(88) (89) (50)



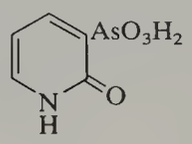
i	15%	3%	2%	trace
ii	35%	7.5%	2.5%	5%
iii	17.5%	12%	2%	1%
iv	20%	1%	2.5%	1%

i, $Hg(OAc)_2$, HOAc, 130 °C, 2 h, X = OAc; ii, $HgSO_4$, H_2SO_4, 165–175 °C, 5 h, X = SO_4; iii, $HgSO_4$, H_2SO_4 excess, 165–175 °C, 5 h, X = SO_4; iv, $HgCl_2$, 150–160 °C, 5 h, X = Cl

Scheme 38

2.05.3.7 Arsonation

Direct arsonation of pyridine is a little studied reaction but from the evidence available it appears to be a reversible process. Fusing pyridin-2-one with arsenic acid yields a mixture of mainly 5- with some 3-pyridinearsonic acid. Longer reaction times (24 h) lead to the isolation of chiefly the 3-isomer ⟨66AHC(6)229⟩. The 5-isomer can be prepared from pyridin-2-one using either chloroarsonic acid, or a mixture of As_2O_3–$AsCl_3$ followed by reduction and oxidation with hydrogen peroxide. 1-Methylpyridin-2-one gives the 3-arsonic acid (**90**) on reaction with arsenic acid.

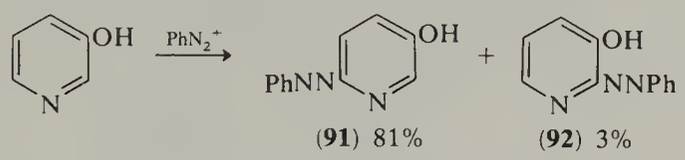


(**90**)

2.05.3.8 Diazo Coupling

Diazo coupling usually takes place *para* to an activating substituent, which is necessary for reaction in a pyridine. Pyridin-2-one furnishes the 5-phenylazo derivative, and 3-hydroxypyridine a mixture of (**91**; 81%) and (**92**; 3%) (equation 51). The 5-phenyl group in 3-hydroxy- 4-methyl-5-phenylpyridine appears to exert a significant effect on the orientation of phenylazo coupling; here the ratio of 2- to 6-substitution is 1:1 ⟨75RCR823⟩. 3-Hydroxy-2,6-dimethylpyridine does not undergo coupling at C-4 with benzenediazonium chloride, demonstrating again how difficult is electrophilic substitution at the 4-position in pyridine. The corresponding *N*-oxide does, however, readily undergo phenylazo coupling at C-4. The presence of two activating substituents makes azo coupling quite easy. The 3-hydroxy group (*para* directing) directs azo coupling of 3-hydroxypyridin-2-one and 3-hydroxy-2-methoxypyridine to the 6-position ⟨75RCR823⟩. 6-Hydroxypyridin-2-one reacts easily at C-3. Nuclear substitution has not been reported for monoaminopyridines. 2-

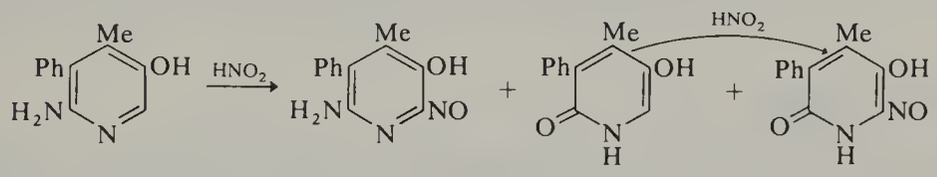
Aminopyridine gives 2-benzenediazoaminopyridine on treatment with benzenediazonium chloride. However, coupling reactions (at position 3) are documented for 2,6-diaminopyridine and use of excess diazonium salt will even give 3,5-disubstitution. 3-Hydroxyquinoline couples at the 4-position, and quinolin-4-one at C-3 with further substitution at nitrogen ⟨72BAU452⟩. 3-Hydroxypyridine 1-oxide does not undergo diazo coupling even with picryldiazonium ions. Quinoline 1-oxides also do not react readily; the 8-hydroxy isomer does azo couple at C-5.



(**91**) 81% (**92**) 3% (51)

2.05.3.9 Nitrosation

The attachment to the pyridine ring of at least two activating substituents is required for *C*-nitrosation. The monoaminopyridines undergo *N*-nitrosation to yield pyridinones and this reaction accompanies *C*-nitrosation (Scheme 39) ⟨75RCR823⟩.

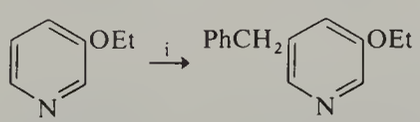


Scheme 39

2-*N*-Methylaminopyridine undergoes *N*-nitrosation, but the product does not undergo Fischer–Hepp rearrangement on treatment with sulfuric acid. *N*-Nitrosodemethylation is a side reaction that accompanies the nitration of the three isomeric monodimethylaminopyridines ⟨72JCS(P2)1940⟩. 2,6-Diaminopyridine, 6-aminopyridin-2-one and 6-hydroxypyridin-2-one all nitrosate at the 3-position. Kinetic studies of the diazotization of primary β-aminopyridines ⟨81JCS(P2)248⟩, and the nitrosation of methylaminopyridines and their *N*-oxides, have been reported recently ⟨81JCS(P2)239⟩. Diazotization of heterocyclic amines has been reviewed ⟨75CR241⟩.

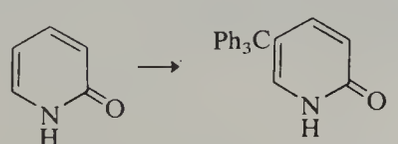
2.05.3.10 Acylation and Alkylation

At last, a good example of a Friedel–Crafts reaction has been recorded in the pyridine series (equation 52), but details are sparse ⟨77JOU1231⟩. Formerly, only two instances had been quoted ⟨66AHC(6)229⟩. Pyridin-2-one and its *N*-methyl derivative give a product (**93**) of uncertain orientation (equation 53) ⟨49JA387⟩; the second involves an aluminum chloride-catalyzed Fries rearrangement of 2-benzoyloxypyridine to 5-benzoylpyridin-2-one in 1% yield. A couple of other reactions ought to be mentioned under this heading. Treatment of pyridin-2-one with sulfur dichloride yields a dipyridyl sulfide (equation 54) ⟨64ACS(B)269⟩. There is also the interesting conversion, formally an arylation (equation 55), where pyridine plays the rôle of acylating agent, but this is better considered as belonging to another family



(1 equiv.) (52)

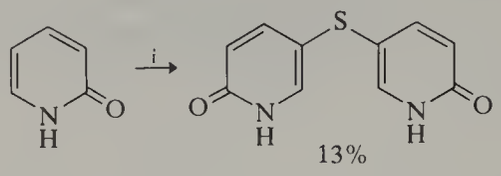
i, $PhCH_2Cl$ (1 equiv.), $AlCl_3$ (3 equiv.), 180 °C, 5 h



(**93**) i 45–60% (53)
ii 45–60%

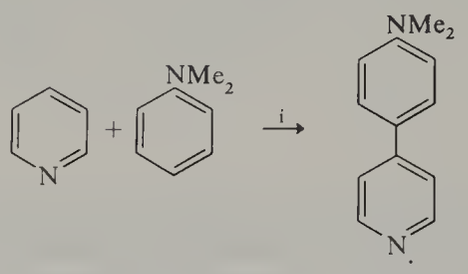
i, Ph_3COH, conc. H_2SO_4, 250 °C, 20 min; ii, Ph_3CCl, 250 °C, 20 min

of reactions (see Section 2.05.4.7.4) ⟨65JOU2059⟩. Quinolines and isoquinolines undergo Friedel–Crafts reaction in the benzene ring. The Friedel–Crafts reaction is not successful with pyridine 1-oxides.



(54)

i, SCl_2, PhH, reflux, 1 week



(55)

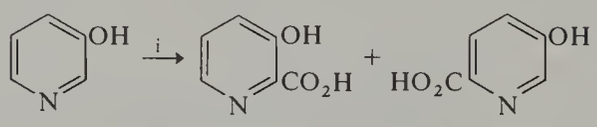
i, PhCOCl, 100 °C, 1 h; $AlCl_3$, 100 °C, 2 h

2.05.3.11 Carbonylation

3-Hydroxypyridine reacts with formaldehyde and base to give the 2-hydroxymethyl derivative which reacts further, ultimately to yield the 2,6-disubstituted product. No 4-substitution is detected in this case or with 3-hydroxy-2,6-dimethylpyridine when it is treated under the same conditions ⟨75RCR823⟩. 3-Hydroxypyridine readily undergoes bis-aminomethylation at the 2- and 6-positions.

2.05.3.12 Carboxylation

Pyridin-2-one undergoes the Kolbe reaction with carbon dioxide under pressure to give a good yield of the 5-carboxylic acid (60%). Pyridin-4-one also reacts readily to give 3-mono- or 3,5-di-carboxylic acids. The nature of the products derived from a Kolbe reaction with 3-hydroxypyridine is very susceptible to the reaction conditions. This is illustrated by the difference in behaviour of the sodium and potassium salts (equation 56). When the sodium salt is heated rapidly to 280 °C with carbon dioxide at atmospheric pressure the 2-carboxylic acid (8%) is the only product. Under the same conditions the potassium salt gives a mixture of 2- (3%) and 6- (24%) carboxylic acids ⟨75RCR823⟩.



(56)

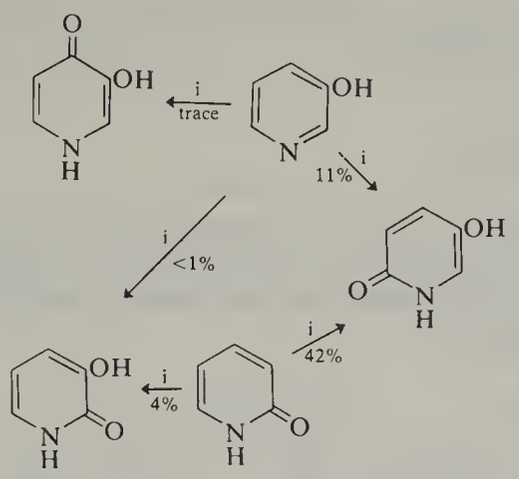
i, K_2CO_3, CO_2, 280 °C

2.05.3.13 Hydroxylation

3-Hydroxypyridine and pyridin-2-one are sufficiently reactive to undergo Elbs oxidation, and in both cases the substituent directs hydroxylation mainly *para* (Scheme 40) ⟨58JA3717⟩. Quinoline may be converted into 3-hydroxyquinoline (6% yield) by Udenfriend oxidation (ascorbic acid and oxygen in the presence of iron(II)) which is believed to involve attack by OH^+ rather than radicals ⟨54JBC(208)741⟩.

2.05.3.14 Thiocyanation

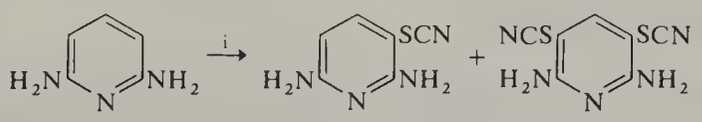
2,6-Diaminopyridine undergoes 3-thiocyanation and 3,5-dithiocyanation (equation 57) ⟨62JCS3464⟩. 6-Substituted 3-aminopyridines react under similar conditions at C-2 and the



i, NaOH aq., 5 °C, $FeSO_4$, $K_2S_2O_8$, 5–20 °C slowly, then 20 °C, 20 h

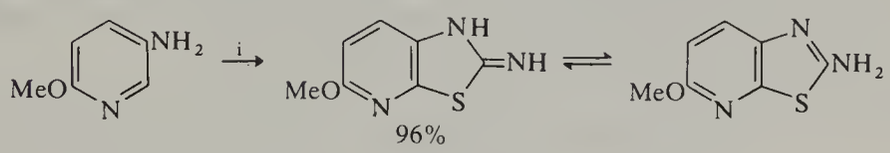
Scheme 40

product cyclizes spontaneously (equation 58) ⟨73JOC4383⟩. The difference in the nature of the products of these two reactions reflects the greater nucleophilicity of a 2- compared with a 3-amino group. 3-Aminoquinoline and quinolin-2-one also undergo thiocyanation ⟨51JA5815⟩.



(57)

i, NH_4SCN, HOAc, 50% v/v, Br_2, glacial HOAc, 20–25 °C

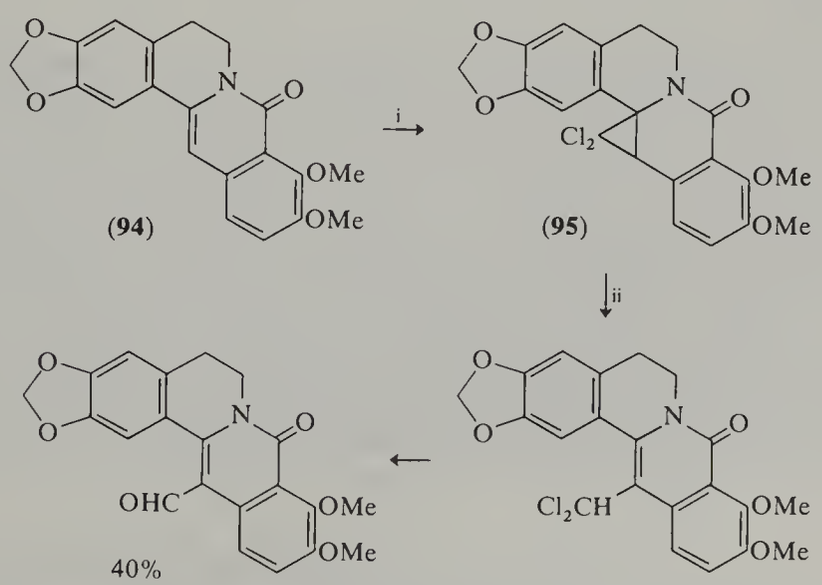


(58)

i, glacial HOAc, KSCN, then Br_2 added at 0 °C, over 2 h, r.t., 10 h

2.05.3.15 With Carbenes

This reaction is extremely rare, even for activated pyridines and pyridinones. Several preliminary reports have appeared of late on the addition of dichlorocarbene to pyridines, quinolinones and their salts which involve subsequent ring transformation (see Section 2.05.8). There is one example reported of the addition of dichlorocarbene under phase transfer conditions to oxyberberine (**94**), which gives a stable adduct (**95**; Scheme 41)



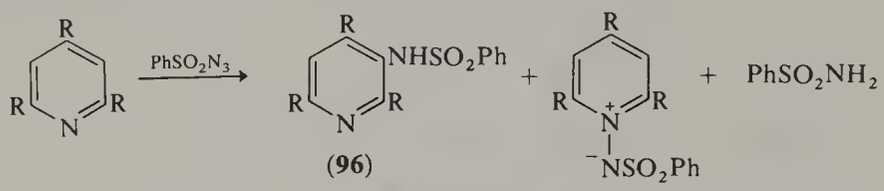
i, 50% NaOH, $CHCl_3$, $PhCH_2\overset{+}{N}Me_2EtI^-$, 50 °C, 2 h; ii, 10% HCl, MeOH

Scheme 41

⟨81JOC386⟩. However, this adduct is readily hydrolyzed to oxyberberine-13-carbaldehyde, a Reimer–Tiemann type product.

2.05.3.16 With Sulfonylnitrenes

A few years ago an old reaction, that of the thermal decomposition of arylsulfonyl azides in pyridines, was re-examined (Scheme 42) ⟨72JOC2022⟩. Among the products identified was the 3-phenylsulfonamido derivative (**96**), which was proposed to arise by an electrophilic attack by phenylsulfonylnitrene.

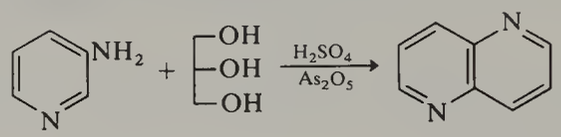


	(96)		$PhSO_2NH_2$
R = H	—	30%	>18%
R = Me	15%	15%	61%

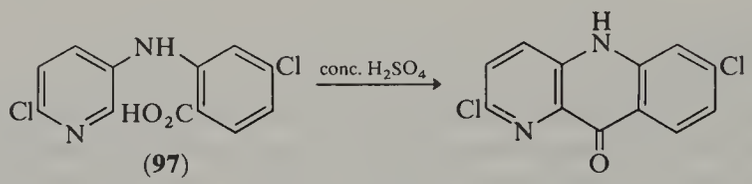
Scheme 42

2.05.3.17 Electrophilic Cyclizations

Several of the well known cyclization reactions of aromatics that are used for the preparation of benzoheterocycles also work for pyridines ⟨66AHC(6)229⟩. 3-Aminopyridine undergoes the Skraup reaction (equation 59), and the substituted 3-amino derivative (**97**) undergoes intramolecular Friedel–Crafts reaction (equation 60). Further examples of these reactions can be found in the appropriate part of Chapter 2.06.



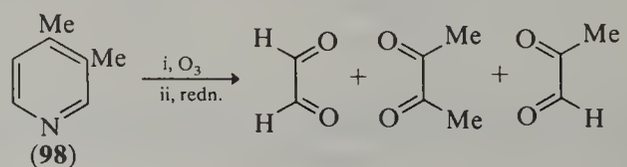
(59)



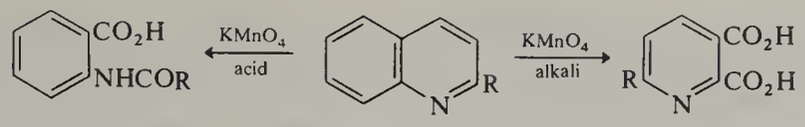
(60)

2.05.3.18 Oxidation

The pyridine ring is not oxidized easily, which is one reason why pyridine is often used as a solvent for oxidations. Ozonolysis of a substituted pyridine (**98**) yields products that formally correspond to addition of ozone to both Kekulé forms (equation 61). Oxidation of quinoline may take place in either ring; treatment with alkaline permanganate affords quinolinic acid (**99**; R = H). By contrast, 2-alkyl or 2-aryl substituted quinolines undergo oxidation of the pyridine ring with acid permanganate (Scheme 43). Ozonolysis of quinoline gives products that are predictable by considerations of double bond fixation at positions 5,6 and 7,8 and easier reaction in the benzene ring (equation 62). The two rings in isoquinoline are almost equally susceptible to oxidation; employment of alkaline permanganate gives a mixture of phthalic and cinchomeronic acids (Scheme 44). Neutral permanganate affords mainly phthalimide (**100**). Just how closely balanced the reactivities of the two rings are is nicely demonstrated by comparing the oxidation of 5-amino- (benzene ring oxidation) and 5-nitroisoquinoline (pyridine ring oxidation) (equations 63 and 64).

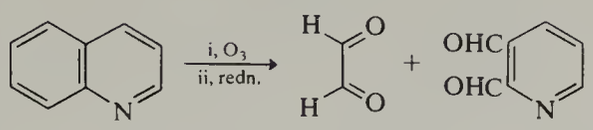


(61)

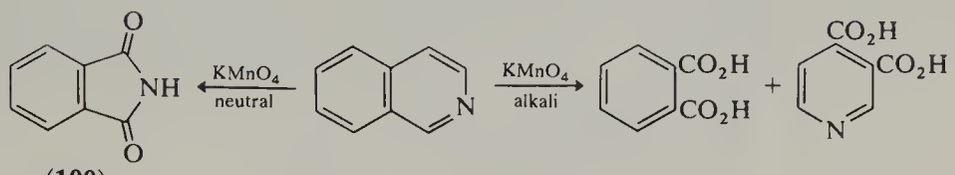


(**99**)

Scheme 43

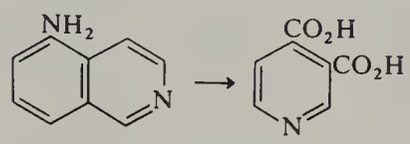


(62)

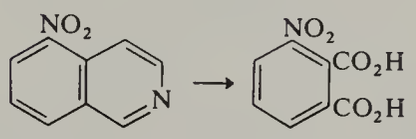


(**100**)

Scheme 44



(63)



(64)

Acridine is readily oxidized to acridone by sodium dichromate and acetic acid. Pyridin-2-one and nicotinic acid have been found to undergo oxidation to oxalic acid on treatment with Fenton's reagent ⟨69CHE563⟩.

2.05.4 NUCLEOPHILIC ATTACK AT CARBON

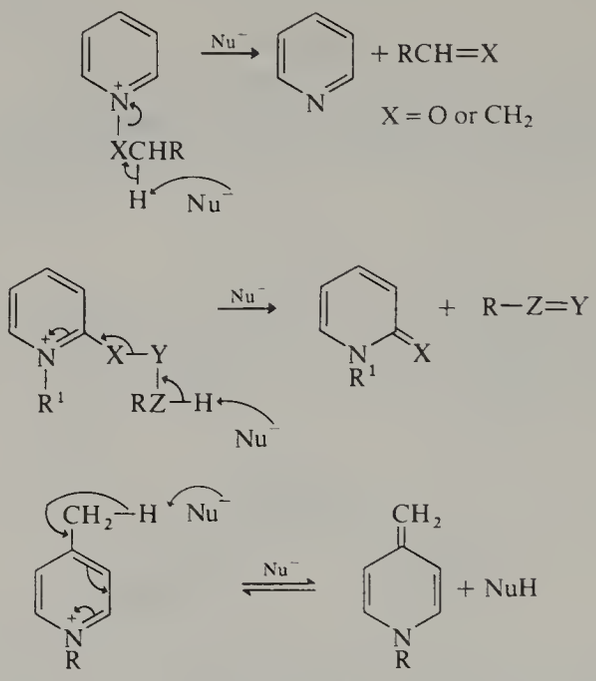
2.05.4.1 Introduction

Suitably substituted pyridines (*e.g.* 2- or 4-chloropyridine) undergo nucleophilic substitution readily, but only the strongest nucleophiles (*e.g.* NH_2^-) can replace hydrogen by expulsion of H^-. Replacement of hydrogen is easier in pyridinium (and quinolinium) salts, and in *N*-oxides and their salts, but these reactions proceed by an addition–elimination rather than an S_NAr process. In general, a nucleophile may attack C- or H-atoms at almost any position (ring or substituent) in appropriately substituted pyridines and quinolines. The consequences of initial nucleophilic attack are quite diverse and several fall outside the scope of this chapter; nevertheless they are categorized below. The chemistry of pyridine and quinoline abounds with examples of addition–elimination reactions. The first step involves either 1,2- or 1,4-addition to C=N. The second, elimination, is greatly facilitated by a good leaving group attached to the pyridine nitrogen. For the purposes of this chapter, the classification of Katritzky ⟨69T4291⟩ Type A–D and Abramovitch ⟨74HC(14-S1)1⟩ Type E pathways for reactions of *N*-oxides and their salts is extended to include other derivatives. The reason for doing this is to classify a wide range of apparently unrelated reactions under five headings which, with two others, constitute the major reaction paths open to pyridine-like heterocycles with nucleophiles. Bold letters (**A–E**) are used to designate these general reaction types in order to distinguish them from those that are specific to *N*-oxides and their salts.

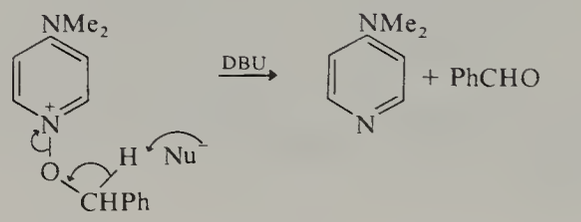
2.05.4.1.1 Illustration of the types of pathway

Type **A** behaviour involves initial nucleophilic attack at a *hydrogen* attached to a *substituent*, with subsequent elimination or anhydrobase formation (Scheme 45). Chapter 2.06

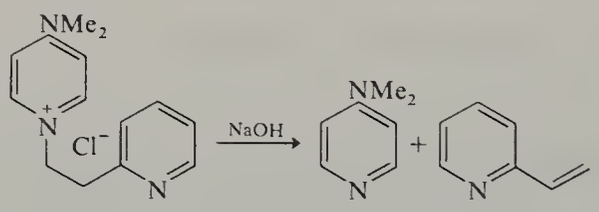
should be consulted for a comprehensive treatment of reactions of this type; however, a few illustrative examples are given here: equations (65) ⟨81BCJ2221⟩, (66) ⟨79USP4158093⟩, (67) ⟨79AG(E)707⟩ and (68). The Type **A** path is promoted by steric effects and might provide a viable alternative to the Hofmann elimination (equation 69) ⟨81CC96⟩.



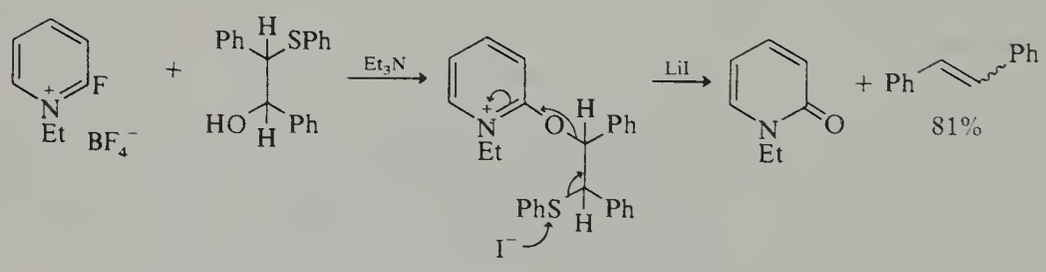
Scheme 45



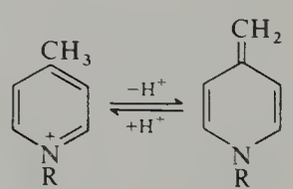
(65)



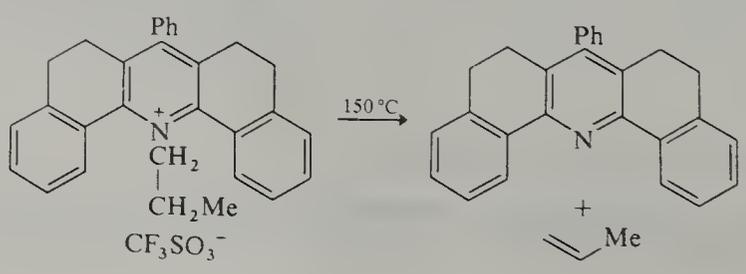
(66)



(67)

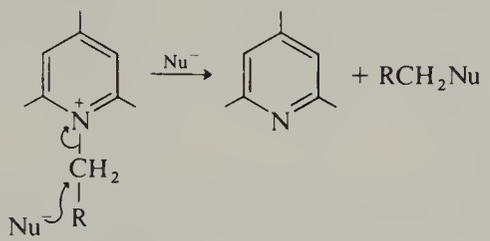


(68)

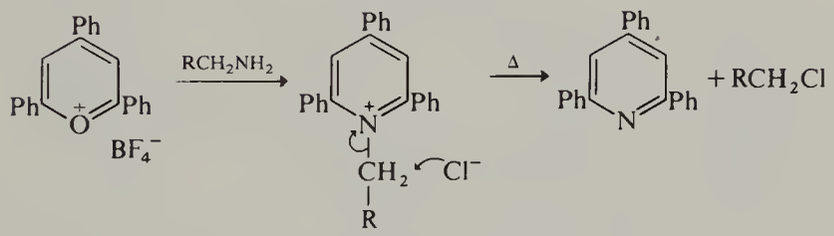


(69)

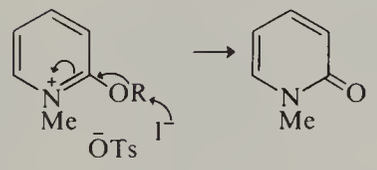
The Type **C** path is also a substituent reaction (Scheme 46) (see Chapter 2.06). In this case the substituent undergoes nucleophilic attack at other than hydrogen, with resultant loss of a pyridine fragment (equation 70). Equations (70) and (71) contain examples of two particularly significant general synthetic approaches that employ the pyridine molecule. The first has been used for the conversion of amines to halides, esters, ethers, aldehydes, thiocyanates, alkanes, nitroalkanes, *etc.* ⟨80T679⟩; complementary to this is the elimination, path **A** (equation 69). The second method has been applied to the synthesis of esters, amides, thiolesters, macrocyclic lactones, alkyl halides, nitriles, isocyanides, thiols, isothiocyanates, carbodiimides, amines and other functionalities, where *N*-alkyl-pyridone or -pyridinethione acts as the leaving group (equation 71). Implicit in both of these approaches is suppression of **B**, **D** and **E** pathways (*vide infra*) and promotion of leaving group ability by careful substituent selection in the pyridine moiety ⟨79AG(E)707⟩. Equation (72) is included to illustrate that nucleophilic attack on an anhydrobase can compete very successfully with path **B** ⟨81JHC939⟩.



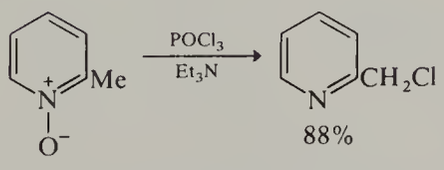
Scheme 46



(70)

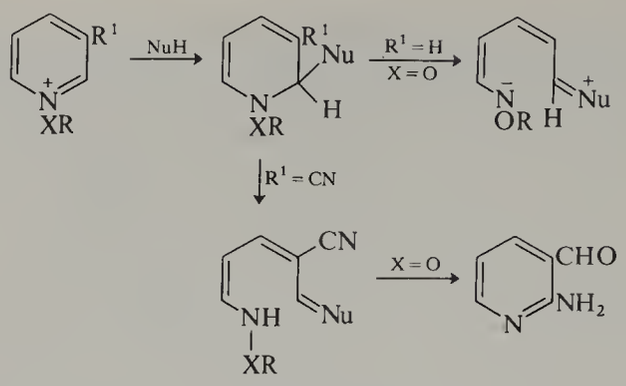


(71)

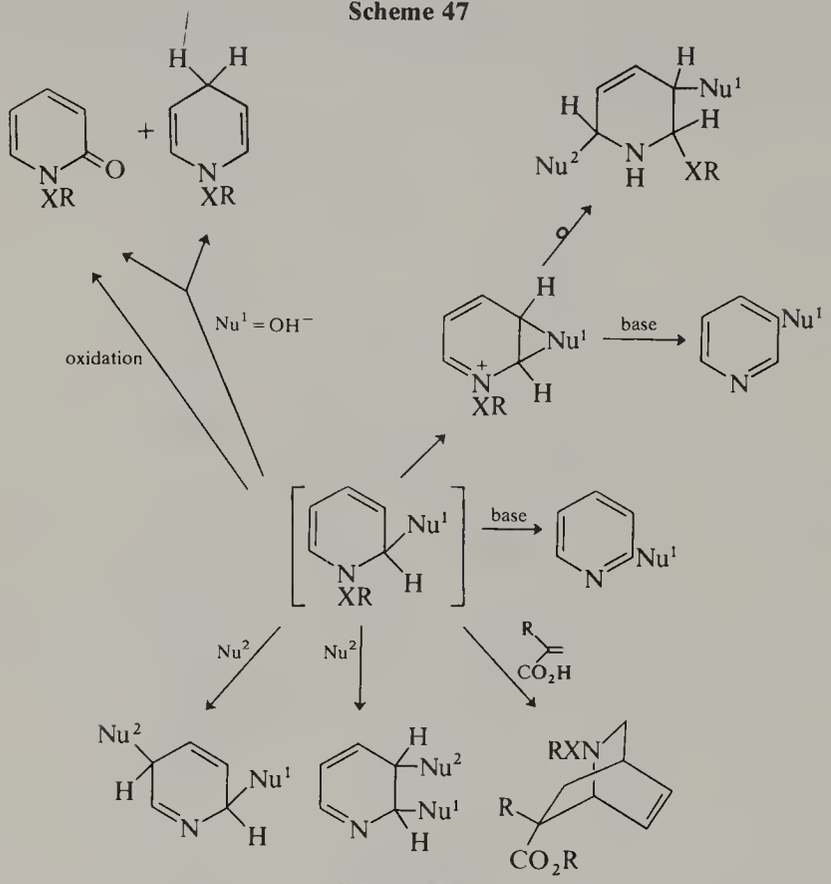


(72)

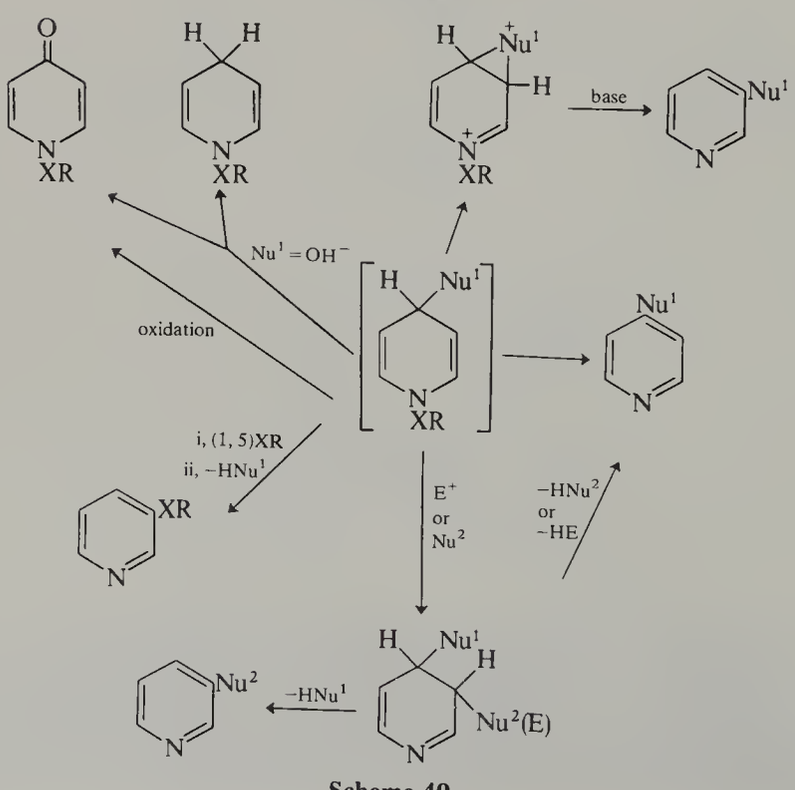
Type **B** and **D** behaviour involve initial nucleophilic attack at C-2 or C-4 to form a dihydro intermediate, the fate of which determines the behaviour type. Formation of a dihydro intermediate that undergoes ring opening, with or without subsequent ring closure, constitutes Type **D** behaviour (Scheme 47) ⟨81T3423⟩. Some of the other fates that can befall 1,2- (Scheme 48) or 1,4- (Scheme 49) intermediates is described as Type **B** behavior.



Scheme 47

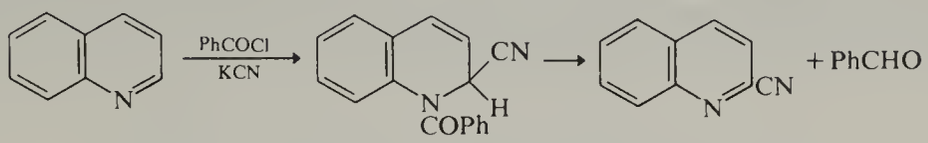


Scheme 48

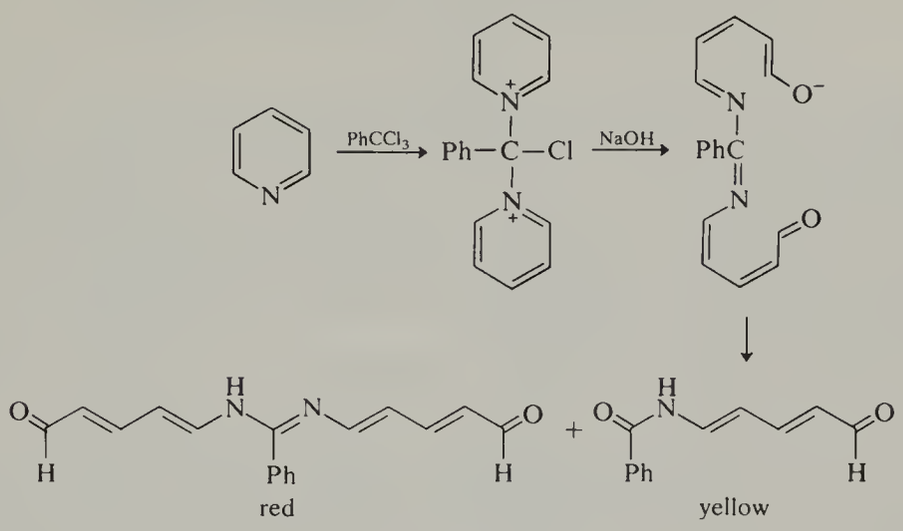


Scheme 49

The Reissert reaction exemplifies the **B** pathway (equation 73), and is of course a notable method for aldehyde and alkaloid synthesis. The Fujiwara reaction ⟨81JOC3175⟩, a colour test, provides an example of Type **D** behavior (Scheme 50).

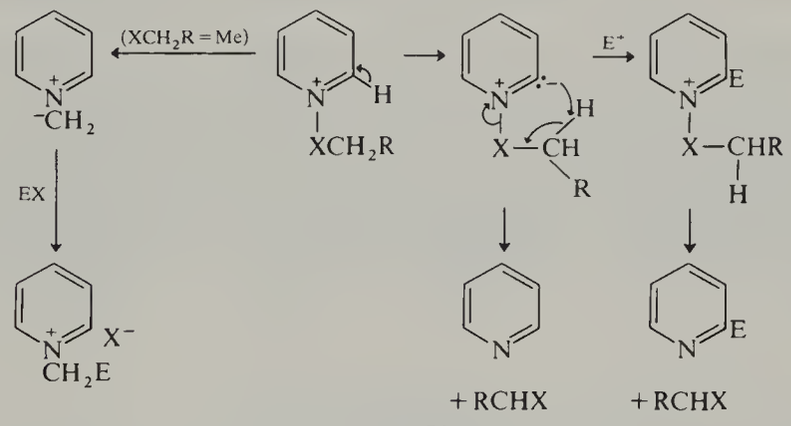


(73)

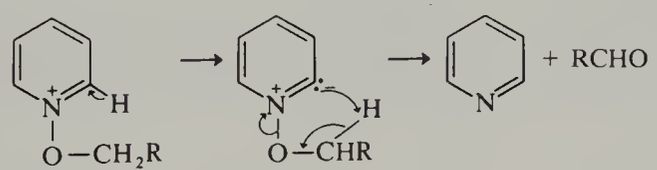


Scheme 50

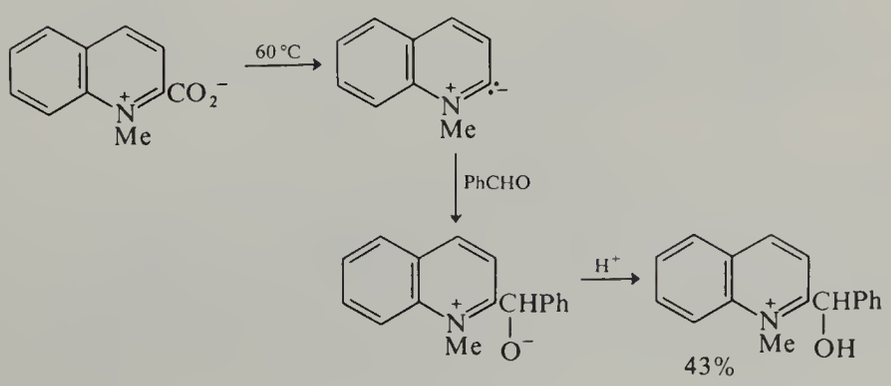
Formation of an ylide, which can react further with an electrophile or by proton abstraction, is defined as Type **E** behaviour (Scheme 51). The ylide may arise either by nucleophilic attack at a hydrogen atom (equation 74) or by, for instance, an α-elimination of carbon dioxide, the Hammick reaction (Scheme 52) ⟨70LA(732)43⟩.



Scheme 51

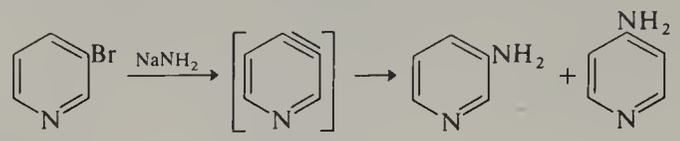


(74)



Scheme 52

Two other important modes of substitution require mention here. They are the S_NAr and elimination–addition reactions. Actually, it is sometimes difficult to distinguish between true aromatic nucleophilic substitutions and addition–elimination processes. The second group involves pyridyne intermediates (Scheme 53). Both of these reaction types are discussed fully under substituent reactions (Chapter 2.06).



Scheme 53

The essential points about Type **A**–**E** behaviour are summarized:

A. Nucleophilic attack at a SUBSTITUENT HYDROGEN with subsequent ELIMINATION (Scheme 45);

B. 1,2- or 1,4-ADDITION followed by ELIMINATION; further ADDITION; REARRANGEMENT then ELIMINATION; *etc.* (Schemes 48 and 49);

C. Nucleophilic attack at a SUBSTITUENT ATOM other than hydrogen followed by ELIMINATION (Scheme 46);

D. 1,2-ADDITION followed by RING OPENING with or without subsequent ring closure (Scheme 47);

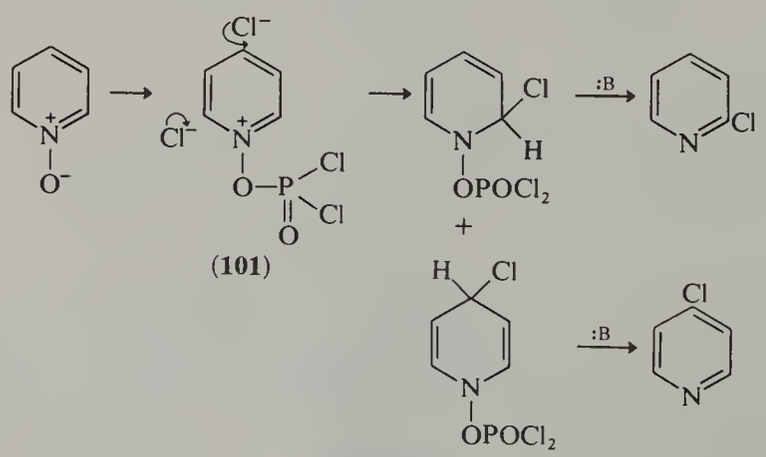
E. YLIDE formation followed by electrophilic ADDITION (Scheme 51).

An understanding of the foregoing helps the synthetic chemist achieve the best control over the initial position of nucleophilic attack and its ultimate outcome. The use of substituent effects (or the lack of them) has been mentioned, but the choice (if available) of nucleophile and conditions also play a crucial rôle. Generally speaking, strong nucleophiles attack at a ring carbon to give **B** and/or **D** behaviour, but weaker ones (*e.g.* N_3^-, NO_2^-, I^-, CNS^-, *etc.*) attack at a substituent (Type **A** or **C**). It has been suggested ⟨68JA223⟩ that hard nucleophiles (*e.g.* BH_4^- or OH^-) attack at C-2, but soft ones react at C-4. However, there are many exceptions to this, perhaps because of the many other factors involved.

Often the desired product is not the pyridine formed, but the other fragment, *e.g.* an aldehyde or alkene (Type **A**), aldehydes, carboxylic acids or alcohols (Type **B**), RCH_2X (Type **C**), unsaturated aldehydes and their derivatives (Type **D**). Pyridine is being used in these reactions as a reagent which is recoverable ⟨80T679⟩. Synthetic approaches of this type have not only stimulated many ingenious applications of the current knowledge of pyridine chemistry, but also extended it. Appropriate examples will be highlighted in the following sections, which are divided up according to the nature of the element that attacks the pyridine ring.

2.05.4.2 Halides: Formation of a Carbon–Halogen Bond

The chloride ion is a very weak nucleophile, and no reaction is observed with uncharged pyridines, or with pyridine 1-oxides unless they are coordinated at oxygen. Chlorination of *N*-oxides may be carried out fairly easily by treatment with phosphorus oxychloride (at 40 °C to reflux for 0.5 to 5 h) or sulfuryl chloride (at 110 °C for 2 h) (Table 11). In the first



(101)

Scheme 54

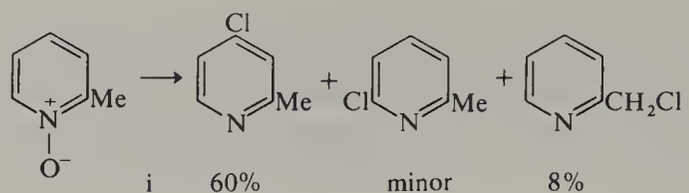
step, the reagent reacts with the *N*-oxide oxygen to form (**101**) and a chloride ion is displaced. This adds to (**101**) at C-2 (inter- or intra-molecularly) and/or C-4 (inter-molecularly) to initiate the Type **B** pathway (Scheme 54). Chlorination of pyridine 1-oxide with PCl_5 gives more 4-substitution than 2, but use of phosphorus oxychloride yields mainly 2-chloropyridine. This with other results (Table 11) suggests that the contribution of the intramolecular mechanism is greater with the latter reagent.

Table 11 Chlorination of *N*-Oxides with Inorganic Chlorides[a]

		Yield of products (%)		
Substituent	*Reagent*	2-*Cl*	4- *or* 6-*Cl*	*Others*
Pyridine 1-oxide	$POCl_3$	43	4-, 20	—
	PCl_5	4.5	4-, 4	—
	$POCl_3$–PCl_5	5	4-, 3	—
	SO_2Cl_2	major	4-, minor	—
2-Me	$POCl_3$	—	4-, 60 6-, minor	2-CH_2Cl, 8
2-Ph	$POCl_3$	—	4-, 5–43 6-, 24–35	—
2-Cl	$POCl_3$	—	6-, 91	—
3-Me	$POCl_3$	29.5	4-, 42.5 6-, 24.5	—
	PCl_5	8.5	4-, 15.5 6-, 6	—
	$POCl_3$–PCl_5	16	4-, 23 6-, 12	—
3-Cl	$POCl_3$	37	6-, 14	—
3-Br	SO_2Cl_2	minor	4-, major 6-, minimus	—
3-$CONH_2$	$POCl_3$–PCl_5	52	—	—
3-CO_2H	$POCl_3$–PCl_5	41	5	—
3-NO_2	$POCl_3$	30	6-, 8	—
3-CH_2CN	$POCl_3$	27	6-, 14	—
4-Me	$POCl_3$	34	—	—
	$POCl_3$–PCl_5	7.5	—	—
4-Cl	SO_2Cl_2	20–30	—	—
4-$CONH_2$	$POCl_3$–PCl_5	—	—	2-Cl-4-CN, 50–60
4-CN	$POCl_3$–PCl_5	—	—	3-Cl-4-CN, 73
4-NO_2	SO_2Cl_2	—	—	2,4-Cl_2, 35–40
2,6-Me_2	$POCl_3$	—	4-, 60–70	6-Me-2-CH_2Cl, 1–2
3,4-Cl_2	SO_2Cl_2	50–60	6-, minor	—
3,5-Br_2	SO_2Cl_2	60	4-, 40	—
3,5-$(OEt)_2$	SO_2Cl_2	—	—	2,6-Cl_2-3,5-$(OEt)_2$, 15–20
Quinoline 1-oxide	SO_2Cl_2	2-, 1	4-, 1.7 6-, major	—
2-Ph	$POCl_3$	—	4-, 5–43	—
4-NO_2	$POCl_3$	—	—	4-Cl-$\overset{+}{N}$—O^-, 98
5-NO_2	$POCl_3$	35	4-, 10	3-Cl-5-NO_2, 20
6-NO_2	$POCl_3$	16	4-, 56	3-Cl-6-NO_2, 3.5
3-Br	$POCl_3$	major	—	—
2-OH	$POCl_3$	—	—	2,4-Cl_2, major
Isoquinoline 1-oxide	$POCl_3$	—	—	1-Cl, 62
1-OH	$POCl_3$	—	—	1,4-Cl_2, 43
5-NO_2	$POCl_3$	—	—	1-Cl-5-NO_2, 77

[a] For a more complete compilation of data see ⟨B-67MI120501, B-71MI120500, 74HC(14-S2)1⟩.

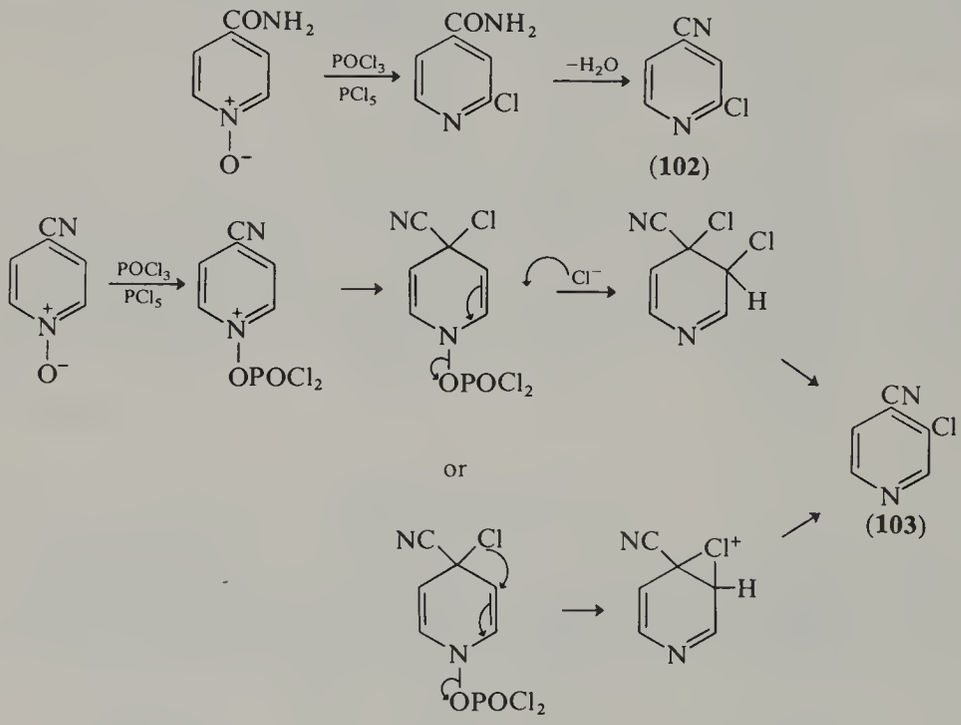
It is hard to draw firm conclusions from the results in Table 11 regarding orienting effects of substituents, as they have been obtained under such different conditions. However, it does appear that pyridine 1-oxides which bear electron donating or withdrawing 3-substituents undergo chlorination preferentially at C-2. Nitro groups at position 4 in pyridine and quinoline 1-oxides are replaced by chloro groups on reaction with phosphorus oxychloride. Chlorination at methyl substituents, *via* an anhydro base, competes with ring substitution (Scheme 55).



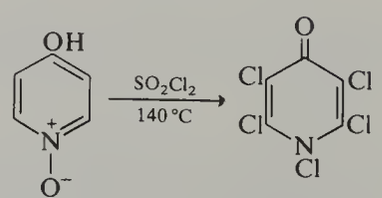
i, $POCl_3$; ii, $POCl_3$, CH_2Cl_2; iii, TEA

Scheme 55

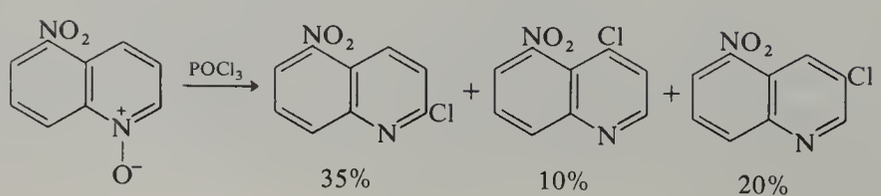
Lately, a method has appeared that describes how to achieve exclusive substituent chlorination (Scheme 56) ⟨81JHC939⟩. Treatment of 4-carboxamidopyridine 1-oxide with a mixture of phosphorus oxychloride–phosphorus pentachloride yields 2-chloroisonicotinonitrile (**102**) (equation 75). Contrary to what one might expect, similar treatment of isonicotinonitrile 1-oxide affords the 3-chloro product (**103**), rather than (**102**). Two possible pathways are suggested for this reaction (Scheme 56) ⟨78JHC683⟩. Polychlorination has been observed when sulfuryl chloride is used, especially at higher temperatures (equation 76). Chlorination of *N*-oxides in the quinoline series, like the pyridines, usually leads to α- or γ-substitution, but odd orientations are more common. Some nitroquinoline 1-oxides undergo 3-chlorination (equations 77 and 78) ⟨44JOC302⟩, and 2,4-dibromoquinoline 1-oxide is chlorinated chiefly at C-6 (equation 79) ⟨57MI20500⟩. Isoquinoline 2-oxides readily give 1-chloroisoquinolines in good yield. Acridine *N*-oxide forms 9-chloroacridine (**104**) on treatment with phosphorus pentachloride. Phenanthridine 5-oxide is chlorinated at position 6, but 6-phenylphenanthridine 5-oxide gives a 2-chloro derivative (**105**). Bromination of *N*-oxides with inorganic acid bromides has been much less well studied, but it appears to follow the same course as chlorination (equation 80).



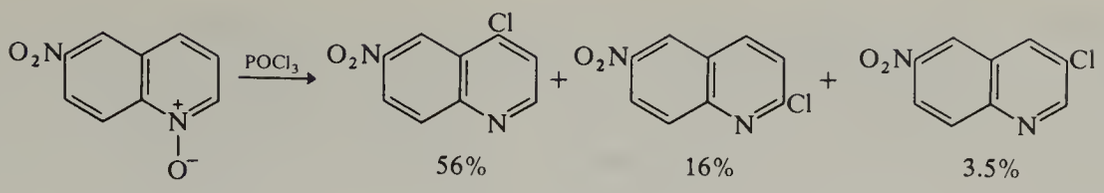
Scheme 56



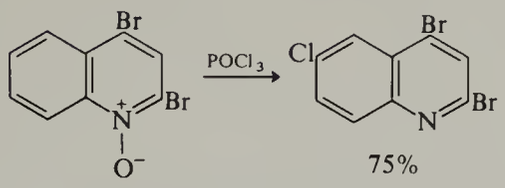
(76)



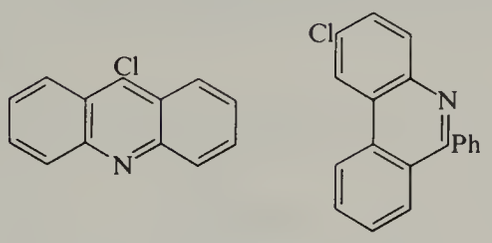
(77)



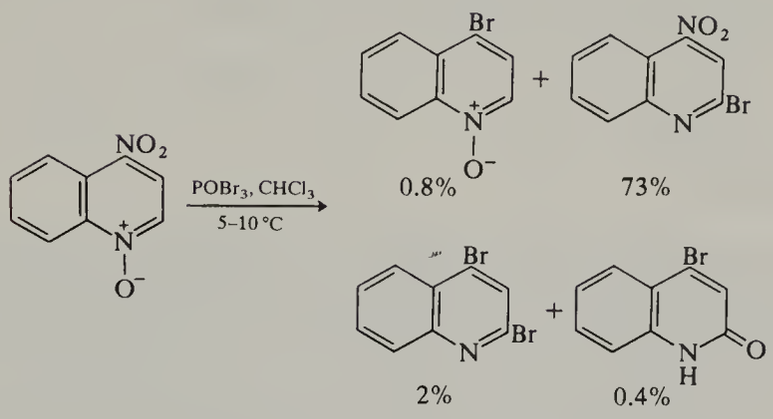
(78)



(79)

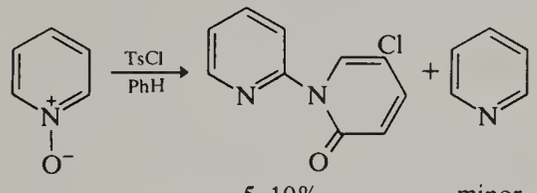


(104) **(105)**

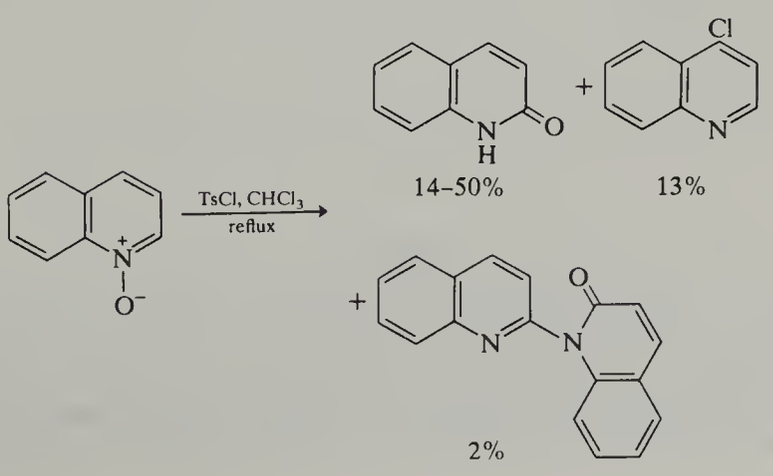


(80)

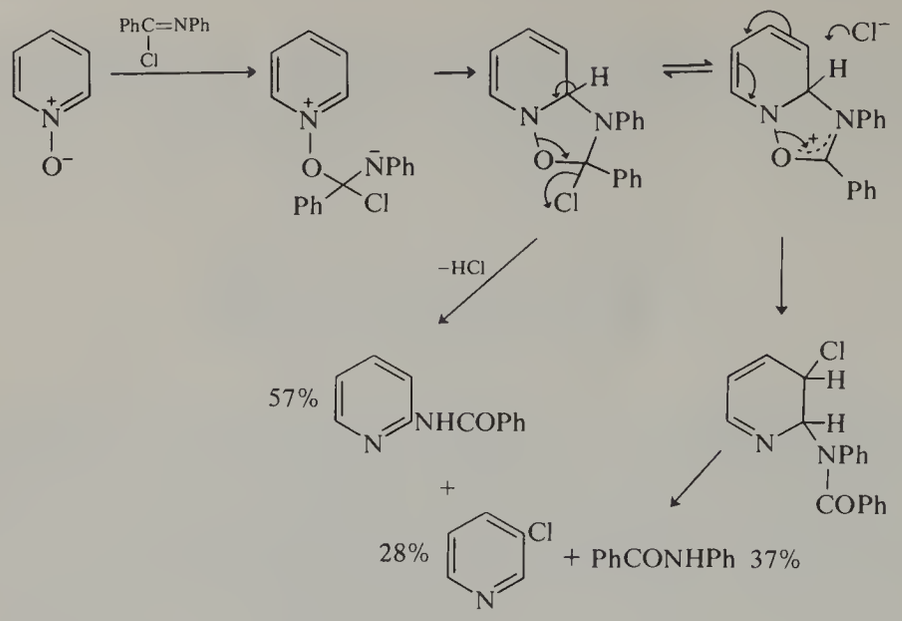
Discussion so far has concentrated on inorganic acid halides, because use of organic acid halides usually gives other products (see Section 2.05.4.3). Chlorination in low yield can be attained using tosyl chloride (equations 81 ⟨56RTC1303⟩ and 82 ⟨B-67MI20501⟩). A much better nucleophile (*e.g.* added cyanide) is required to observe ring substitution with these reagents (see Section 2.05.4.7). In keeping with this, *N*-alkoxy quaternary salts do not react with chloride ion; the stronger nucleophile cyanide is needed for a Feely–Beavers–Tani reaction (see Section 2.05.4.7). Chlorination at C-3 is, however, a significant side reaction



(81)



(82)



Scheme 57

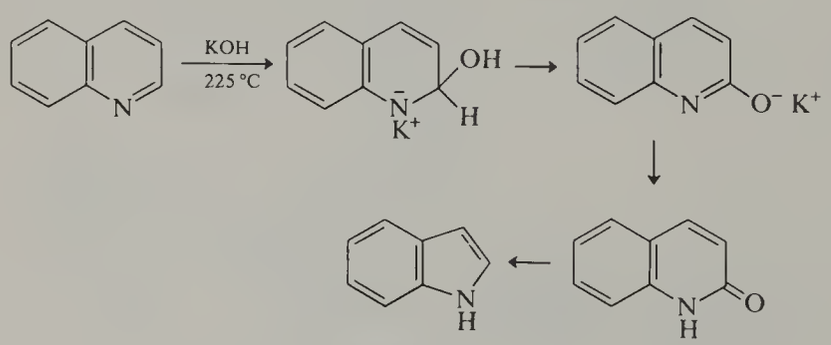
in the acylamination of pyridine 1-oxide with *N*-phenylbenzimidoyl chloride, but a special mechanism is operative in this case (Scheme 57) ⟨74JOC1795⟩.

2.05.4.3 Oxygen Nucleophiles

2.05.4.3.1 Hydroxide

Pyridine and its congeners undergo reaction with hydroxide ions by paths **A** (Chapter 2.06), **B**, **C** (Chapter 2.06), **D** and **E** (Section 2.05.5). The most important types of reaction with hydroxide are **B** and **D**; these will be described here considering Type **B** reactions first.

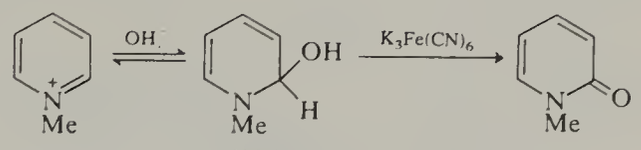
Uncharged pyridines are resistant to attack by hydroxide at temperatures up to 100 °C, but pyridine itself reacts with KOH on fusion in air at *ca.* 300 °C to give pyridin-2-one. Predictably, this reaction is easier for pyridines bearing electron withdrawing substituents or with annelated benzene rings. Production of quinolin-2-one from quinoline and absolutely dry potassium hydroxide requires a lower temperature (225 °C) than the corresponding reaction with pyridine (Scheme 58). The main product is accompanied by some indole, and hydrogen (equal to the amount of quinoline charged) is evolved, which suggests a mechanism similar to that of the Chichibabin reaction (see Section 2.05.4.5). This conversion also may be achieved, in lower yield, using barium oxide. Quinoline forms quinolin-2-one on treatment with hypochlorous acid or hypochlorites. Attack by Cl^+ at nitrogen and subsequent nucleophilic attack at C-2 has been postulated to explain this result ⟨77HC(32-1)319⟩. Isoquinoline is hydroxylated at C-1 by fusion with potassium hydroxide at 220 °C. When C-1 is blocked, no hydroxylation is observed at C-3.



Scheme 58

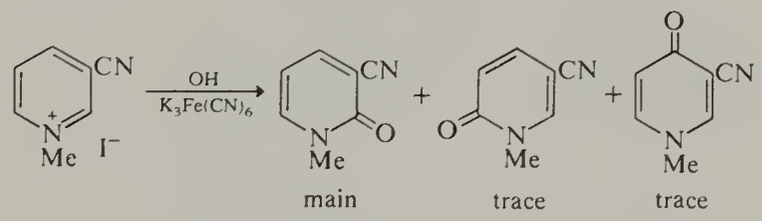
Alkaline solutions of alkylpyridinium salts contain increasing amounts of pseudobases (**106**; equation 83) in equilibrium with the charged form as the series 1-methylquinolinium, 2-methylisoquinolinium, 10-methylphenanthridinium and 10-methylacridinium is traversed. Such species were first postulated as a result of the observation that alkaline solutions of quaternary salts do not obey the Beer–Lambert law. Pseudobase formation at

the α-position is favoured in all the above systems except the last. Several courses for further reaction are open to these intermediates, namely oxidation, disproportionation, dimerization and ring opening. The last of these often competes with the others, especially if the *N*-substituent is strongly electron-withdrawing. This will be discussed under path **D** behaviour. Methylpyridinium ions can be oxidized with potassium ferricyanide in alkaline solution to give pyridin-2-ones (equation 83). *N*-Substituted quinolin-2-ones, isoquinolin-1-ones, phenanthridin-6-ones (α-substitution) and acridin-9-one (γ-substitution) may be obtained similarly from the appropriate quaternary salts. Pyridin-4-one formation by this method has been recorded in only one instance (equation 84). The effect of substituents on this reaction in the pyridine series has been examined qualitatively ⟨66NKK884⟩. A 3-cyano group is activating (C-2 directing), 3-methoxycarbonyl deactivating (C-6 directing), and 3-methyl is activating (rather surprisingly) and C-2 directing. The mechanism of this oxidation is complicated, but it does involve rate determining ferricyanide complex formation (Scheme 59) ⟨71JCS(B)131⟩.

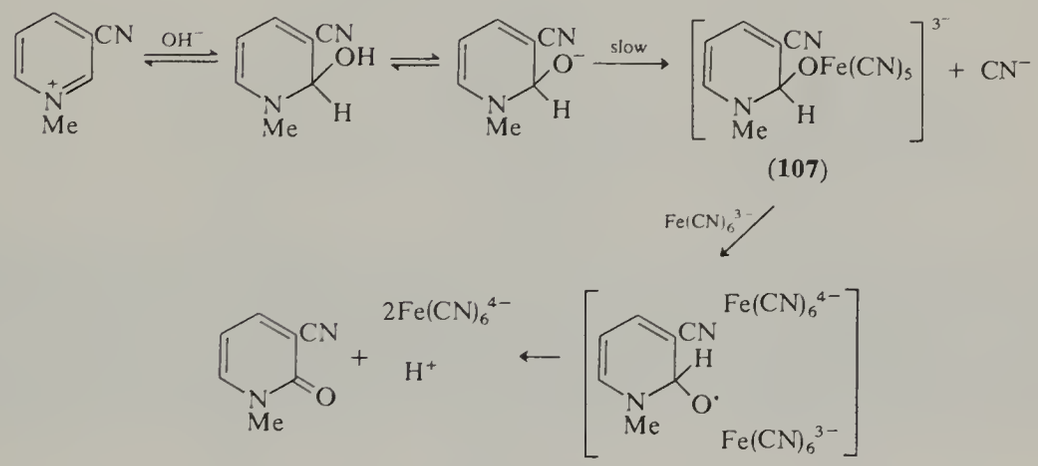


(83)

(**106**)



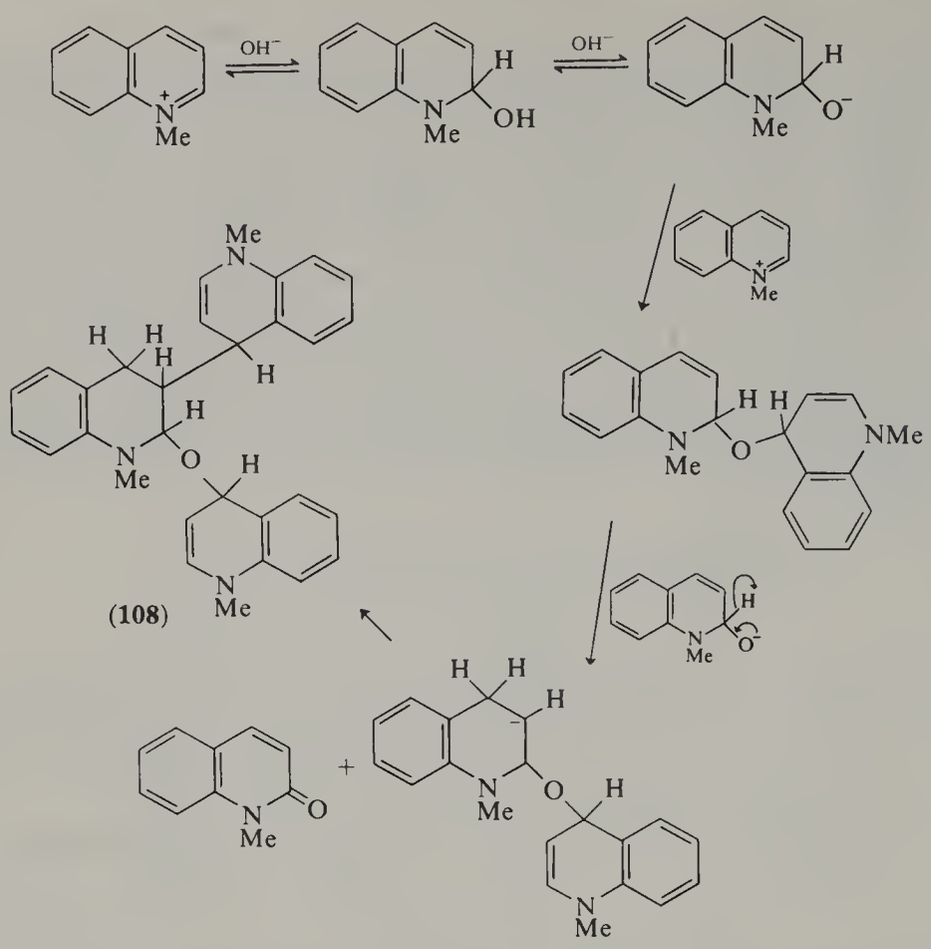
(84)



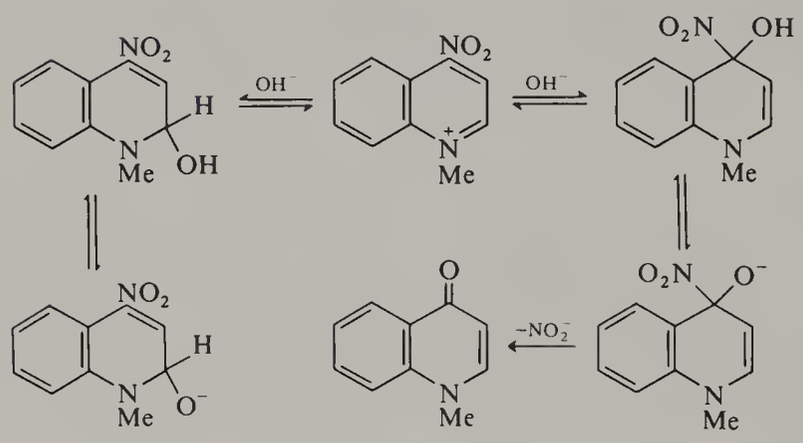
Scheme 59

1-Methylnicotinamide pseudobase is readily oxidized to the corresponding pyridin-6-one by the quinine-oxidizing enzyme of rabbit liver ⟨48JA2172⟩. The pseudobase derived from 1-methylquinolinium has been studied quite extensively ⟨77H(6)475⟩. Two products are isolated when the salt is treated with alkali, 1-methylquinolin-2-one and (**108**), which probably arises as shown (Scheme 60). A 4-nitro substituent changes the pattern of reactivity, and attack at C-2 and C-4 is now possible (Scheme 61). The UV spectrum indicates that the 2-methylisoquinolinium ion does not form a pseudobase in aqueous solution below pH 14. Attack at C-1 occurs at higher pH. However, the 4-nitro derivative undergoes addition of hydroxide at much lower pH. Great interest in the isoquinolinium system stems from its occurrence in many alkaloids, some of which have potent antitumor activity ⟨B-78MI20501⟩.

An example of disproportionation to (**109**) and (**110**) is provided by the behaviour of the berberinium ion in alkaline solution (Scheme 62). The pseudobase of the 5-methylphenanthridinium cation is present even in neutral solution (equation 85). Attack at position 9 in acridinium salts is also very easy, and they rearrange to pseudobases in a few minutes in alkaline solution. These pseudobases, unlike the others described, do not undergo ring opening. They readily disproportionate or are oxidized to acridin-9-ones by air when the starting salt is unsubstituted at C-9 ⟨B-78MI20502⟩. Pyridine 1-oxides and their analogues

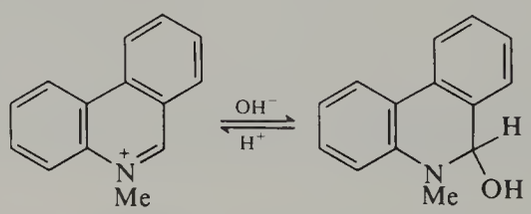


Scheme 60

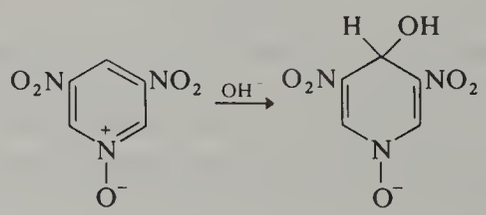


Scheme 61

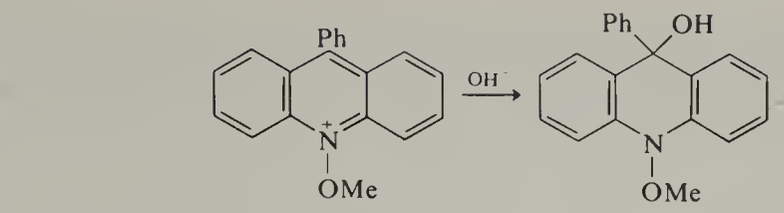
are not usually attacked by water or hydroxide ions, but strong electron withdrawing 3- and 5-substituents allow Meisenheimer complex formation (equation 86). Quaternary salts of *N*-oxides normally react with hydroxide by path **D**, but certain quaternary acridine *N*-oxide derivatives do form stable pseudobases (equation 87).



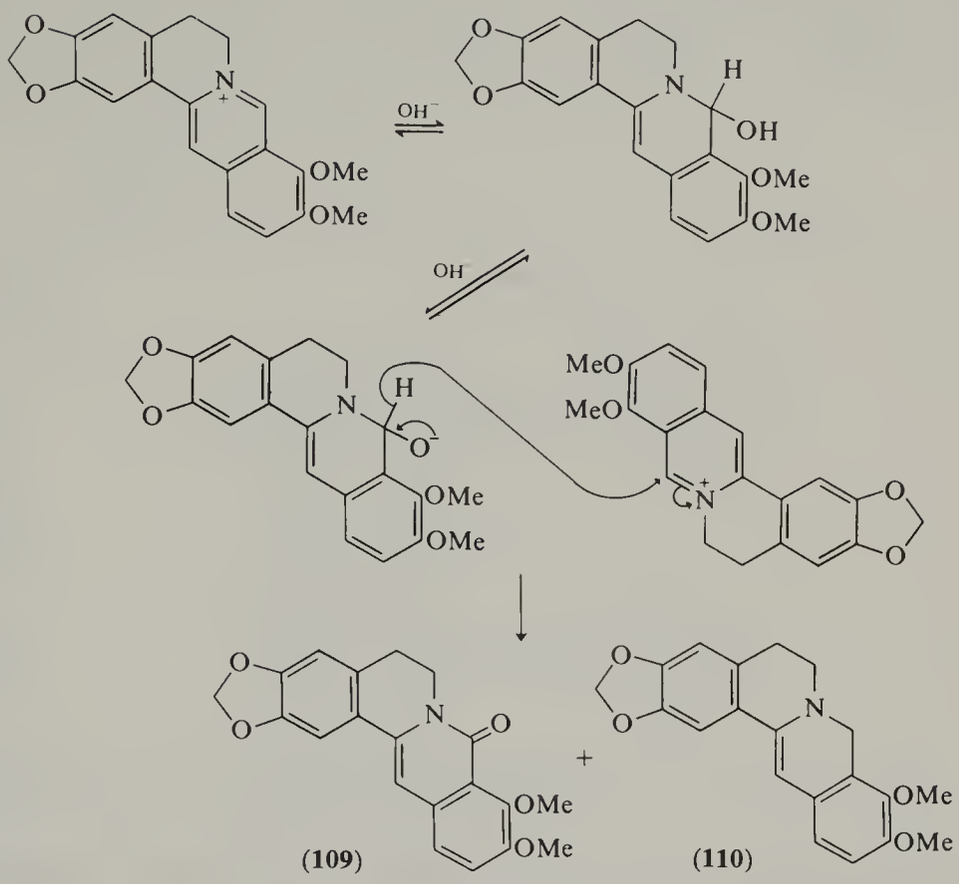
(85)



(86)

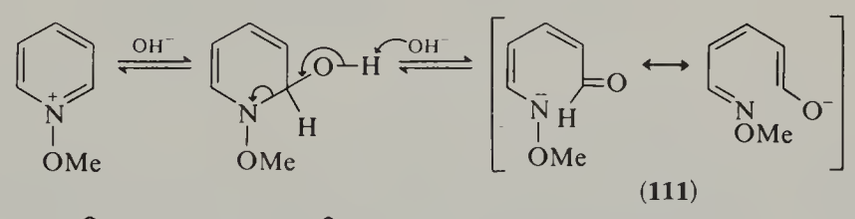


(87)



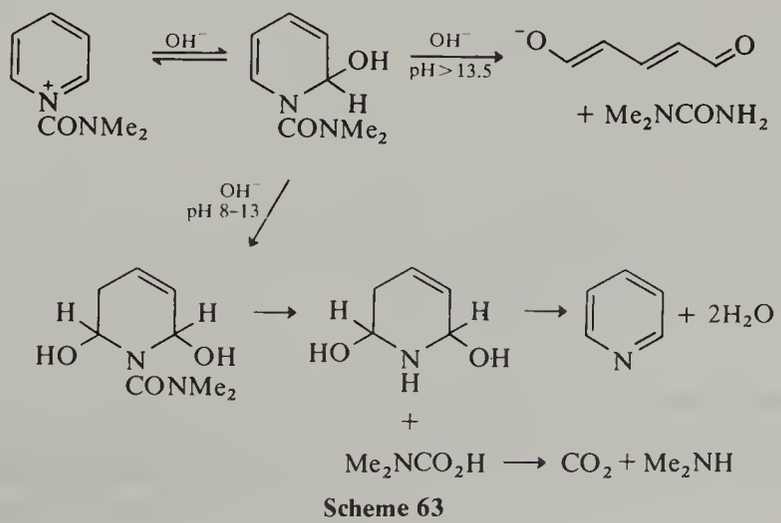
Scheme 62

Path **D** behaviour is favoured when the *N*-substituent is electron withdrawing, for example 1-methoxypyridinium yields the glutacondialdehyde derivative (**111**) in alkali (equation 88). The reaction of a 1-dimethylcarbamoylpyridinium salt in alkaline solution is pH dependent and two courses are followed (Scheme 63). The kinetics of both are first order in quaternary salt and second order in hydroxide ion. Treatment of 1-methylnicotinonitrile



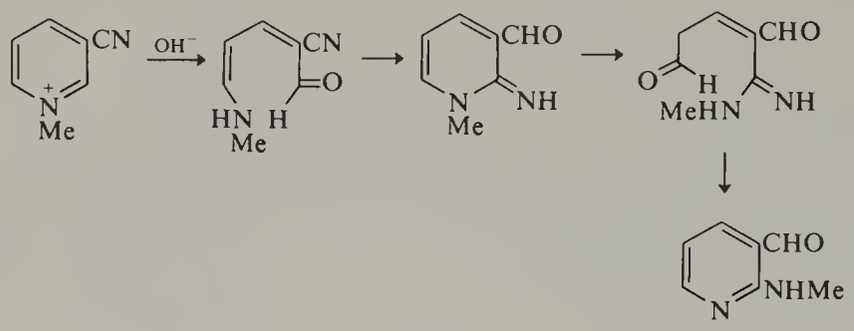
(88)

(**111**)

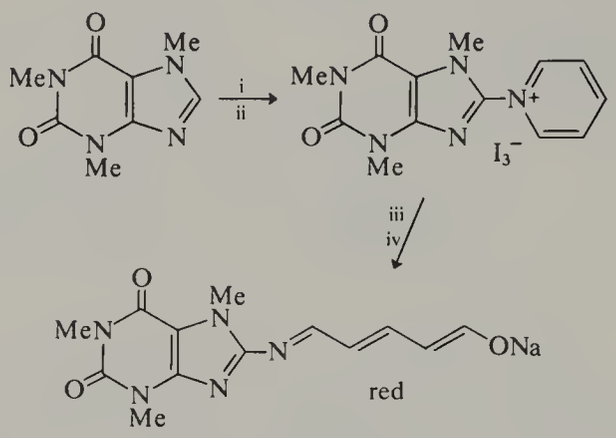


Scheme 63

with dilute hydroxide gives ring opening followed by ring closure to the 3-substituent (Scheme 64). Ring-opened products are often highly coloured and this fact has been put to use for the colorimetric determination of caffeine by the hypochlorous acid–pyridine method (Scheme 65) ⟨76H(4)1257⟩.



Scheme 64

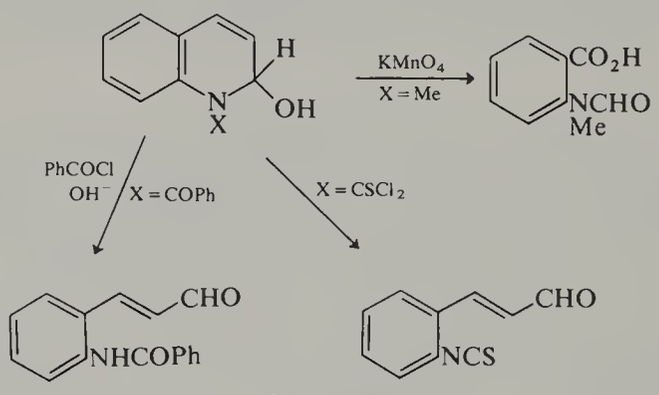


i, pyridine, NaOCl, aq. AcOH, pH 5.36–5.71, 0–3 °C; ii, I_2; iii, Na_2SO_3; iv, NaOH

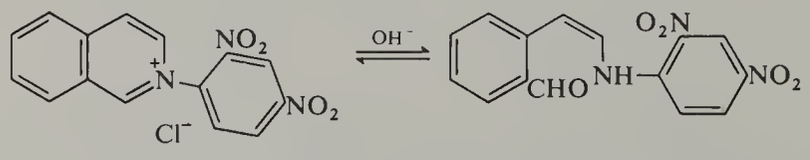
Scheme 65

A recent review entitled 'Pyridine Ring Nucleophilic Recyclizations' ⟨81T3423⟩ gives a comprehensive treatment of Type **D** behaviour.

Oxidation of 1-methylquinolinium salts with potassium permanganate results in ring fission, as does reaction with benzoyl chloride and alkali, or thiophosgene (Scheme 66). An electron withdrawing *N*-substituent is usually necessary for ring opening of an isoquinoline ring (equation 89), but acridinium ions do not appear to give this reaction.



Scheme 66



(89)

2.05.4.3.2 Acetate–acetic anhydride reaction

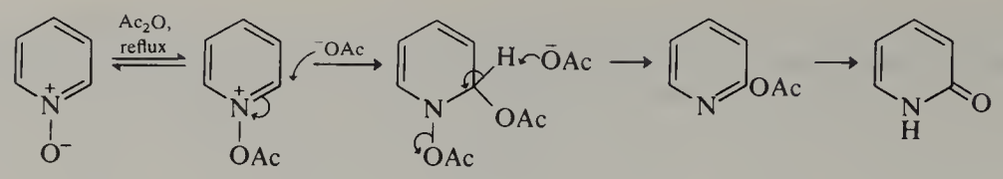
The acetate ion is too weak a nucleophile to attack pyridines, pyridinium salts or their analogues at a ring carbon. *N*-Oxides require coordination at oxygen before they can react.

Acetic anhydride has been found to be the reagent of choice for introducing oxygen functionality directly into pyridines. Some examples of the products obtained from the reactions of *N*-oxides with acetic anhydride are given in Table 12, but more complete surveys are available ⟨B-67MI20501, B-71MI20500, 74HC(14-S2)1, 77H(6)583⟩. These reactions are usually carried out by heating the *N*-oxide under reflux with excess acetic anhydride for *ca.* 1–5 h. Benzoic anhydride behaves similarly, but trifluoroacetic anhydride is considerably more reactive. For example, treatment of 2- or 4-cyanoquinoline 1-oxides with trifluoroacetic anhydride yields the respective 4- or 2-cyanoquinolones; acetic anhydride fails to effect this conversion ⟨58HCA2148⟩. α-Substitution usually predominates for pyridine 1-oxide, with few exceptions (see equation 94). Again in cases of 3-substituted *N*-oxides, attack at C-2 is favoured over that at C-6.

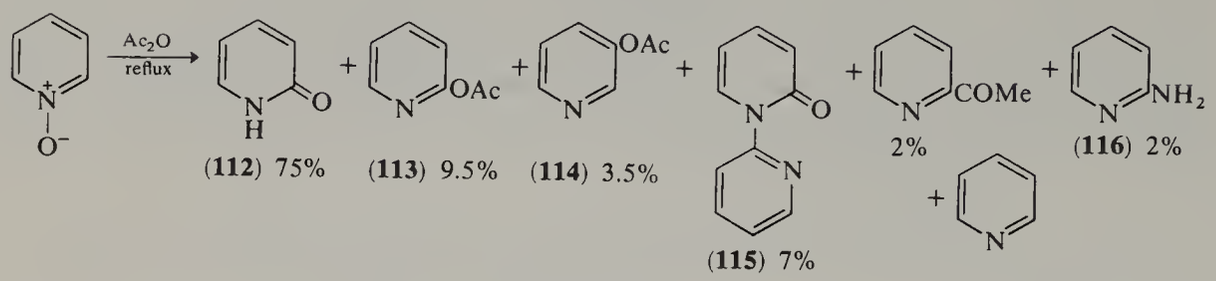
Table 12 Products of the Reaction of *N*-Oxides with Acetic Anhydride

System *Substituent*	*Products (yield %)*
Pyridine 1-oxide	
None	see Scheme 68
2-Me	3-OAc (66), 5-OAc (16), 2-CH_2OAc (18)
2-OMe	2-OMe-6-oxo (34)
2-OEt	1-OH-2-oxo (61)
2-OPh	1-OH-2-oxo (84)
2-CO_2H	2-CO_2H 1-oxide (60), 2-OAc (18)
2-CO_2Me	6-CO_2Me-2-oxo (34)
2-Cl	1-OH-2-oxo (71)
3-Me	see equation (93)
3-CO_2H	2-OAc-3-CO_2H-1-oxo (30), 5-CO_2H-2-oxo (3), 3-CO_2H-2-oxo (18)
3-CO_2Me	3-CO_2Me-2-oxo (28), 5-CO_2Me-2-oxo (16)
3-NO_2	3-NO_2-2-oxo (50)
3-Cl	3-Cl-2-OAc (61)
4-Me	see equation (95)
4-CO_2H	4-CO_2H (22), 4-CO_2H-2-oxo (7)
4-CO_2Me	4-CO_2Me-2-oxo (56)
4-OMe	4-OMe-2-oxo (56)
Quinoline 1-oxide	
None	2-oxo (20–35)
x-Br; *x* = 3, 4, 5, 6 or 7	*x*-Br-2-oxo (*ca.* 70)
6-NO_2	6-NO_2-2-oxo (45)
Isoquinoline 2-oxide	
None	1-oxo (53), 4-OH (9)
3-Cl	3-Cl-4-oxo (61), 3-Cl-1-oxo (1)
3-Me	1-oxo (40)
Acridine 10-oxide	
None	9-oxo (86)
Phenanthridine 5-oxide	
None	6-oxo (70)

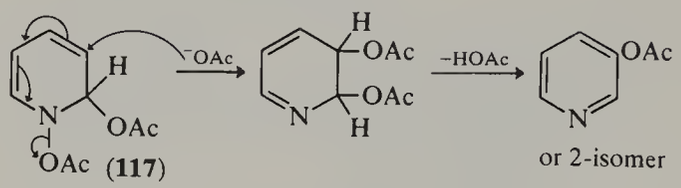
The gross mechanism of formation of pyridin-2-one from pyridine 1-oxide is outlined (Scheme 67). This involves initial attack of the anhydride by the *N*-oxide, addition of acetate at C-2 (rate determining), and formation of 2-acetoxypyridine which can be hydrolyzed readily. However, a careful analysis of the product mixture from this reaction revealed the presence of six minor products (Scheme 68) ⟨74HC(14-S1)1⟩. The mechanism by which (**112**) and (**113**) arise has just been discussed. However, the modes of formation of (**114**), (**115**) and (**116**) are worth mentioning in a little detail as they are often major pathways in related reactions (*vide infra*). 3-Acetoxypyridine (**114**) might derive from a 1,5-sigmatropic shift of the *N*-acetoxy group in (**117**), or by addition of acetate to (**117**; equation 90). Alternatively, intramolecular rearrangement of the 2-acetoxy group to C-3 *via* the cyclic intermediate (**118**) is possible (equation 91). Formation of (**115**) is believed to occur as a result of attack by unreacted pyridine 1-oxide on the *N*-acetoxypyridinium salt with subsequent rearrangement (Scheme 69). This salt may also be trapped by anisole (equation 92) ⟨72JOC55⟩; for a striking analogy see equation (55). Compound (**116**) is a hydrolysis product of (**115**). 3-Methylpyridine 1-oxide behaves very much like the parent system in this reaction (equation 93).



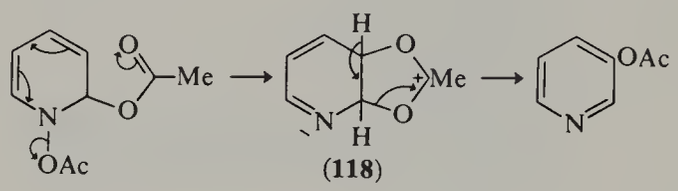
Scheme 67



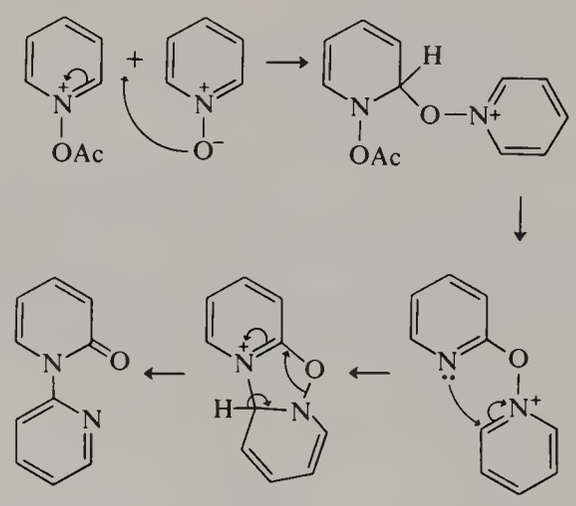
Scheme 68



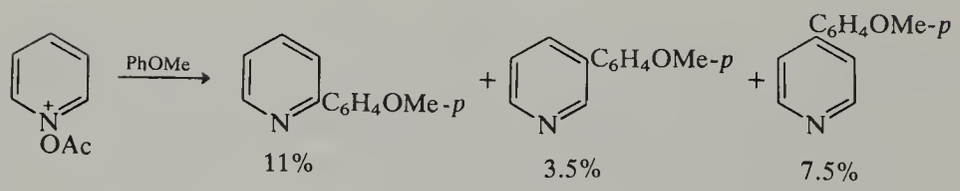
(90)



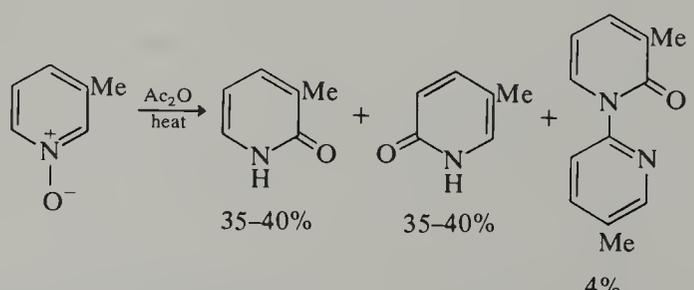
(91)



Scheme 69

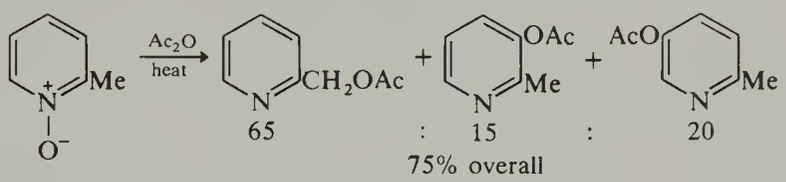


(92)

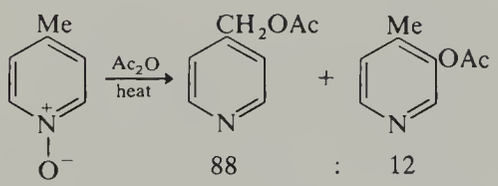


The reaction of acetic anhydride with 2- and 4-methylpyridine 1-oxides has been the testing ground for the mechanism of reactions of this type. These two methylpyridine 1-oxides, unlike the 3-isomer, yield mainly 2- (or 4-) acyloxymethylpyridines. Equations

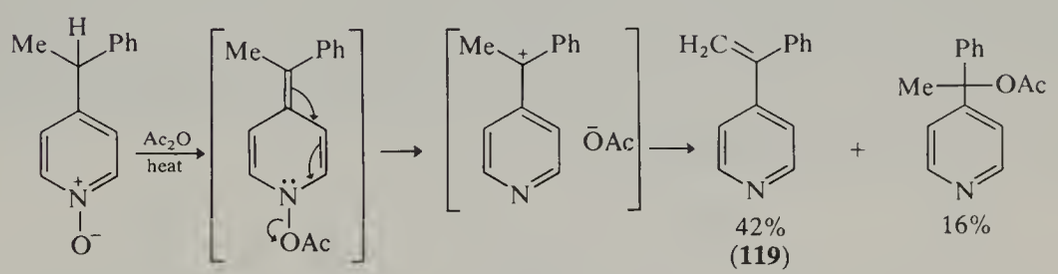
(94) and (95) illustrate typical examples. Rearrangement on to the methyl groups and substitution at the β-position involves an anhydrobase, which cannot form with the 3-isomer. The mechanism of the rearrangement may involve an ion or radical pair intermediate (Scheme 70). Isolation of (**119**) suggests carbenium ion involvement in this case ⟨74JA7289⟩, but see Chapter 2.06 for a full discussion. Quinoline and isoquinoline *N*-oxides undergo mainly α-substitution, although other products (**120**), (**121**) and (**122**) are encountered. Formation of (**120**) has an analogy (Scheme 69); (**121**) is formed because the 4-cyano group activates the 3-position to nucleophilic attack. 4-Hydroxyisoquinoline is derived from isoquinoline *N*-oxide (Scheme 71) on reaction with acetic anhydride. Acridine 10-oxide affords acrid-9-one by a complex mechanism. Labelling studies with ^{18}O indicate two distinct paths for the intramolecular rearrangement step which are described as sliding (**123**) and cyclic (**124**) ⟨66T3143⟩. Examples of the use of acetic anhydride to promote attack by other nucleophiles on *N*-oxides will be encountered later.



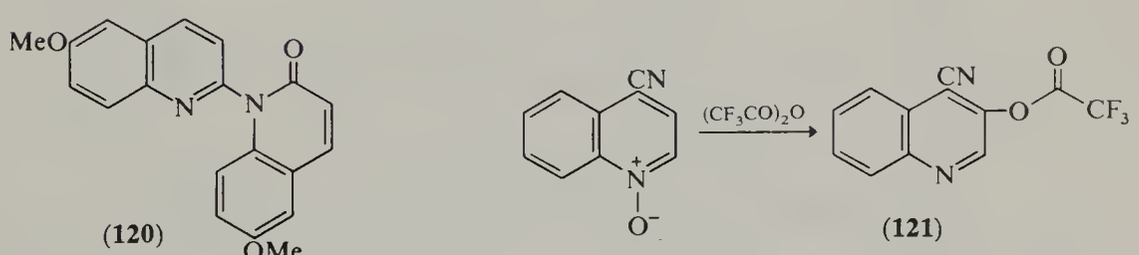
(94)

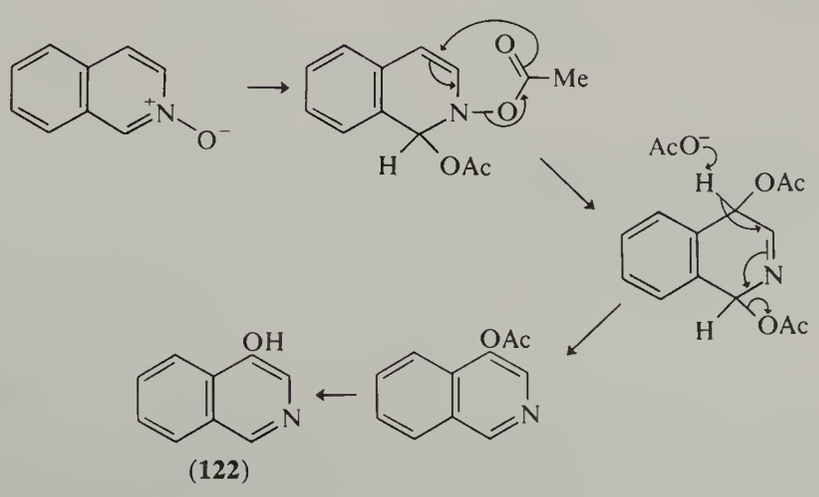


(95)

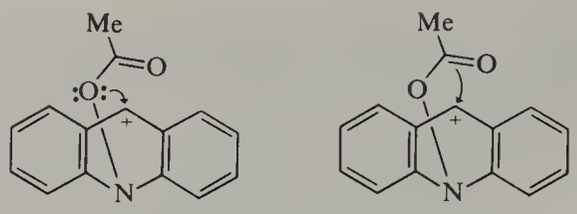


Scheme 70





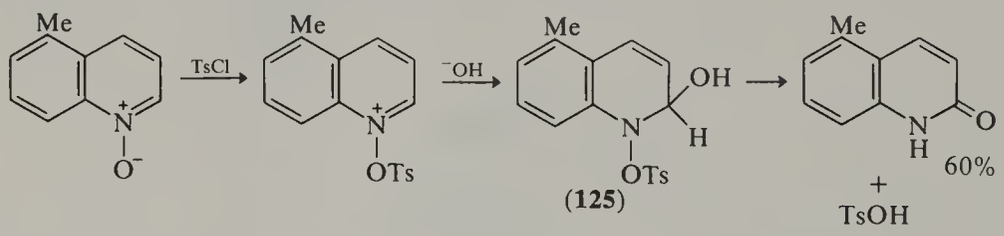
Scheme 71



(123) (124)

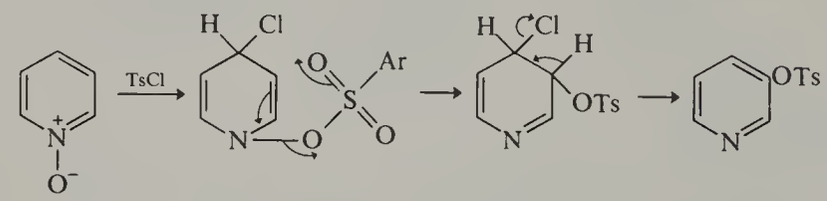
2.05.4.3.3 Arenesulfonyl chlorides

N-Oxides react with sulfonyl chlorides in the presence of aqueous base to give α-oxo products. Quite a different course is followed in the absence of base, where β-sulfonyloxy-, α- or γ-chloro- (Section 2.05.4.2) or pyridyl-pyridinones (Section 2.05.5.4.5) are formed. The first reaction provides a useful method for introducing an oxo substituent into the 2-position of the quinoline ring (Scheme 72), but it fails in the pyridine series. In this particular example the intermediate (**125**) can be isolated ⟨61MI20500⟩. 3-Tosyloxypyridine is formed in low yield when pyridine 1-oxide is heated with tosyl chloride. An intimate ion pair mechanism has been suggested to explain this conversion (equation 96) ⟨77H(6)583⟩. By contrast, 2-methylpyridine 1-oxide reacts with tosyl chloride to furnish 2-chloromethylpyridine in good yield. Treatment of quinoline 1-oxide with tosyl chloride at 200 °C does not yield the β-sulfonyloxy derivative; four other products are obtained, namely quinolin-2-one, 2,2′-diquinolyl ether, 4-chloroquinoline and 1-(2-quinolyl)quinolin-2-one ⟨B-71MI20500⟩. However, the sulfonyloxy group may be introduced into the β-position of 2,4-diphenyl- and 4-styryl-quinoline 1-oxide using tosyl chloride. The quinoline 1-oxide–boron trifluoride complex does give 3-tosyloxyquinoline, among other products, on heating with *p*-toluenesulfonyl chloride (equation 97). 2-Aminoquinoline 1-oxide and 1-hydroxyquinolin-2-one are substituted in the benzene ring, the former at C-6 to yield (**126**), while the latter affords (**127**) by reaction at C-8. Isoquinoline 2-oxide behaves similarly to form 4-tosyloxyisoquinoline in good yield (75%) and a little isoquinolone (10%). Isotopic labelling and other studies indicate that this rearrangement proceeds intramolecularly *via* a tight ion pair (Scheme 73) ⟨77H(6)583⟩.

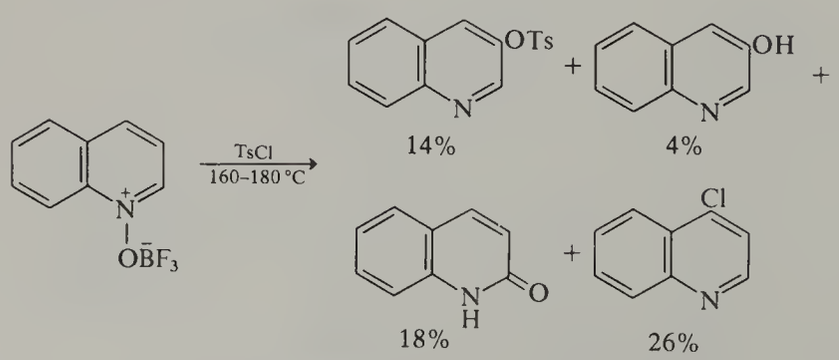


(125)

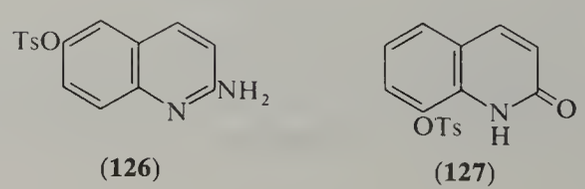
Scheme 72



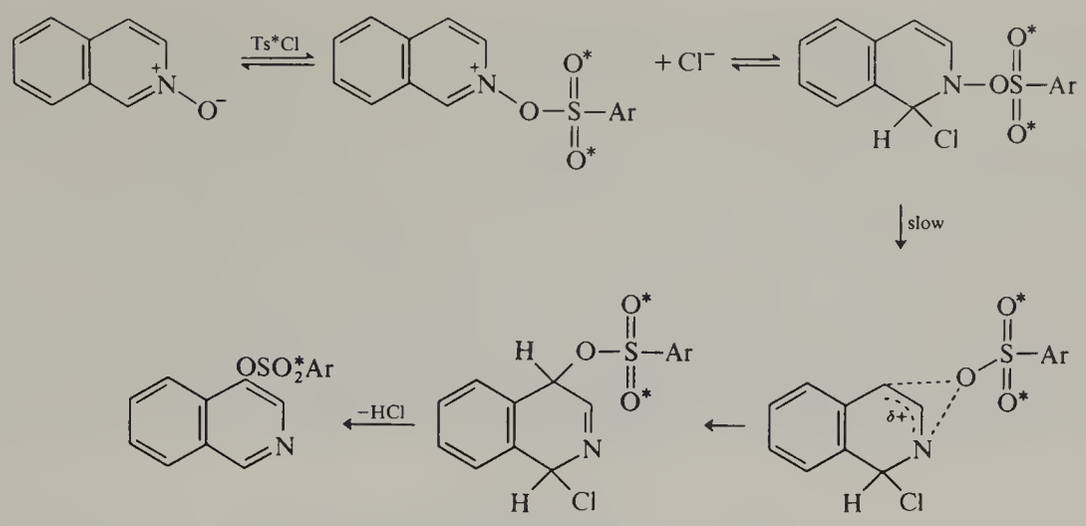
(96)



(97)



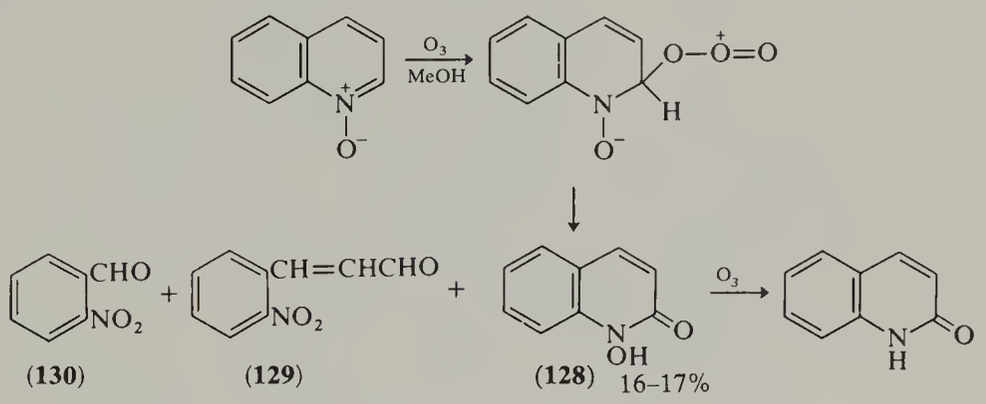
(126) (127)



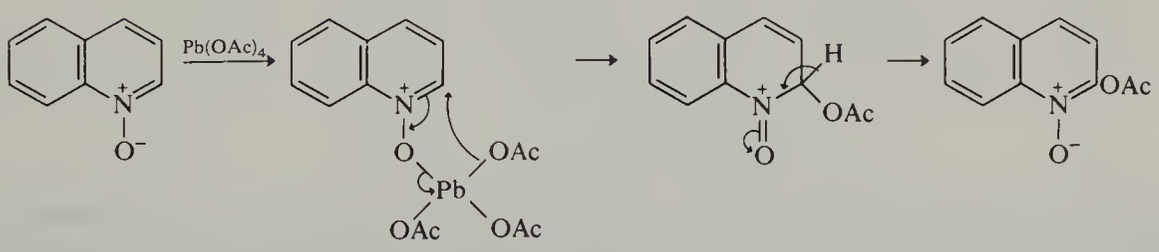
Scheme 73

2.05.4.3.4 Other nucleophiles

Quinoline 1-oxide undergoes nucleophilic attack by ozone to yield a hydroxamic acid (**128**), and 40% of the starting *N*-oxide is recovered (Scheme 74). When an excess of ozone is employed the aldehydes (**129**) and (**130**) are obtained. Formation of these products has been attributed to electrophilic attack by ozone rather than further oxidation of (**128**), because in a separate experiment (**128**) yielded carbostyril on treatment with ozone. Isoquinoline 2-oxide yields 2-hydroxyisoquinolin-1-one, and acridine 10-oxide gives 10-hydroxyacridone and acridone in a similar manner to the above. Likewise, phenanthridine 5-oxide affords mainly 5-hydroxyphenanthridone. Quinoline 1-oxide undergoes oxidation by lead tetraacetate as shown (Scheme 75).



Scheme 74



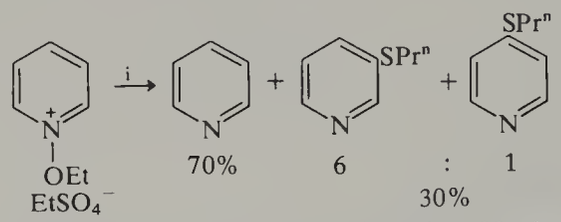
Scheme 75

2.05.4.4 Sulfur Nucleophiles

2.05.4.4.1 Thiols

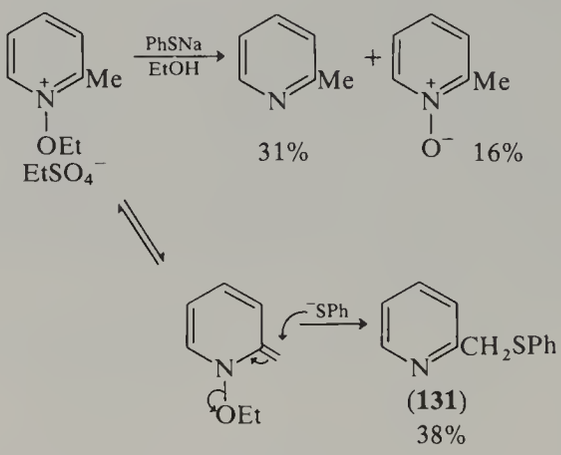
Aliphatic and aromatic thiols react with pyridine 1-oxides and their quaternary derivatives by Type **A**, **B** and/or **C** pathways, but no such reactions have been reported for pyridine or its salts. 1-Ethoxypyridinium ethosulfate reacts with sodium *n*-propanethiolate to give mainly pyridine (Type **A**), and a 6:1 mixture of 3- and 4-pyridyl propyl sulfides (equation

98) ⟨63JOC1320⟩. Introduction of a methyl group at C-2 or C-4 in the starting salt, and variation of the nature of the *O*-alkyl group and the thiol, were employed to demonstrate the main factors that determine the type of pathway followed ⟨63JOC1323⟩. No ring substitution was detected when the ethoxy quaternary salt of 2-methylpyridine was treated with sodium thiophenoxide (Scheme 76). The products are 2-methylpyridine (by Type **A**), its *N*-oxide (Type **C**) and (**131**), which derives from attack on the anhydrobase. In the case of the 1-methoxy-4-methylpyridinium salt, reaction with sodium thiophenoxide results in very little C—S bond formation; the Type **A** and **C** pathways predominate. However, the corresponding 1-ethoxy salt gives mainly the 4-phenylthiomethyl derivative on reaction with an excess of sodium thiophenoxide (equation 99). Thioalkylation of 1-ethoxy-4-methylpyridinium at ring positions can be achieved by using sodium *n*-propanethiolate (equation 100). The minor product (**132**) is probably formed by further reaction of 4-picoline with the anhydrobase of the starting quaternary salt.

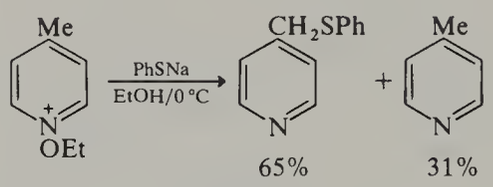


(98)

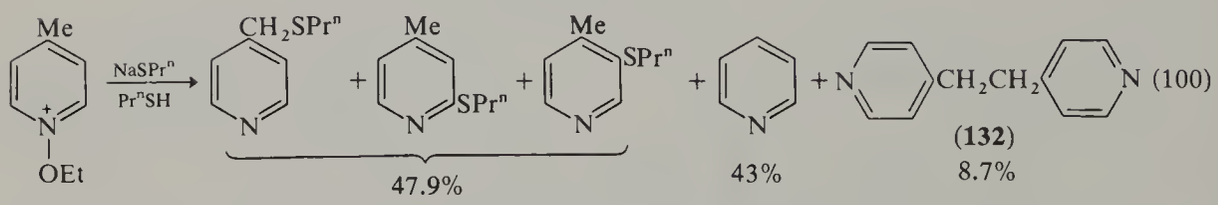
i, $NaSPr^n$, Pr^nSH, EtOH, 6:1 w/w, reflux, 30 min



Scheme 76



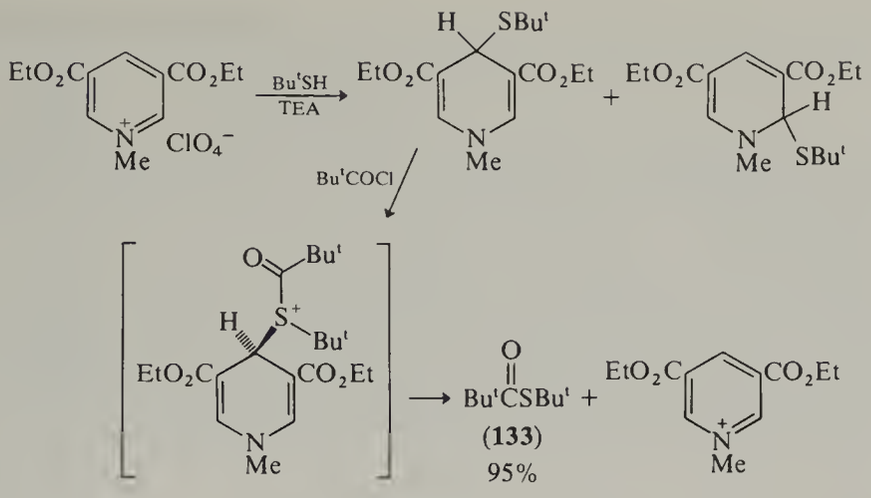
(99)



(100)

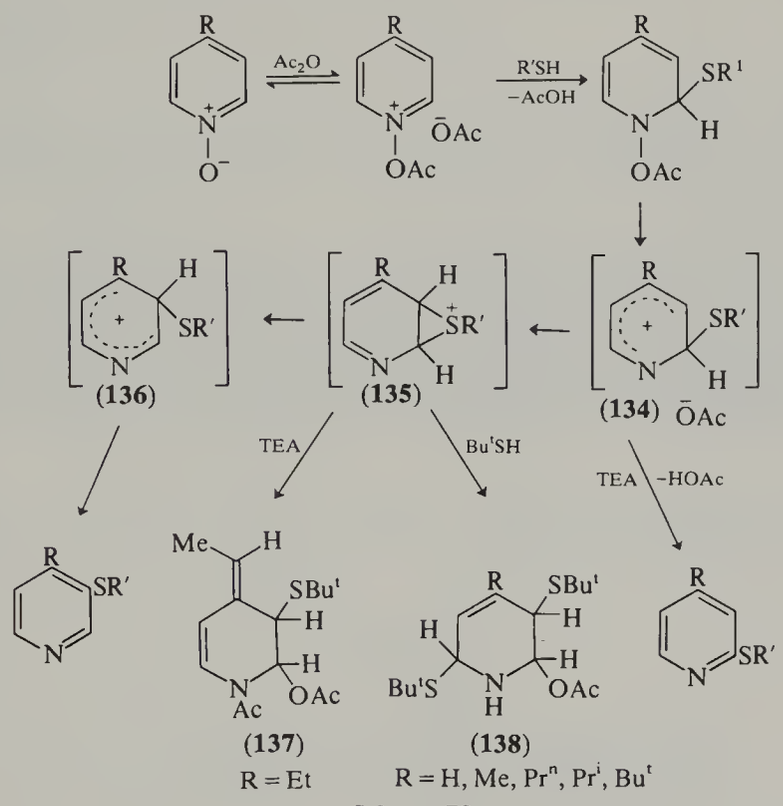
Recently, treatment of the esters or amides of 1-methylpyridinium-3,5-dicarboxylic acid salts with an alkanethiol and TEA in methylene chloride was found to give a mixture of dihydropyridines (Scheme 77) ⟨80CC1147⟩. These yellow adducts are particularly useful as thiolate transfer agents. Excellent yields of thioesters, for example (**133**), are formed by the reaction of the adducts with activated acid derivatives.

Pyridine 1-oxide and a series of its methyl analogues undergo thioalkylation at the α- and γ-positions when heated with an alkanethiol in acetic anhydride at 95 °C for 3 h (Table 13). Under these conditions, attack by thiol at 2- or 4-methyl groups does not seriously compete with ring substitution. β-Substitution does not occur at C-3 in 2-methylpyridine, but it does so at C-5 where the adjacent α-position is vacant. Notice that again a 3-methyl substituent tends to direct substitution to C-2 rather than C-6. This is also true for 3,4-dimethylpyridine. Increasing the size of the 4-substituent does reduce the relative



Scheme 77

amount of C-3 substitution, but attack by 2-methylpropanethiol is not completely suppressed even when a *t*-butyl group is attached at C-4. When the reaction is carried out in the presence of TEA, a superior base to acetate, α-substitution is promoted at the expense of β. This is particularly true the larger the 4-substituent. These observations are consistent with the mechanism shown in Scheme 78. β-Substitution is proposed to occur *via* an episulfonium ion intermediate (**135**). This mechanism also accounts for the enhancement of α-substitution by TEA. The ion pair (**134**) rapidly eliminates acetic acid in the presence of TEA to afford the 2-pyridyl alkyl sulfide; thus rearrangement to (**135**) and formation of the 3-isomer *via* (**136**) is suppressed.



Scheme 78

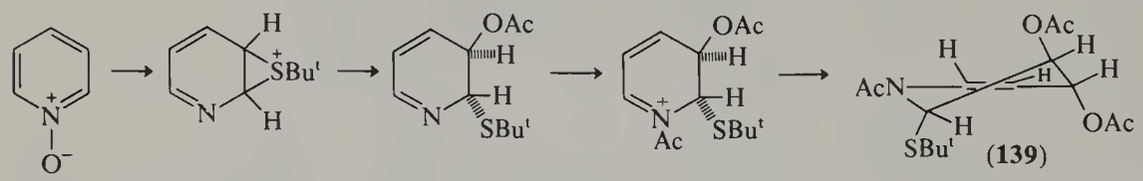
Perhaps the strongest evidence in favour of episulfonium ion involvement comes from the isolation of the 4-substituted 1-acetyltetrahydropyridines (**137**) and (**138**). Product (**138**) arises by addition of another molecule of 2-methylpropanethiol to (**135**). 4-Ethylpyridine 1-oxide on reaction with 2-methylpropanethiol, acetic anhydride and TEA yields another type of tetrahydropyridine (**137**). In this case TEA promotes elimination by abstraction of an ethyl proton, before 2-methylpropanethiol can attack position 6. Conversely, tetrahydropyridines are formed when R=Me, Pr^n or Pr^i, as 2-methylpropanethiol (Scheme 78) is a better nucleophile (at C-6) than TEA is a base (at the 4-substituent). A different tetrahydropyridine (**139**) is obtained if the starting *N*-oxide has a vacant 4-position (Scheme 79). Structural determination of compounds of this type has been greatly facilitated by the availability of ^{13}C NMR ⟨78JHC785⟩. It should be remembered that while 3-substitution

Table 13 Reaction of Pyridine 1-Oxides with Alkene- and Arene-thiols (RSH)

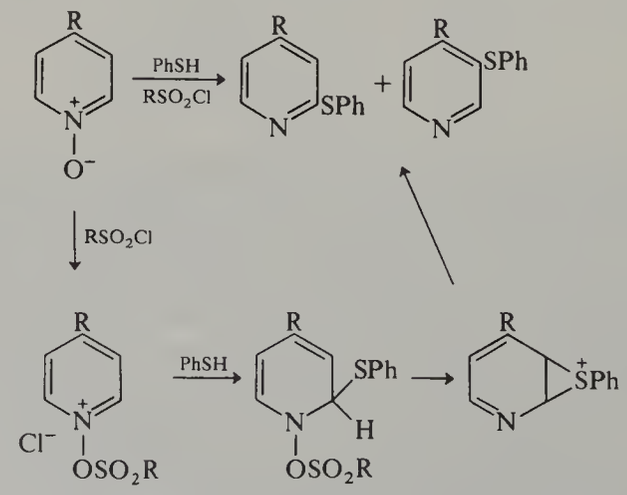
Substituent	*R*	*Method*	*Yield* (%)	*Pyridyl sulfides Isomer distribution* 2-	3-	5-	6-	*Other products*	*Yield* (%)
H	Me	A[a]	38	52	48	—	—	—	—
H	Pr^n	A	46	76	24	—	—	—	—
H	Bu^n	A	67	61	39	—	—	—	—
H	Bu^t	A	62	70	30	—	—	—	—
H	Bu^t	B[b]	41	90	10	—	—	—	—
H	Ph	C[c]	27	40	60	—	—	PhSSPh	60
H	Ph	D[d]	30	41	59	—	—	PhSSPh	53
2-Me	Bu^t	A	32	—	—	16	84	2-Bu^tSCH_2py[e]	10
3-Me	Bu^t	A	66	45	—	36	19	—	—
3-Me	Bu^t	B	20	95	—	5	—	—	—
4-Me	Pr^n	A	31	50	50	—	—	4-Pr^nSCH_2py	3
4-Me	Bu^t	A	41	71	29	—	—	—	—
4-Me	Bu^t	B	33	82	18	—	—	—	—
4-Me	Ph	C	41	56	44	—	—	PhSSPh	37
4-Me	Ph	D	61	67	33	—	—	PhSSPh	20
4-Et	Bu^t	A	49	67	33	—	—	—	—
4-Et	Bu^t	B	32	87	13	—	—	—	—
4-Pr^n	Bu^t	A	54	63	37	—	—	—	—
4-Pr^n	Bu^t	B	45	70	30	—	—	—	—
4-Pr^i	Bu^t	A	61	62	38	—	—	—	—
4-Pr^i	Bu^t	B	39	80	20	—	—	—	—
4-Bu^t	Bu^t	A	48	83	17	—	—	—	—
4-Bu^t	Bu^t	B	48	96	4	—	—	—	—
4-Bu^t	Ph	D	25	57	43	—	—	—	—
4-Ph	Bu^t	A	18	44	56	—	—	—	—
2,6-Me_2	Bu^t	A	—	—	—	—	—	2-Bu^tSCH_2py	1
3,4-Me_2	Bu^t	A	35	48	—	29	—	—	—
3,5-Me_2	Bu^t	A	66	100	—	—	—	—	—
2,4,6-Me_3	Ph	D	9.5	—	—	—	—	—	—

[a]Method A, Ac_2O, EtOH, 95 °C. [b] Method B, Ac_2O, TEA, EtOH, 95 °C. [c] Method C, $MeSO_2Cl$, PhH. [d] Method D, $PhSO_2Cl$, PhH. [e] py = pyridinyl.

via episulfonium ion participation has been proposed, the possibility of nucleophilic attack at C-3 on a 1,2-dihydropyridine cannot be entirely ruled out. To induce attack on the pyridine *N*-oxide ring by less nucleophilic thiols such as thiophenol, alkyl and arylsulfonyl chlorides have been employed as acylating agents (Table 13), and similar considerations to those just discussed apply to these reactions (Scheme 80) ⟨64JOC2183⟩.



Scheme 79

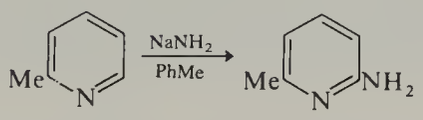


Scheme 80

2.05.4.5 Nitrogen Nucleophiles

2.05.4.5.1 Amination: The Chichibabin reaction

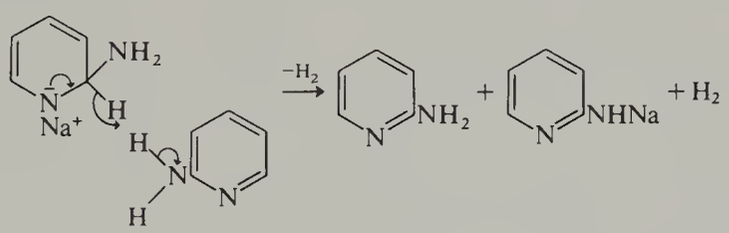
Chichibabin and Seide ⟨14MI20500⟩ found when they attempted to metallate 2-methylpyridine with sodamide in toluene that instead amination took place at the vacant α-position (equation 101). Thus was discovered perhaps the most celebrated reaction in pyridine chemistry. Aminations of pyridine-containing heterocycles are not alone in bearing the name of Chichibabin (this transliteration is preferred by *Chemical Abstracts*). Condensations of aldehydes with ammonia, which provide the industrial route to basic pyridine feedstocks, are also known as the Chichibabin reaction ⟨46BSF501⟩. It is somewhat surprising that there are so few reviews on this important amination ⟨33CRV(12)43, 42OR91, 66AHC(6)229⟩. Two more ⟨B-71MI20502, 78RCR1042⟩ highlight recent work, most of which appropriately comes from the USSR.



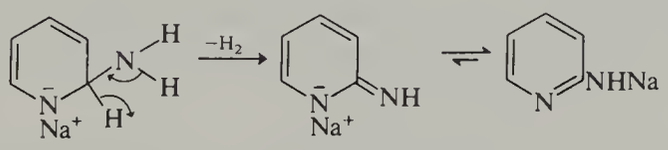
(101)

The synthetic and industrial importance of this reaction lies in its generality, and the ease with which the amino substituent in the products can be subsequently transformed into other functionalities. Pyridine itself is more difficult to aminate than quinoline or isoquinoline, and it does not react with potassium amide in liquid ammonia even on prolonged treatment. However, pyridine is aminated in good yield by sodamide in toluene, and di- and tri-amination can be achieved with excess sodamide at higher temperatures. The 4-position is substituted last in triamination; γ-amination is very difficult indeed and only takes place when all α-positions are occupied.

The Chichibabin reaction proceeds by an addition–elimination pathway (Type **B**) and mechanisms that account for hydrogen evolution are summarized in Schemes 81 and 82 ⟨78RCR1042, 65CJC725⟩. Yet, more than 50 years later the precise mechanism is still not adequately defined. The problem comes from the difficulties inherent in studying heterogeneous processes. Aminations with sodamide are usually carried out in aprotic solvents such as dimethylaniline or aromatic hydrocarbons, in which sodamide is only sparingly soluble. Sodamide is soluble in liquid ammonia but reaction is usually slow under these conditions, and pyridine does not react at all. Chichibabin reactions have also been carried out in a sodamide melt, but yields are generally poorer than with solvents. The factors that influence α- and γ-substitution under hetero- and homo-geneous conditions are considered by examining first the addition, then the elimination step.

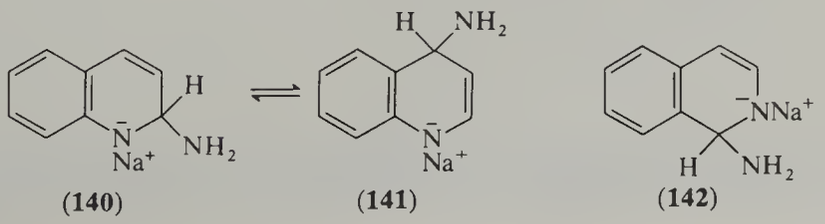


Scheme 81



Scheme 82

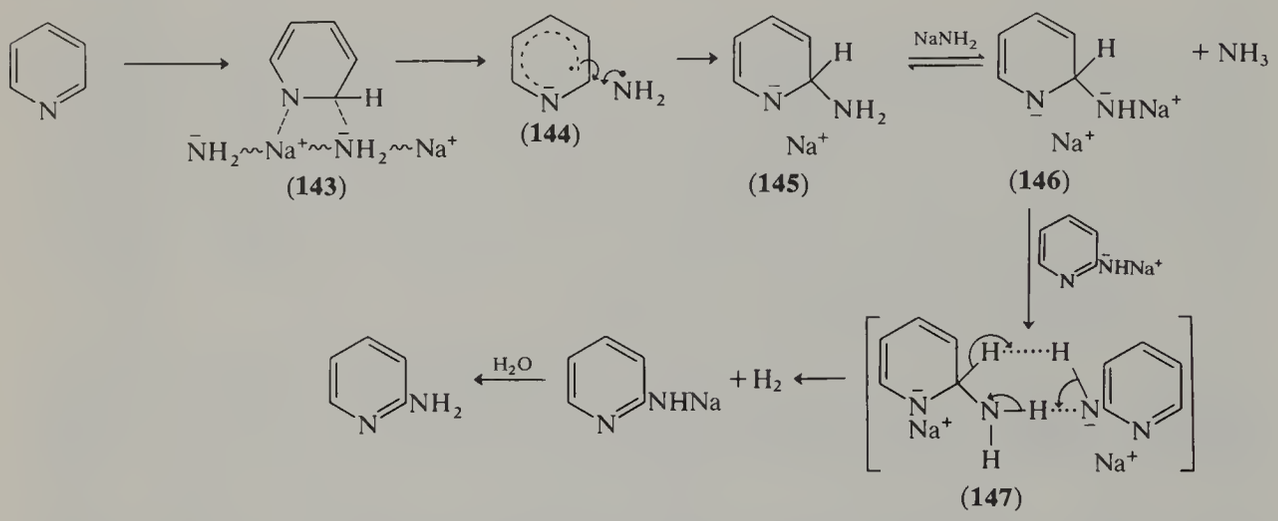
Under heterogeneous conditions 1,2- is favoured over 1,4-addition of sodamide. Addition complexes of sodamide with quinoline (**140**, **141**) and isoquinoline (**142**) in liquid ammonia have been observed by NMR ⟨73JOC1947, 73JOC1949⟩. These complexes have a characteristic



(140) **(141)** **(142)**

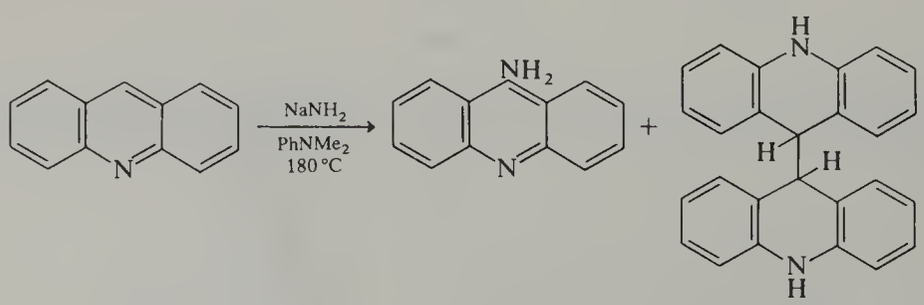
red colour; reaction mixtures in the Chichibabin series are also highly coloured. The 1,2-quinoline adduct (**140**) is formed under kinetic control and it rearranges to the 1,4-adduct.

Heterocycles that bear the highest degree of positive character on the α-carbon atom usually undergo amination most easily. The pK_a of the heterocycle has little effect on the ease of amination in liquid ammonia (homogeneous conditions), although the nature of the cation of the amide salt is important. For instance, barium and potassium amide aminate quinoline more effectively than does sodamide in liquid ammonia. The contrary is true under heterogeneous conditions, where the basicity of the heterocycles has a significant effect upon amination. Heterocycles with pK_a values of 5–6 aminate most successfully. The reason for this difference has been attributed to initial reversible coordination of the pyridine to the surface of the sodamide to give (**143**) (heterogeneous conditions) which activates the substrate towards amination at the α-position (Scheme 83). It appears that a balance between pK_a and α-carbon positive charge density is required for success, and heterocycles with a pK_a 5–6 aminate the best. Those with a higher pK_a are very difficult to aminate, although even 4-dimethylaminopyridine (pK_a = 9.37) undergoes reaction in low yield under extreme conditions.



Scheme 83

It is easy to see (formation of **143**) why γ-amination is so unfavourable for pyridines under heterogeneous conditions, even though C-4 is more electropositive than C-2. In fact, γ-amination under heterogeneous conditions has never been convincingly demonstrated for pyridine or quinoline. Under homogeneous conditions, α-substitution is still favoured over γ- (6:1) in the amination of quinoline by sodamide in liquid ammonia ⟨34JA1748⟩. γ-Amination is easier in liquid ammonia because metal amides are highly dissociated in this solvent. 2-Substituted quinolines undergo 4-substitution in good yield in liquid ammonia (Table 14), but a similar reaction is very difficult for 2,6-dimethylpyridine. Acridine (for which Chichibabin reaction is favoured on both pK_a and γ-carbon positive charge density grounds) provides an interesting example of how reaction conditions can dramatically change the nature of the products formed. Acridine undergoes 9-amination in high yield with sodamide in liquid ammonia, but 9,9′-biacridanyl is the main product of amination in dimethylaniline (equation 102). This large drop in the yield of 9-aminoacridine has been attributed to the effect of the large distance between the amide ion and C-9 in the adsorption complex, which allows a side reaction to compete.



(102)

The formation of 9,9′-biacridanyl and the suppression of amination by free radical inhibitors ⟨78RCR1042⟩ brings up the question of whether radical intermediates are involved

Table 14 Amination of Pyridines and Quinolines

Substituent	*Conditions*[a]	*Yield of products (%)*[e] 2-NH_2	4-NH_2	6-NH_2	*Others*	
Pyridine	1:1[a] A	70–85	—	—	—	—
	1:2[a] A	—	—	—	2,6-$(NH_2)_2$	55
	1:3[a] A				2,4,6-$(NH_2)_3$	low
2-Ph	—	—	—	87	—	—
2-Me	A	—	—	+[c]	—	—
2-OH	A	—	—	+[c]	—	—
3-Me	A	45	—	4	—	—
3-Et	—	50	—	14	—	—
3-Bu^n	—	40	—	10	—	—
3-C≡CH	—	—	—	—	7-azaindole	54[b]
3-OH	—	—	—	—	2,6-$(NH_2)_2$	55[b]
3-CO_2H	A	—	—	—	2,6-$(NH_2)_2$	12[b]
3-$CONH_2$	A	—	—	—	2,6-$(NH_2)_2$	44[b]
3-NH_2	A	+[c]	—	—	—	—
3-NHMe	A	+[c]	—	—	—	—
3-NMe_2	—	62	—	—	—	—
4-Me	—	60	—	—	—	—
4-Et	—	52–64	—	—	—	—
4-Pr^n	—	76	—	—	—	—
4-$Amyl^n$	—	60	—	—	—	—
4-CH_2Ph	1:2[a]	<40	—	—	—	—
4-OH	—	—	—	—	2,6-$(NH_2)_2$-4-OH	69–75
4-CO_2H	A	—	—	—	2,6-$(NH_2)_2$	55
4-$CONH_2$	A	—	—	—	2,6-$(NH_2)_2$	38
2,5-Me_2	—	32	—	—	—	—
2,4-Me_2	—	+[c]	—	—	—	—
3,5-Me_2	—	20	—	—	—	—
2,6-Me_2	—	6	—	—	—	—
3,4-$(OH)_2$	—	40	—	—	—	—
Quinoline	A	32	—	—	—	—
	B[d]	69	10	—	—	—
2-Ph	—	—	91	—	—	—
2-CO_2H	—	—	81	—	—	—
2-OMe	—	5[b]	—	—	—	—
2-SO_3H	—	74[b]	—	—	—	—
2-NHMe	—	15[b]	—	—	—	—
4-Me	—	46	—	—	—	—
4-CO_2H	—	70	—	—	—	—
4-$CONH_2$	—	54	—	—	—	—
6-Me	—	17	—	—	—	—
6-CO_2H	—	60	—	—	—	—
6-Ph	—	86	—	—	—	—
6-NMe_2	—	34	—	—	—	—
8-Me	—	35	—	—	2-NH_2-8-Me 3,4-Dihydro	1
8-Ph	—	88	—	—	—	—
8-OEt	—	76	—	—	—	—
Isoquinoline	A	—	—	—	1-NH_2	100
	B	—	—	—	1-NH_2	87

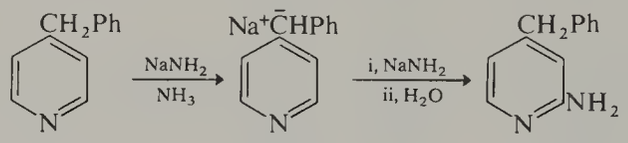
[a] A, heterogeneous conditions (ratio of substrate:sodamide); B, homogeneous conditions. [b] With substituent loss. [c] No yield quoted. [d] Potassium amide. [e] +, Product found.

in the Chichibabin reaction. Recent work ⟨78RCR1042⟩ suggests that conversion of the pyridine–sodamide complex (**143**) to the σ-complex (**145**) involves a single electron-transfer step *via* (**144**; Scheme 83). This mechanistic refinement is attractive because it also provides an explanation of why heterocycles bearing certain substituents (*e.g.* nitro or arylazo) do not undergo the Chichibabin reaction. Such groups should be expected to decrease the spin density at C-2, which prevents radical recombination to a σ-complex.

Several pathways (Schemes 81 and 82) have been suggested for the elimination step which involve a simple one-step loss of hydrogen ⟨34JA1748, 57CRV525, 65CJC725⟩. These mechanisms account for the loss of hydrogen and are consistent with the fact that the nucleophiles that react most readily all have a labile hydrogen atom. Sodium salts of secondary amines, for example, do not undergo this reaction. A recent study of the kinetics of the Chichibabin reaction by analysis of gases evolved under heterogeneous conditions

has led to the proposal of a two-stage transformation of σ-complex (**145**) to products (Scheme 83) ⟨76CHE210⟩. The first step is considered to involve abstraction of an amino proton by amide to convert (**145**) to a dianionic complex (**146**) and ammonia. In the second step, the sodium salt of 2-aminopyridine acts as a bifunctional catalyst to form 2-aminopyridine sodium salt and hydrogen *via* a transition state like (**147**). Addition of such sodium salts has been found to have an autocatalytic effect on Chichibabin reactions, and to decrease the induction period if added at the beginning of the reaction. This mechanism is consistent with the observation that the gas evolved early in the reaction contains a greater concentration of ammonia than after *ca.* 15 min, when it levels to a concentration that is maintained until completion. This suggests a build up of an intermediate, the decomposition of which is rate determining. It is doubtful that amide ion catalyzes the last step as it is much inferior to aminopyridine sodium salt as a bifunctional catalyst. This bifunctional catalysis indicates that the transition state for the elimination stage more closely resembles (**146**) than the σ-complex (**145**) as previously thought.

The results of some of the many aminations of pyridine and its derivatives that have been carried out appear in Table 14. Yields are quoted where possible but these should not be used for quantitative comparisons as reaction and work up conditions vary widely. 2-Alkylpyridines aminate at the vacant α-position, except when the substituent is very large. 2-*t*-Butylpyridine does not undergo the Chichibabin reaction, probably because the bulky 2-*t*-butyl group prevents adsorption on to the sodamide surface. In contrast, 2-phenylpyridine undergoes amination in very good yield. Aminations of 2- and 4-methylpyridines do not involve attack on the anhydrobases in aprotic solvents, but some ionization does take place in liquid ammonia. 4-Benzylpyridine forms a carbanion (**148**) which is only aminated with difficulty by a second mole of sodamide (equation 103).



(103)

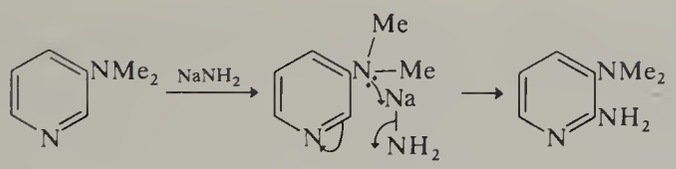
(**148**)

3-Alkylpyridines are aminated preferentially at the 2-position, but reaction is slower than in the parent system. Quinoline is difficult to aminate and only a low yield of 2-aminoquinoline (32%) is obtained from reaction with sodamide in toluene. When dimethylaniline is employed as solvent, 2-amino-3,4-dihydroquinoline (24%) becomes the major product, and the yield of 2-aminoquinoline drops to 7%. The best yields of 2-aminoquinoline (53–69%) have been obtained by using barium or potassium amide in liquid ammonia. Use of the potassium salt also produces a 10% yield of the 4-amino isomer. The 2- and 4-methylquinolines form anhydrobases in liquid ammonia, but the 2-isomer is aminated in dimethylaniline. Isoquinoline reacts very readily to form the 1-amino derivative almost quantitatively with sodamide in both liquid ammonia and in dimethylaniline. Acridine undergoes γ-amination in high yield with sodamide in liquid ammonia. This is in contrast to 2,6-dimethylpyridine, which only gives a 6% yield of the 4-amino product. Phenanthridine undergoes Chichibabin reaction chiefly at C-6. 3-Ethynylpyridine is aminated at the 2-position to give a product which undergoes 5-*endo-dig* closure to furnish 7-azaindole in good yield.

Substituents attached to a pyridine ring are quite often lost during the course of amination, and in the quinoline system some groups attached at C-2 are replaced by amino. The 3-hydroxy group is lost during amination, but 3,4-dihydroxypyridine undergoes amination without loss of either hydroxyl group. Both 2- and 4-pyridone undergo amination without substituent loss. Nicotinic and isonicotinic acids are readily decarboxylated during amination, and the product is 2,6-diaminopyridine in both cases. In the quinoline series a 2-carboxy group directs the attacking amide ion to the 4-position, but 4-quinolinic acid aminates at C-2 with retention of the carboxylic acid function.

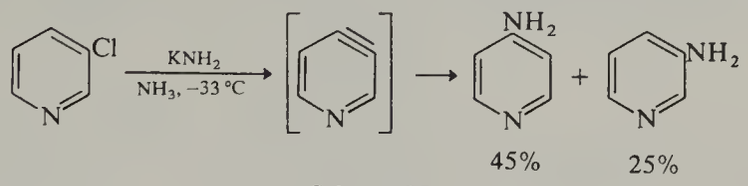
A special mechanism has been postulated to account for the fact that 3-dimethylaminopyridine undergoes exclusive 2-amination (Scheme 84). Amination of 2-dimethylaminopyridine yields 2,6-diaminopyridine (30%), but the 4-isomer aminates at C-2 (low yield) with retention of the 4-substituent.

Reactions of halopyridines with amide ions involve the substituent and are therefore covered in Chapter 2.06. However, a few examples are included here to illustrate possible

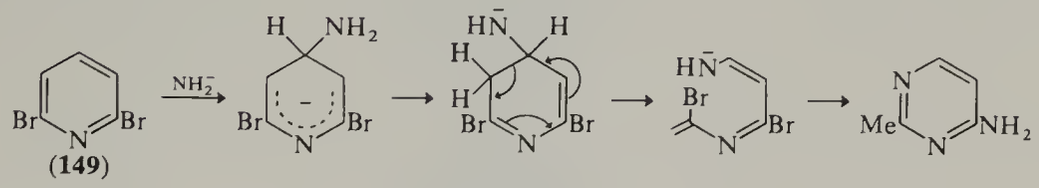


Scheme 84

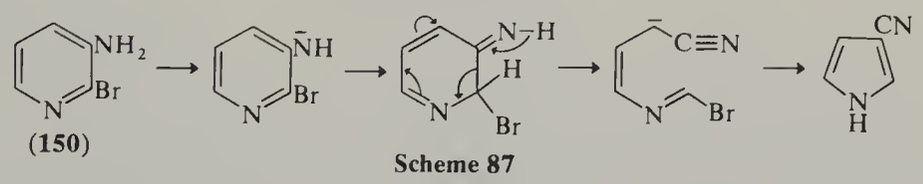
competing pathways to the Chichibabin reaction. 3-Chloropyridine gives a mixture of 3- and 4-aminopyridines by addition of ammonia to a 3,4-pyridyne (Scheme 85) ⟨61RTC1376, 61AG65⟩. The possibility that a pyridyne is involved in 'normal' aminations was once proposed ⟨63CI(L)1621⟩, but this has been convincingly refuted ⟨65CJC725⟩. Ring opening (Type **D**) is always a potential, and often unwanted, competitor to desired reactions of pyridines under nucleophilic conditions. It becomes the major path when α-bromopyridines (**149**) and (**150**) are treated with sodamide (Scheme 86 ⟨65RTC1569⟩ and Scheme 87 ⟨67TL5089⟩).



Scheme 85



Scheme 86



Scheme 87

Alkyl- and aryl-aminations of pyridines have not been nearly as well investigated as amination itself. Mention of low yield phenylamination of pyridine appeared along with the first report of amination ⟨14MI20500⟩. Improvements in the yield from this reaction have not been forthcoming. On the other hand, alkylamination appears from the limited data available to provide a satisfactory method for the direct introduction of an alkylamino group at C-2 in pyridine and quinoline (Table 15) ⟨46JOC239, 61RTC47⟩. It might be assumed that the pathway followed by this reaction is directly analogous to that for amination, but this has been questioned ⟨61RTC47⟩.

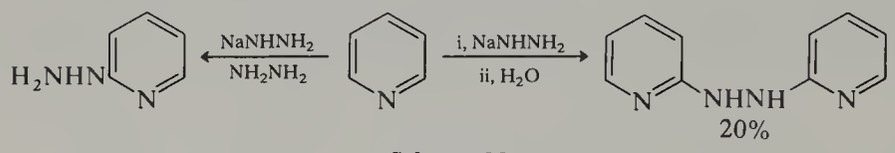
Table 15 Alkylamination of Pyridines and Quinoline

Heterocycle	*Amine*	*Method*[a]	*% Yield of 2-alkylamino product*[b]
Pyridine	Cyclohexyl	A	34
	Cyclohexyl	B	12
	n-Butyl	A	64
	n-Butyl	B	50
	n-Heptyl	A	21
	Methyl	A	73
	Benzyl	B	11
	Dodecyl	B	52
	β-Dimethylaminoethyl	B	79
2-Me	β-Dimethylaminoethyl	B	75
Quinoline	Cyclohexyl	A	59
	n-Butyl	A	40
	β-Dimethylaminoethyl	B	59

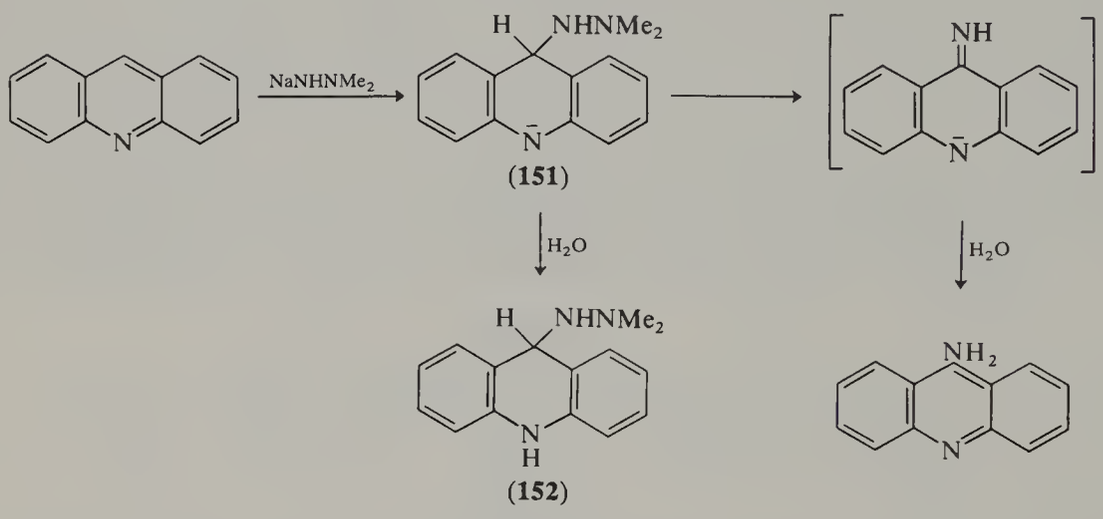
[a] A, $NaNH_2/KNH_2$ eutectic, alkylamine, KNO_3 ⟨46JOC239⟩; B, powdered Na or K metal, alkylamine, boiling toluene ⟨61RTC47⟩.

[b] Invariably accompanied by bipyridyls or biquinolyls.

Pyridine reacts with sodium hydrazide in the presence of hydrazine to yield 2-hydrazinopyridine; in the absence of free hydrazine a hydrazo compound is formed (Scheme 88) ⟨64AG(E)342⟩. A difference between hydrazination and amination is the formation of 1,4-adducts which cannot be rearomatized even on heating. This is reflected in the behaviour of quinoline, which gives only a 0.5% yield of α-hydrazino product, whereas 4-methylquinoline is hydrazinated in 76% yield ⟨64AG(E)342⟩. Acridine behaves differently: with sodium hydrazide/hydrazine, 9,10-dihydroacridine is formed almost quantitatively, but reaction in the absence of hydrazine yields 9-aminoacridine (65%). An even higher yield of 9-aminoacridine is obtained when sodium *N,N*-dimethylhydrazide is used (Scheme 89). Good evidence for intermediacy of (**151**) comes from the isolation of (**152**) on hydrolysis of (**151**).

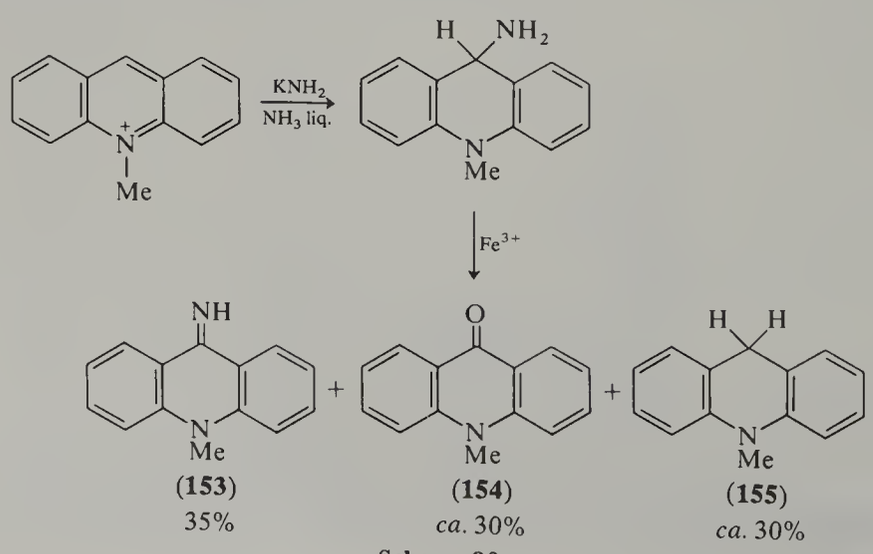


Scheme 88

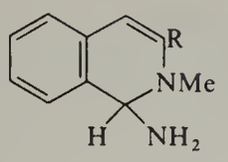


Scheme 89

Amination of *N*-alkylpyridinium salts with amide ions, which in principle should be easier than the reaction with the parent pyridine, has been little studied. The main reason for this is that solvent selection is difficult. Metal amides are only soluble in liquid ammonia (with which pyridinium salts react easily, *vide infra*), and pyridinium salts are soluble in solvents that are not suitable for use with metal amides. The *N*-methylacridinium cation undergoes direct imination to give (**153**) in 35% yield by treatment with potassium amide and iron(III) nitrate in liquid ammonia. Two other products (**154**) and (**155**) are also formed, probably by hydrolysis and subsequent disproportionation (Scheme 90). One might question whether sodamide is necessary to the above transformation in light of the fact that quinolinium, isoquinolinium and certain pyridinium ions give σ-complexes (**156**), (**157**) and (**158**) in liquid ammonia alone at 0 °C ⟨73JOC1949⟩.

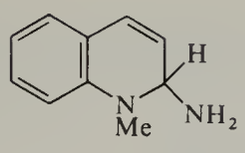


Scheme 90

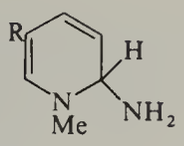


R = H or Me

(156)



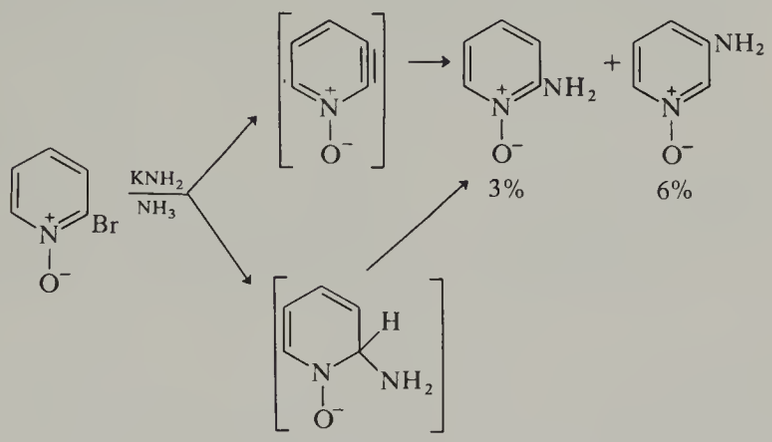
(157)



R = NO_2, SO_2Me, or COMe

(158)

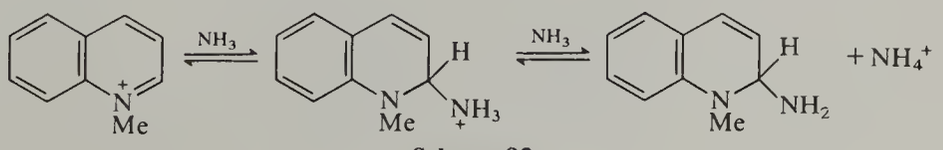
Intermolecular aminations of pyridine 1-oxides with amide ions have not been as well investigated as those of the neutral molecules. Most of the examples studied involve halo *N*-oxides, where a competition between Type **B** behaviour and pyridyne reaction compete (Scheme 91) ⟨67RTC655⟩.



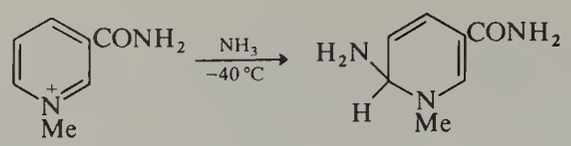
Scheme 91

2.05.4.5.2 Other aminations

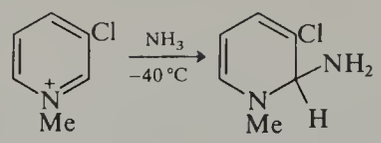
Covalent amination, analogous to covalent hydration, of pyridinium quaternary salts is very facile in liquid ammonia at 0 °C. The nucleophile is ammonia (pK_a 27.7 at 25 °C), and not amide (Scheme 92). NMR spectra indicate that conversion to a σ-complex is quantitative for *N*-methylquinolinium and isoquinolinium cations; no evidence was found for ring opening ⟨73JOC1949⟩. The NMR spectrum shows that only the 2-adduct is formed in the case of *N*-methylquinolinium, and no change occurs in the spectrum on varying the temperature from −50 to 25 °C. This contrasts with the behaviour of quinoline itself in liquid ammonia, where the first formed 1,2-adduct converts to the 1,4-isomer. The 1-methylpyridinium ion does not react with neutral ammonia; however, the addition of powdered potassium hydroxide, or the presence of an electron withdrawing substituent at C-3, changes this ⟨76JOC1303⟩. *N*-Alkylpyridinium ions with strongly electron withdrawing 3-substituents ($CONH_2$, CO_2Me, CF_3 or COMe) undergo addition of ammonia at C-6 (equation 104). On the other hand, 3-chloro- and 3-iodo-1-methylpyridinium ions react at C-2 (equation 105). The 3-cyano-1-methyl- and -1-benzyl-pyridinium ions form at least two adducts at −40 °C (equation 106). The corresponding 1-*p*-nitrobenzyl derivative also forms some 1,4-adduct (equation 107). 1-Methyl- and 1-benzyl-pyridinium ions require the addition of powdered potassium hydroxide to the liquid ammonia solution to drive addition to completion (Scheme 93). Ring opening, path **D**, is not seen in the above cases, but it becomes a significant reaction with the 1-methoxypyridinium ion. Addition to ammonia at −50 °C (potassium hydroxide addition is not required, as *N*-methoxy is sufficiently electron withdrawing to promote addition at C-2) yields the 1,2-adduct and a ring-opened product (equation 108). Predictably, 3-carbamoyl-1-methoxypyridinium (which contains two activating groups) gives only ring opening on reaction with ammonia at −45 °C. The temperature of reaction has to be lowered to −65 °C to observe a C-2 adduct. This is not a simple reaction, and the products identified are thought to arise by a set of rearrangements the intermediates of which are not observable by NMR.



Scheme 92



(104)



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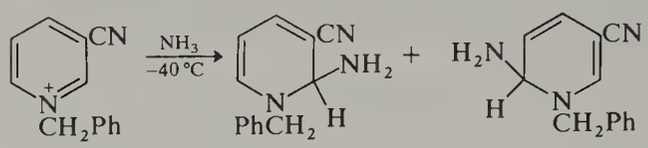

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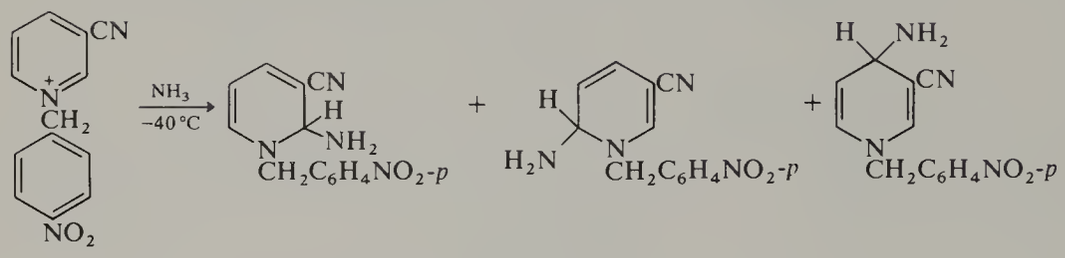

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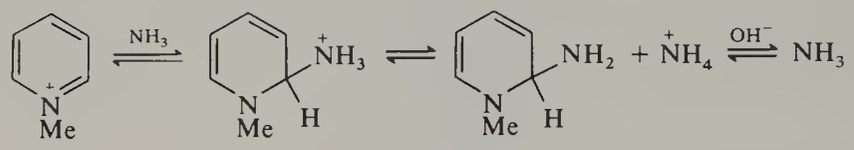
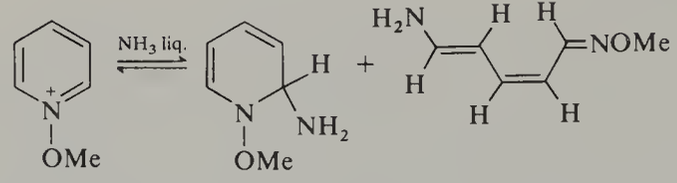
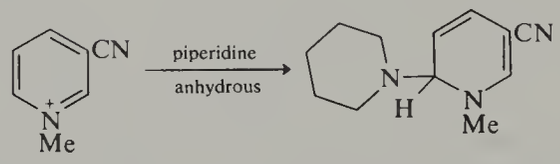


Scheme 93

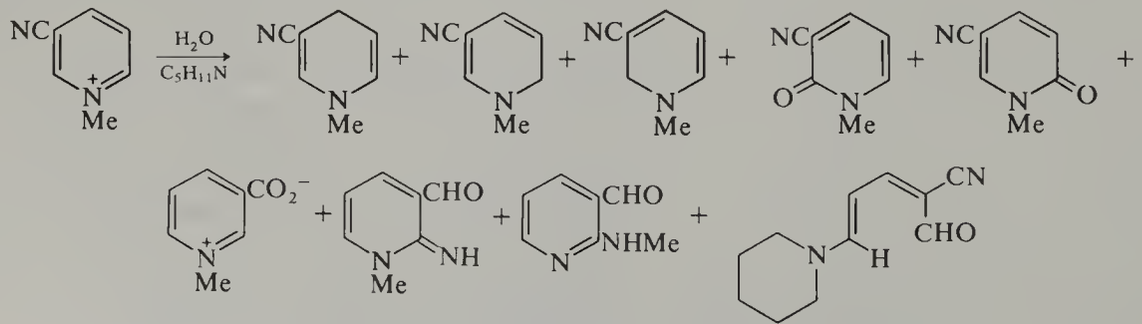


(108)

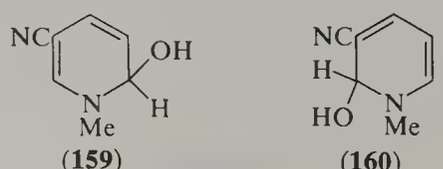


(109)

Similar 3-substituted pyridinium salts give stable solid isolable adducts on reaction with aliphatic amines such as piperidine (equation 109) (Table 16) ⟨80T785⟩. These adducts are stable in apolar solvents, but in water they rapidly dissociate into pyridinium ions and amines, and reactions occur by several pathways (Scheme 94). All may be considered to arise from the covalent hydrates (**159**) and (**160**) which are formed under the aqueous basic conditions.



Scheme 94

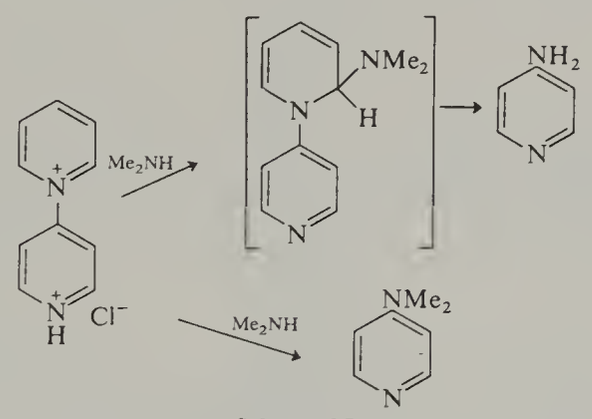


(**159**) (**160**)

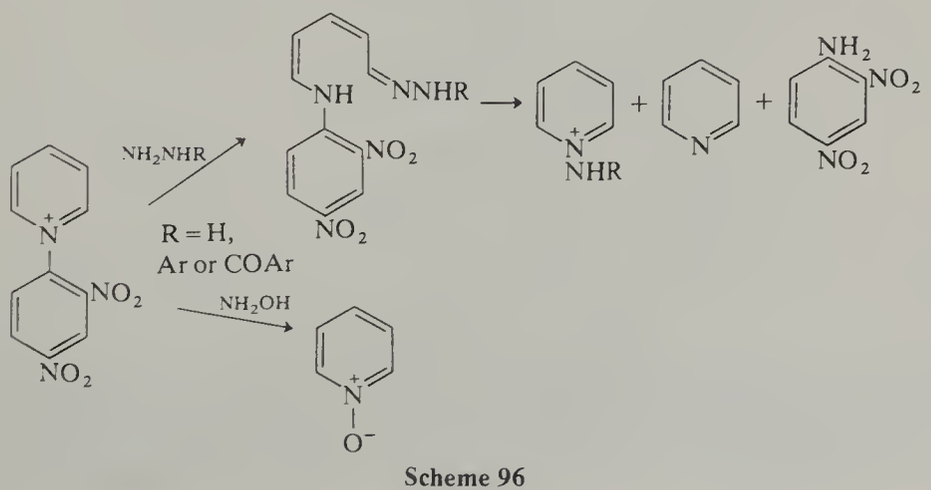
Table 16 Products of the Reaction of 3-Substituted Pyridinium Salts with Piperidine

Pyridinium salt	*Yield of C-6 Adduct* (%)	*Pyridinium salt*	*Yield of C-6 Adduct* (%)
1-Me, 3-CN	80	1-CH_2Ph, 3-COMe	80
1-CH_2Ph, 3-CN	85	1-Me, 3-$CONH_2$	70
1-Me, 3-COMe	70	1-CH_2Ph, 3-$CONH_2$	80

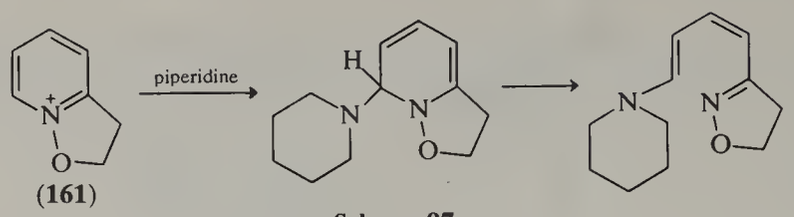
The effect of groups attached to the pyridine ring, and the nature of the *N*-substituent, have been seen to play a decisive rôle in the outcome of nucleophilic attack by amines on pyridinium salts. Ring opening is facilitated by strong electron withdrawing groups, and elements more electronegative than carbon attached to nitrogen. *N*-Alkyl-, *N*-phenyl- and *N*-(*p*-nitrophenyl)-pyridinium salts do not undergo ring opening in the presence of amines alone; more electronegative *N*-substituents are necessary. *N*-Pyridyl-, *N*-(2,4-dinitrophenyl)-, *N*-cyano-, *N*-alkoxy-, *etc.* are cleaved by aromatic amines with increasing facility. 4-Pyridylpyridinium chloride hydrochloride is the least reactive of this group and ring opening competes unfavourably with substituent reaction except at higher temperature (Scheme 95) ⟨B-64MI20500⟩. Suitably substituted 1-(2,4-dinitrophenyl)pyridinium salts react with hydrazine hydrate, acyl- and aryl-hydrazines, and hydroxylamine (Scheme 96). The alkoxy quaternary salt (**161**) is readily fragmented on treatment with piperidine (Scheme 97) ⟨67T2775⟩. The reaction of pyridine with thiophosgene provides a useful approach to certain isothiocyanates (**162**; Scheme 98) ⟨74JCS(P1)1541⟩. Weak electron donating groups attached at C-3 suppress ring opening; 3-dimethylamino-1-(2,4-dinitrophenyl)pyridine is not ring opened even on heating with aniline. Lower yields are also obtained for salts containing electron donating 4-substituents ⟨81T3423⟩. α-Amination is usually preferred to γ-, which is consistent with the postulate that hard nucleophiles (*e.g.* NH_3, RNH_2, N_2H_4, *etc.*) attack at C-2, and soft ones (*e.g.* CN^- and carbanions) at C-4 ⟨68JA223⟩. Of the borderline cases (neither hard nor soft), aniline usually attacks pyridines at C-2, and pyridine attacks pyridine-like heterocycles chiefly at C-4 (equation 110). Attack at C-2 can be just as favoured in some cases (equations 111 and 112) ⟨B-67MI20501⟩. Substitution by amines at positions 2 and 4 is observed in the reaction of activated quinoline 1-oxides with aromatic and aliphatic amines, the former being favoured (equations 113 and 113a). Therefore, prediction on the basis of the above postulate is fraught with difficulty.



Scheme 95

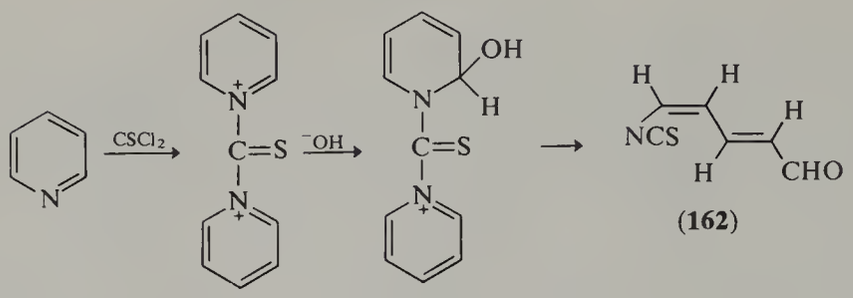


Scheme 96



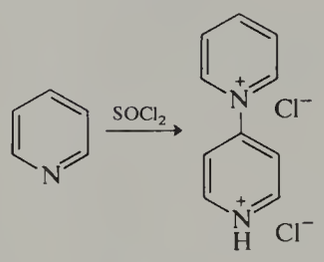
(**161**)

Scheme 97

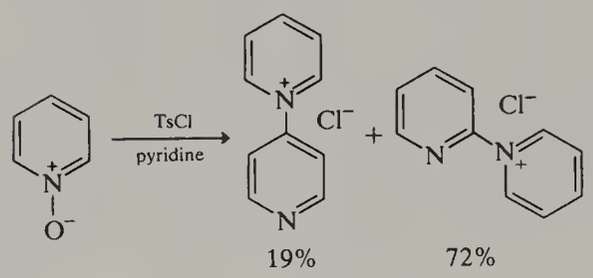


(**162**)

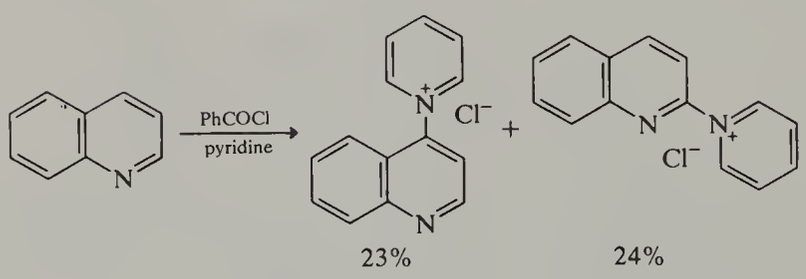
Scheme 98



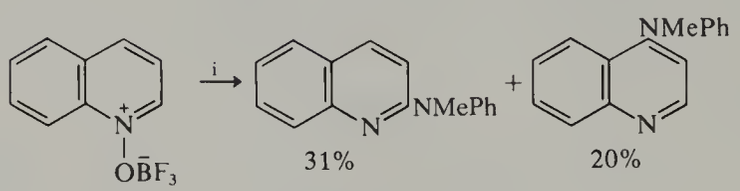
(110)



(111)

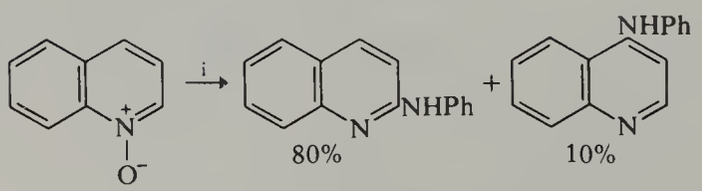


(112)



(113)

i, TsCl, PhNMeCHO, 130–145 °C

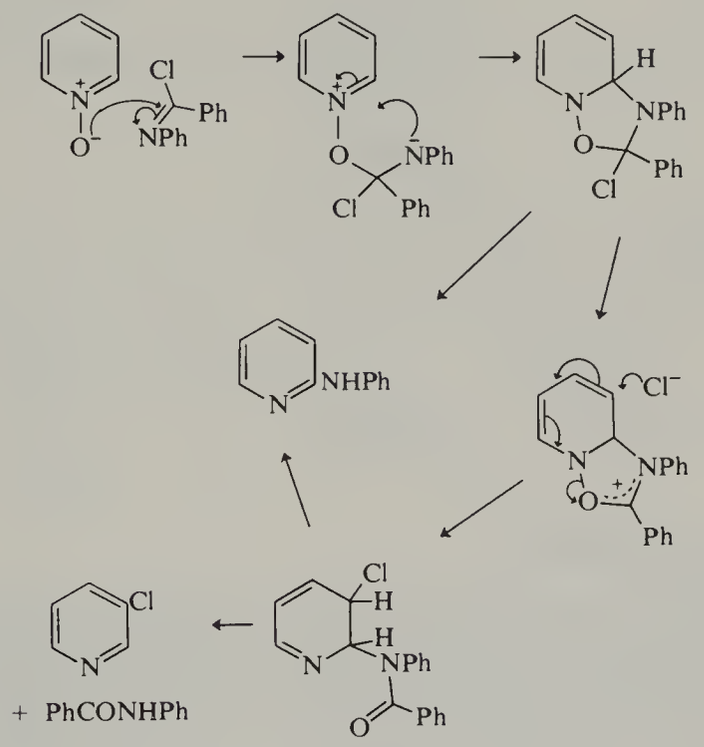


(113a)

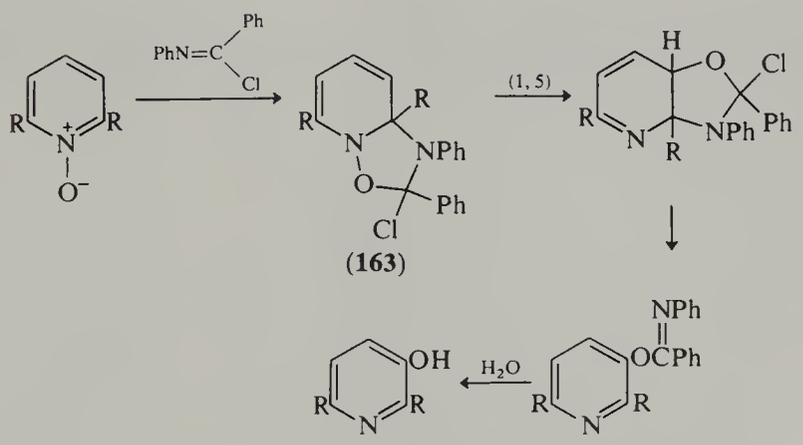
i, $PhNH_2$, TsCl, dioxane, 120–130 °C

Treatment of *N*-oxides with imidoyl chlorides or nitrilium salts can lead to intramolecular amination. This is a useful direct method for the introduction of a 2-arylamino group into the pyridine ring (Scheme 99) ⟨74JOC1795⟩. The by-products that are isolated in some of these reactions are believed to be formed as shown. When the α-positions are blocked a

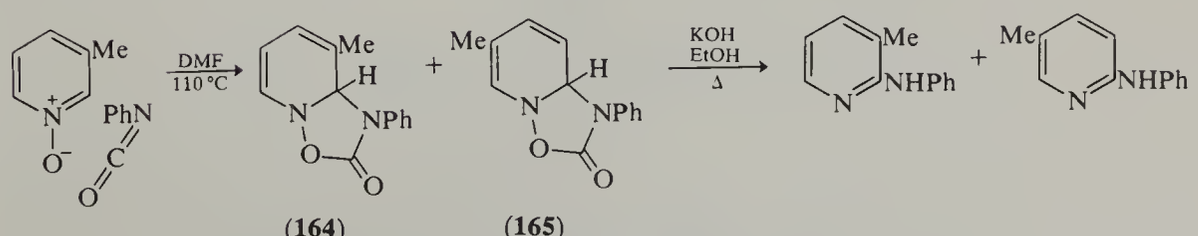
quite different reaction, which is reminiscent of the behaviour of *N*-oxides in acetic anhydride, takes place (Scheme 100) ⟨76ACR192⟩. The 1,2-dihydro intermediates (**164** and **165**; Scheme 101) which correspond to (**163**; Scheme 100) can be isolated from the reaction of 3-methylpyridine 1-oxide with phenyl isocyanate ⟨74CPB1611⟩. These are rearomatized to aminopyridines when they are heated with base. Pyridine 1-oxides react with 2-halopyridines to give 1-(2-pyridyl)pyridin-2-ones, by the mechanism illustrated (Scheme 102) ⟨59JA156⟩. Electron donating groups attached to the *N*-oxide facilitate reaction and electron withdrawing groups hinder it. These reactions are quite general and examples are also known in the quinoline and isoquinoline *N*-oxide series ⟨B-71MI20500⟩. Quinoline 1-oxide reacts with 4-bromopyridine to yield (**166**; Scheme 103) ⟨57RTC647⟩, presumably by the rearrangement indicated. Pyridine 1-oxide forms two products (**167**) and (**168**) on reaction with 2-bromopyrimidine (Scheme 104) ⟨66NKK884⟩. The latter probably arises by hydrolysis of the pyrimidinone intermediate (**169**).



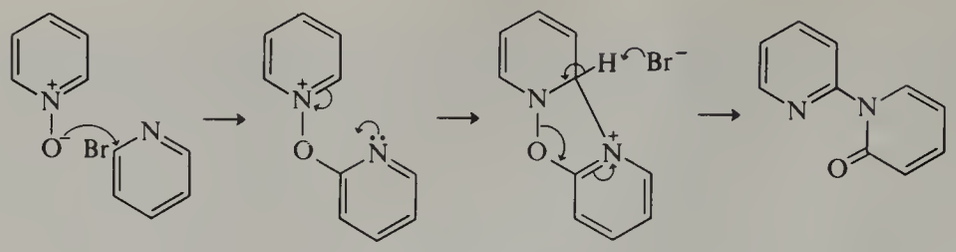
Scheme 99



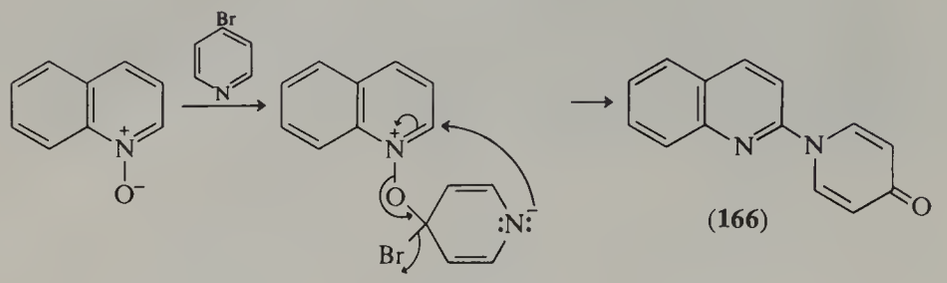
Scheme 100



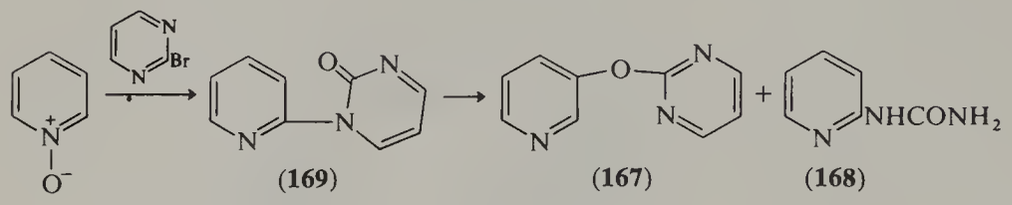
Scheme 101



Scheme 102



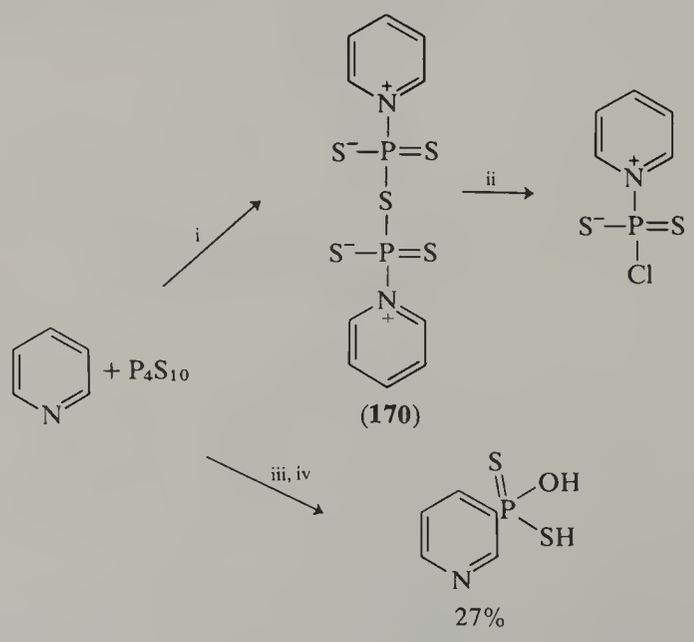
Scheme 103



Scheme 104

2.05.4.6 Phosphorus Nucleophiles

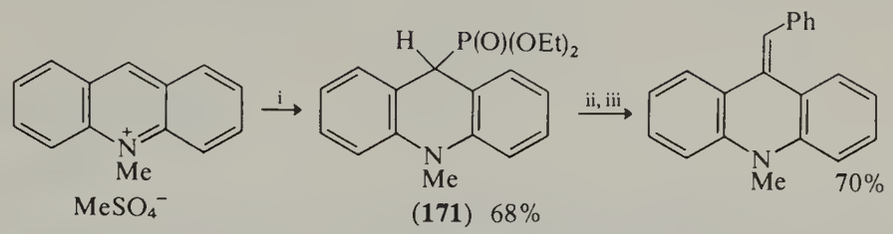
Pyridine compounds in which phosphorus is directly attached to a ring carbon are relatively rare. Phosphorus nucleophiles are not able to replace ring hydrogen atoms in pyridines and pyridine 1-oxides. Some time ago it was found that pyridine yields a zwitterion (**170**) when it is heated under reflux in the presence of tetraphosphorus decasulfide (Scheme 105) ⟨68MI20500⟩. Recently, a product that contains a C—P bond was isolated after extended heating under the same conditions followed by treatment with hydrochloric acid ⟨81JCR(S)285⟩. However, it is uncertain whether free pyridine undergoes reaction in this case. Attack by phosphorus nucleophiles on salts is well established. *N*-Methylacridinium methosulfate affords a stable isolable 9,10-dihydro adduct (**171**) that readily forms a



i, 3 h, reflux; ii, $P(S)Cl_3$, pyridine; iii, reflux, 111 h; iv, HCl, 3 h, 100 °C

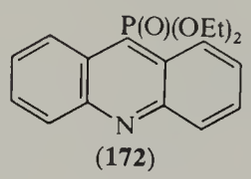
Scheme 105

carbanion on treatment with sodium hydride ⟨69JOC1420⟩ which undergoes Wittig–Horner reaction with benzaldehyde (Scheme 106). 9-Acridinium bromide also forms an adduct with diethyl sodiophosphonate which can be oxidized by tetrachloro-*p*-benzoquinone to the 9-phosphonate (**172**). 1-Methoxy-3-methylpyridinium methosulfate undergoes α-substitution, principally at C-2, by path **B** (equation 114) on treatment with the same reagent. If the α-positions are blocked, substitution at C-4 is observed (equation 114a), but in this case paths **A** and **C** compete ⟨70JOC4114⟩.

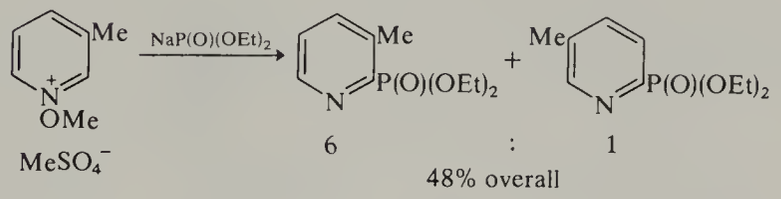


i, $NaP(O)(OEt)_2$, dioxane, 55 °C, then 85–90 °C, 2 h; ii, NaH; iii, PhCHO

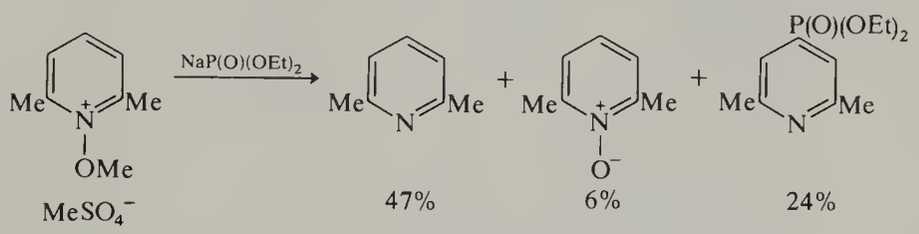
Scheme 106



(172)

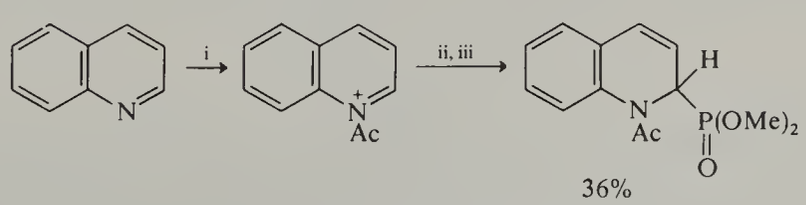


(114)



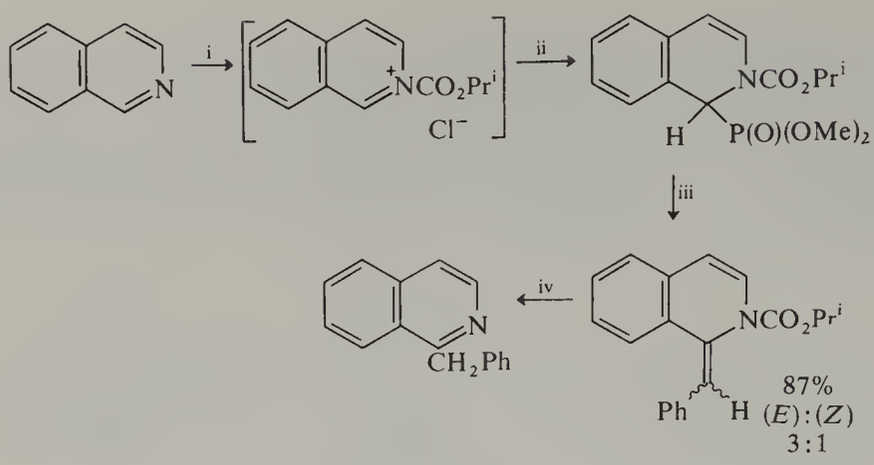
(114a)

Lately, a variation of the above method has appeared which employs *N*-acyl quaternary salts. This provides high yield approaches to a 1,2-quinoline adduct (Scheme 107), and a method for the 1-alkylation of isoquinoline (Scheme 108) ⟨81TL4977⟩. These two procedures bear an obvious resemblance to those based on Reissert intermediates (see Section 2.05.4.7). A more exciting development, however, is the application of this approach in the pyridine series where the Reissert reaction fails. 4-Alkylpyridines can be prepared by a one-pot procedure (Scheme 109) ⟨81TL4093⟩ in which the phosphonyl group adds regiospecifically 1,4, serves to stabilize the carbanion (**173**), and acts as a good leaving group. Attainment of regiospecificity in the addition step, which is crucial, depends upon the size of both alkyl groups (R^1 and R^2) concerned (Scheme 110) (Table 17). Two equivalents of butyllithium are required in the last step, which proceeds by attack on the ethoxycarbonyl group to form (**174**). Evidence for this comes from a separate experiment where an equimolar amount of butyllithium is used. This gives a 1:1 mixture of (**174**) and (**175**), and addition of a second equivalent of butyllithium converts the former into the latter.



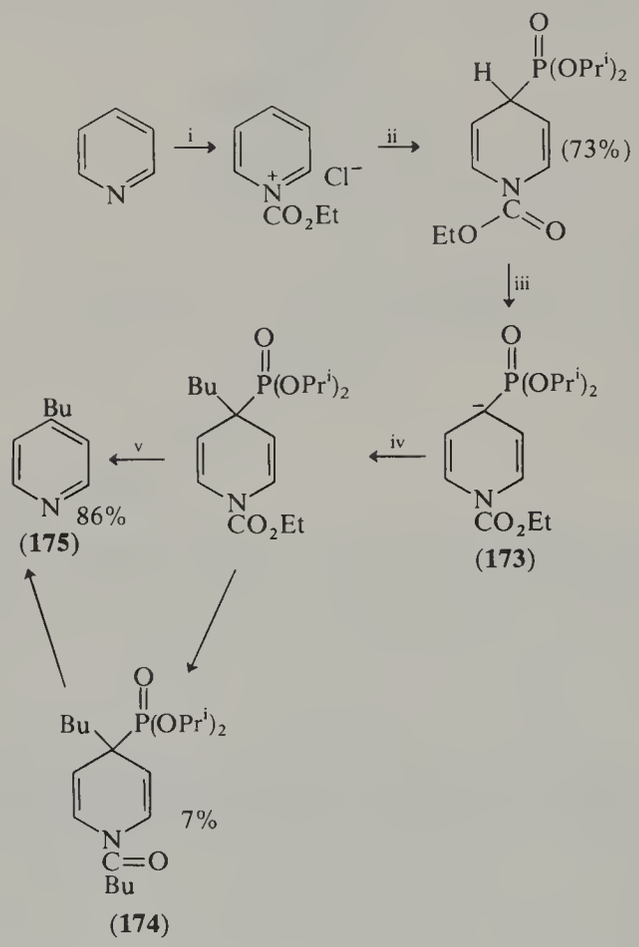
i, AcCl, MeCN, 0 °C; ii, $P(OMe)_3$; iii, NaI

Scheme 107



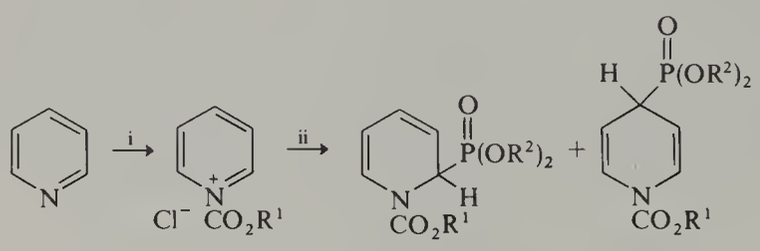
i, $ClCO_2Pr^i$, ii, $P(OMe)_3$; iii, BuLi, PhCHO; iv, HCl

Scheme 108



i, EtOCOCl; ii, $P(OPr^i)_3$; iii, BuLi, THF, −78 °C; iv, BuBr; v, BuLi (2 equiv.)

Scheme 109



i, $R^1COCOCl$; ii, $P(OR^2)_3$

Scheme 110

The work described in the next section on the family of Reissert reactions might provide a clue to the direction of future work with these interesting phosphorus derivatives of pyridine. The reactions discussed above bear direct comparison with the Reissert–Kaufmann (Scheme 106), Feely–Beavers–Tani (equations 113 and 114) and Reissert (Schemes 107–110) reactions. An analogue of the Reissert–Henze reaction has yet to be reported.

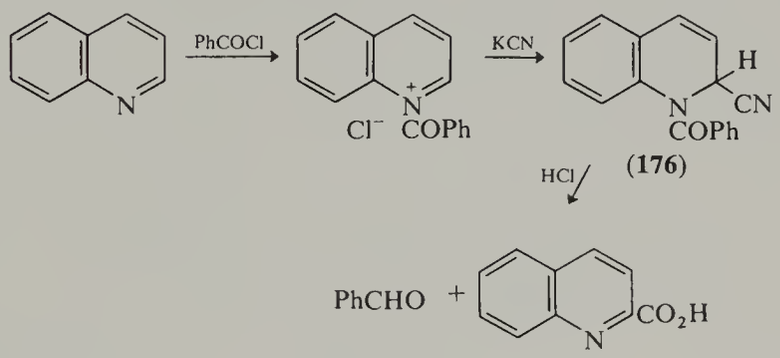
Table 17 Yields of 1,2- and 1,4-Dihydropyridinephosphonates (Scheme 110)

R^1	R^2	*Overall yield* (%)	*Ratio* 1,2- : 1,4-
2,6-Bu^t_2-4-Me-C_6H_2	Me	43	49 : 51
Et	Me	55	46 : 54
Et	Et	70	8 : 92
Et	Pr^i	73	0 : 100

2.05.4.7 Carbon Nucleophiles

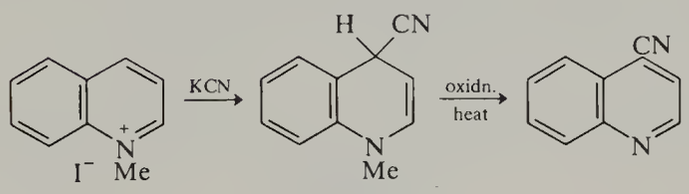
2.05.4.7.1 Cyanide

A hydrogen attached to a pyridine or pyridine 1-oxide nucleus cannot be replaced directly by cyanide; however, addition of cyanide to various quaternary salts constitutes an important class of reactions of synthetic importance. Before surveying these reactions in detail, the four main classes are outlined. In 1905, Reissert reported the first example, the reaction of quinoline with benzoyl chloride in aqueous potassium cyanide (Scheme 111) ⟨05CB1603⟩. This yielded a crystalline product, $C_{17}H_{12}N_2O$, a Reissert compound (**176**) which afforded benzaldehyde and quinaldinic acid on acid hydrolysis (Scheme 111). Kaufmann ⟨09CB3776⟩ treated a 1-methylquinolinium salt with aqueous potassium cyanide and observed 1,4- rather than 1,2-addition (Scheme 112), the Reissert–Kaufmann reaction. Reissert compounds are well known in the quinoline and isoquinoline series, but only rarely have even small yields been found in the pyridine series. On the other hand, cyanide ions add 1,4 with ease to pyridinium salts that have an electron withdrawing substituent at C-3.



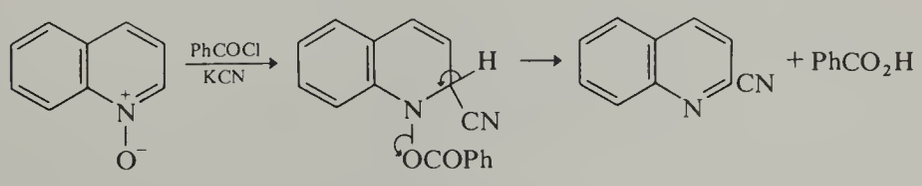
(176)

Scheme 111



Scheme 112

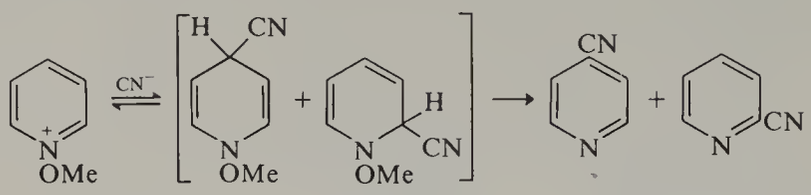
Quinoline 1-oxide reacts with benzoyl chloride and potassium cyanide to furnish 2-cyanoquinoline in good yield (Scheme 113) ⟨36CB1566⟩, the Reissert–Henze reaction. In this case, the 1,2-dihydro intermediate (**177**) is able to undergo elimination readily because initial acylation of the *N*-oxide forms a good leaving group (benzoate) on nitrogen. 1-Alkoxypyridinium salts also undergo addition–elimination reaction with aqueous potassium cyanide where the group eliminated is an alcohol (Scheme 114) ⟨59JA4004, 59CPB130⟩, the Feely–Beavers–Tani reaction. The significance of this reaction was that it



(177)

Scheme 113

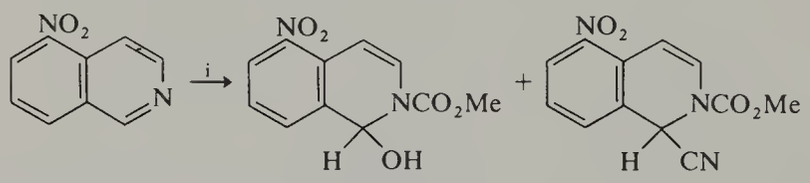
was the only one of the four reactions that was suitable for the introduction of a cyano group directly into the pyridine nucleus. A modified Reissert–Henze procedure has recently been found to provide a high yield method for the regiospecific α-cyanation of pyridines (*vide infra*) ⟨81MI20500⟩.



Scheme 114

(*i*) *Reissert reaction*

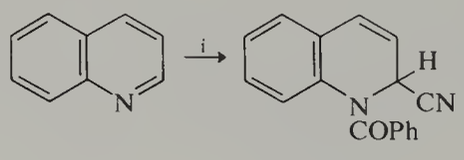
The Reissert reaction has been the subject of three major general reviews ⟨55CRV511, 68AHC(9)1, 79AHC(24)187⟩ which cover the literature to 1978. Another concentrates on the applications of Reissert compounds in isoquinoline alkaloid synthesis ⟨73H(1)165⟩. Two more are concerned with diaza aromatic systems ⟨80H(14)1033, 81BSB609⟩. Originally, Reissert compounds were prepared in aqueous media, by the slow addition of two moles of benzoyl chloride to a suspension of one mole of quinoline in aqueous potassium cyanide (method A) ⟨05CB1603⟩. This method suffers from the disadvantage that neither the substrate, *e.g.* quinoline, nor the product are soluble in water, which leads to reaction mixtures that are difficult to handle. A method was introduced that overcame these difficulties ⟨61JOC4930⟩. The acyl halide, alone or in methylene chloride, was added with vigorous stirring to a mixture of the substrate in methylene chloride and a concentrated aqueous potassium cyanide solution (method B). The methylene chloride method may be improved, particularly when competing pseudobase formation is a problem, by addition of a phase transfer agent ⟨77S497, 77H(6)1905⟩. This was impressively demonstrated by the use of benzyltrimethylammonium chloride which changed the product of the reaction (equation 115) from a low yield of pseudobase to a good yield of Reissert compound ⟨77H(6)1789⟩. The cyanide ion (soft base) is probably transferred from the aqueous to the organic phase by the benzyltrimethylammonium ion (soft acid) in preference to hydroxide (hard base). Preparation in non-aqueous media is usually carried out by employing anhydrous hydrogen cyanide in anhydrous benzene (method C) ⟨55CRV511⟩. However, a new more effective procedure has appeared ⟨77H(6)43⟩ recently in which trimethylsilyl cyanide (soluble in non-aqueous media) is used instead of potassium cyanide (method D) (equations 116 and 117). Some of the many examples of Reissert reactions that are known are given with the yield of Reissert compound in Table 18. Treatment of isoquinoline with potassium cyanide and sulfuryl chloride, which can also act as a chlorinating agent, leads to cyanochlorination rather than obtention of a Reissert compound (Scheme 115) ⟨79JCS(P1)270⟩.



(115)

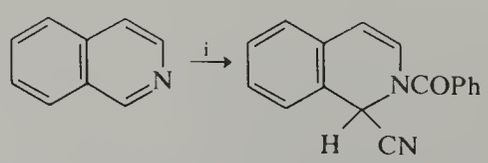
i, $ClCO_2Me$, KCN, H_2O, CH_2Cl_2 15% 2%

i, $+PhCH_2\overset{+}{N}Me_3Cl^-$ — 72%



(116)

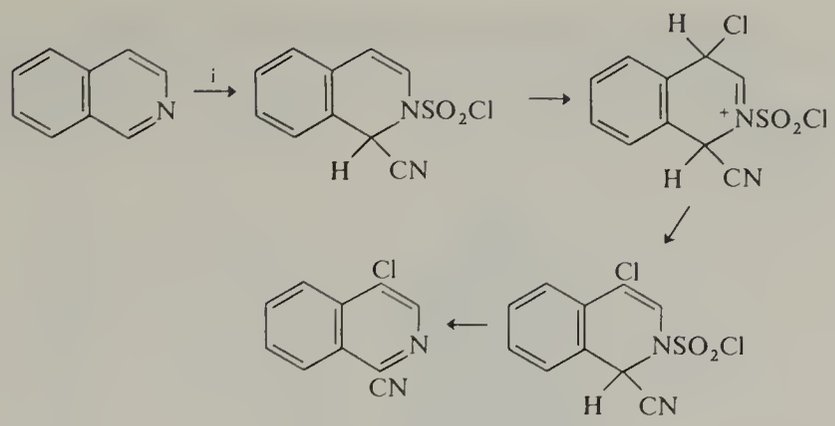
(**178**) 89%



(117)

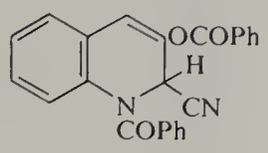
(**179**) 84%

i, $PhCOCl$, Me_3SiCN, CH_2Cl_2, $AlCl_3$(catalytic), 4 h



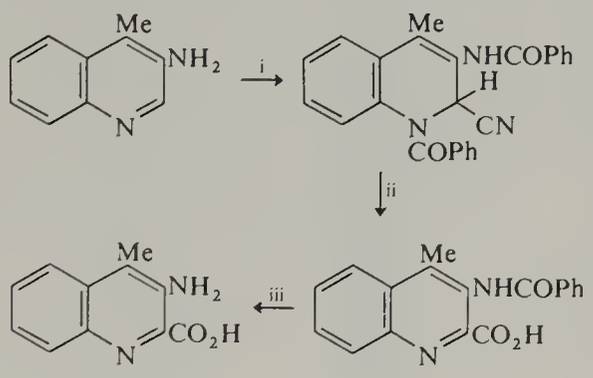
i, SO_2Cl_2 (2 mol), CH_2Cl_2, KCN aq. (5 mol), 0–5 °C

Scheme 115



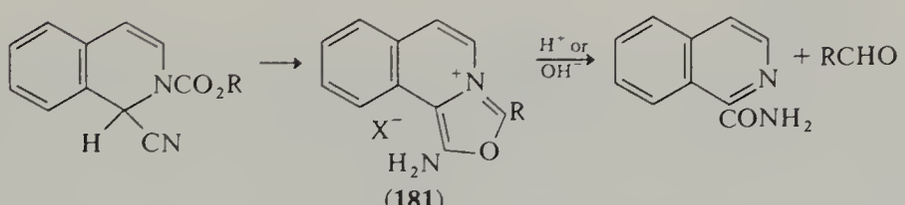
(180)

In the early days, greatest interest was focused on the acid-catalyzed hydrolysis (by hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine) of Reissert compounds to aldehydes and the corresponding heterocyclic carboxylic acid derivatives. This reaction is fairly general for compounds of quinoline (**178**) and isoquinoline (**179**) (Table 18), but it is not applicable to pyridines as they rarely form Reissert compounds. The 3-hydroxyquinoline Reissert compound does not yield benzaldehyde, probably because acylation of the 3-hydroxy group prevents formation of the required cyclic intermediate (**180**). Some nitroquinolines and isoquinolines give low yields of benzaldehyde. Rather curiously, disubstituted quinoline Reissert compounds yield less of the aldehyde than of the corresponding

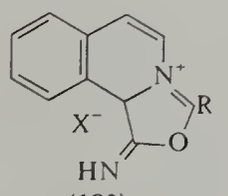


i, PhCOCl, KCN aq., CH_2Cl_2, 6–8 h; ii, HBr, HOAc; iii, hydrolysis

Scheme 116



(181)



(182)

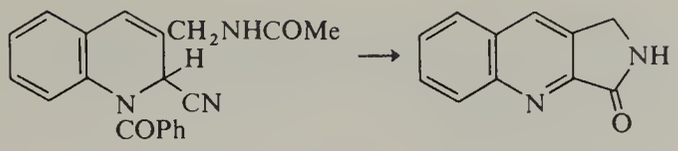
Scheme 117

Table 18 Some Examples of Reissert Compound Formation

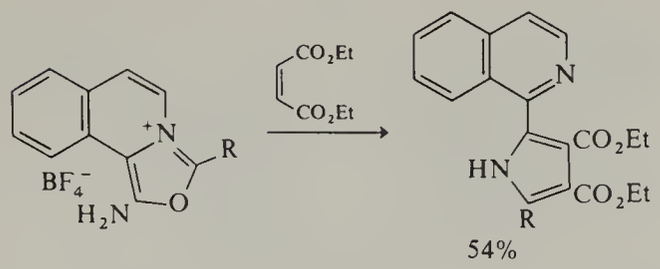
Heterocycle	*Acyl chloride*	*Method*[a]	*Yield of Reissert compound (%)*
Quinoline			
	PhCO-	A	94
	PhCO-	B	—
	PhCO-	C	87
	p-MeC_6H_4CO-	A	42
	o-ClC_6H_4CO-	C	80
	m-ClC_6H_4CO-	C	28
	p-ClC_6H_4CO-	A	26
	p-ClC_6H_4CO-	C	77
	o-$MeOC_6H_4CO$-	C	66
	p-$MeOC_6H_4CO$-	A	51
	p-$MeOC_6H_4CO$-	C	88
	o-$NO_2C_6H_4CO$-	C	80
	MeCO-	C	74
	EtOCO-	B	48
	EtOCO-	B-PTC	57
3-NH_2	PhCO-	A	0
	PhCO-	B	68
3-OH	PhCO-	B	58
3-Br	PhCO-	A	0
3-Br	PhCO-	B	15
4-Me	PhCO-	A	trace
4-Me	PhCO-	B	71
4-OMe	PhCO-	B	82
4-OH	PhCO-	A	0
4-OH	PhCO-	B	98
4-Cl	PhCO-	B	33
5-NH_2	PhCO-	A	0
5-NH_2	PhCO-	B	63
5-NO_2	PhCO-	B	19
5-OH	PhCO-	B	99
6-Me	PhCO-	A	52
6-Me	PhCO-	B	99
6-OMe	PhCO-	A	88
6-OMe	PhCO-	B	89
6-OH	PhCO-	B	99
6-Br	PhCO-	A	40
6-Br	PhCO-	B	48
6-NH_2	PhCO-	B	95
6-NO_2	PhCO-	A	0
6-NO_2	PhCO-	B	29
7-Me	PhCO-	A	54
7-Me	PhCO-	B	64
7-OH	PhCO-	B	89
7-NO_2	PhCO-	B	17
4,6-Me_2	PhCO-	A	0
4,6-Me_2	PhCO-	B	94
4,7-Cl_2	PhCO-	A	0
4,7-Cl_2	PhCO-	B	34
4-Cl-6-OMe	PhCO-	B	87
Isoquinoline			
	PhCO-	A	72
	PhCO-	B	69
	PhCO-	D	84

[a] See text.

quinolinic acid. Newer methods have superseded the Reissert reaction as a synthetic approach to aldehydes. Nevertheless, it still finds some uses for synthesis of the heterocyclic product, for example 3-aminoquinaldinic acids (Scheme 116) ⟨77JHC1053⟩, or cyclic products (equation 118) ⟨71CPB1971⟩. The mechanism of acid-catalyzed hydrolysis has been studied, and the isolable intermediate cation has been shown to have the 5-aminooxazolium tautomeric form (**181**) rather than (**182**), as formerly thought (Scheme 117) ⟨77JA165⟩. Reissert compounds undergo cycloadditions with dipolarophiles (equation 119) ⟨79JOC111⟩, but these are considered as substituent reactions (see Chapter 2.06).

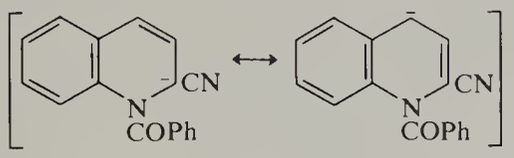


(118)

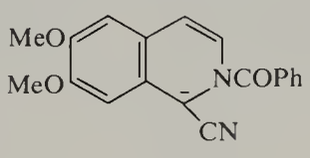


(119)

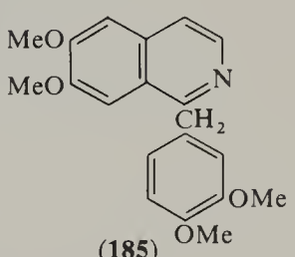
Current interest in Reissert compounds centres on their anions, especially those of isoquinolines which on alkylation afford valuable isoquinoline alkaloids or their precursors. Impetus has been given to the study of this class of alkaloids as several of its members have potent antitumor activity. Therefore, discussion in this section will concentrate on isoquinolines. Anions (**183**) and (**184**) of Reissert compounds are best generated by use of sodium hydride in DMF ⟨68AHC(9)1⟩. Treatment of the anion (**184**) with 3,4-dimethoxybenzyl chloride yields papaverine (**185**; 22%) ⟨57JA3773⟩. The same anion undergoes reaction with a dihalide to offer a means of direct entry into the bis-benzylisoquinoline alkaloid system (Scheme 118) ⟨76JHC573⟩. Note in the last step how use of sodium borohydride ensures reduction of just the pyridine rings. Suitably substituted Reissert compounds undergo cyclization in the presence of sodium hydride in DMF to give tricyclic products (equation 120). Quinoline Reissert compounds behave similarly ⟨79AHC(24)187⟩. Poly(vinylbenzyl chloride) ⟨79AHC(24)187⟩ and allyl chloride ⟨78JPS740⟩ react with Reissert compound anions to furnish (**186**) and (**187**), respectively, after basic hydrolysis (with rearrangement in the latter case) (Scheme 119). Arylation of isoquinolines and quinolines may also be accomplished by this route when fairly reactive aryl halides are used. Rather interestingly, quinoline reacts at C-4 rather than at C-2 (equation 121) ⟨69CJC3261⟩. Reaction of these anions with carbonyl compounds is also a facile reaction which probably follows the course shown (Scheme 120), and provides a good route to a number of isoquinoline alkaloids ⟨73H(1)165⟩. Michael reactions are well documented, and suitable adducts can undergo cyclization (equation 122) ⟨71JA4479⟩. These types of reactions have been extended to quinoline Reissert compounds which have a blocking group at C-4, to afford pyrrolo[1,2-*a*]quinolines and an open chain ketone (Scheme 121) ⟨77JCS(P1)2018⟩. However, yields are not as good as those from the corresponding reactions in the isoquinoline series.



(**183**)

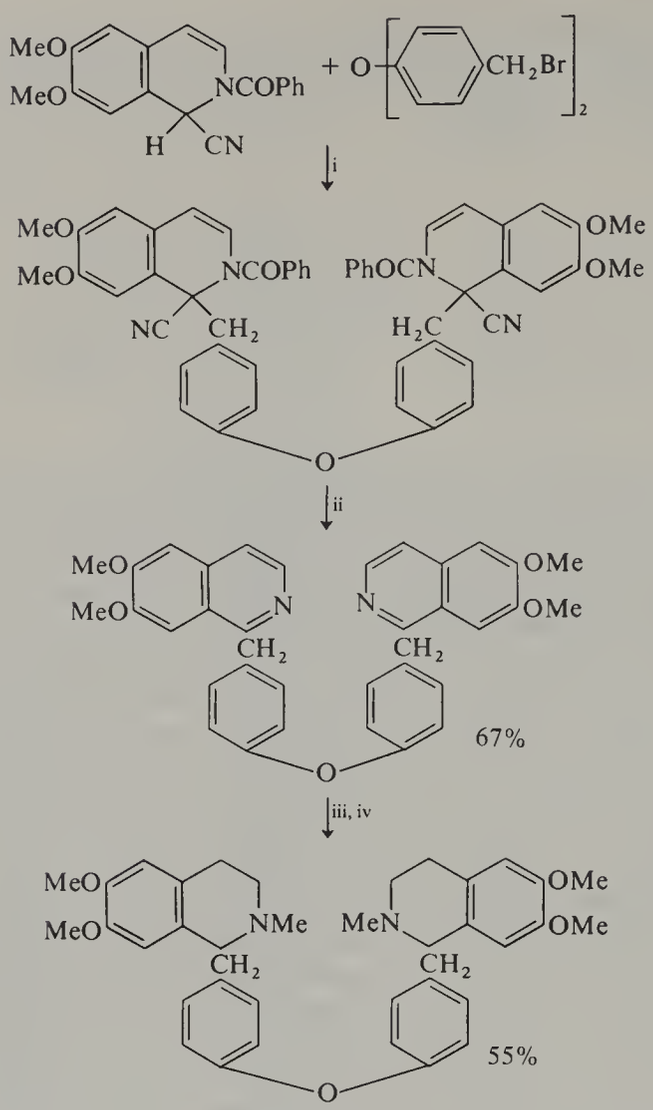


(**184**)



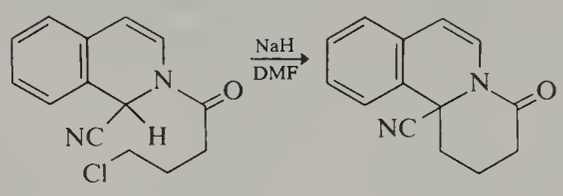
(**185**)

Rearrangement of the acyl group from N to C to give a ketone (**188**) can be induced by treatment of Reissert compounds with sodium hydride in DMF in the absence of a competing electrophile ⟨79AHC(24)187⟩. Reissert derivatives form chlorohydrins on treatment with aqueous hypochlorous acid. These undergo base-induced rearrangements to isochromenes and other isoquinolines (Scheme 122) ⟨79JCS(P1)1298⟩. Hydrogenation (over Raney nickel) and reduction (with sodium borohydride) of Reissert compounds takes place in the heterocyclic ring. Oxidation of isoquinoline Reissert compounds with TTN in methanol results in addition to the 3,4-double bond (equation 123). Similar treatment of quinoline Reissert compounds provided a surprise. Two examples, (**189**) and **190**), underwent ring contraction to indole-3-carbaldehydes on reaction with TTN in TMOF (trimethyl orthoformate) (Scheme 123) ⟨78H(11)481⟩, which provides a rare example of ring contraction of a Reissert compound to an indole derivative (*vide infra*). In contrast, (**191**) undergoes oxidative debenzoylation (Scheme 124). The mechanism of these reactions probably involves initial coordination of the Reissert compound with TTN at the C=C bond and/or the

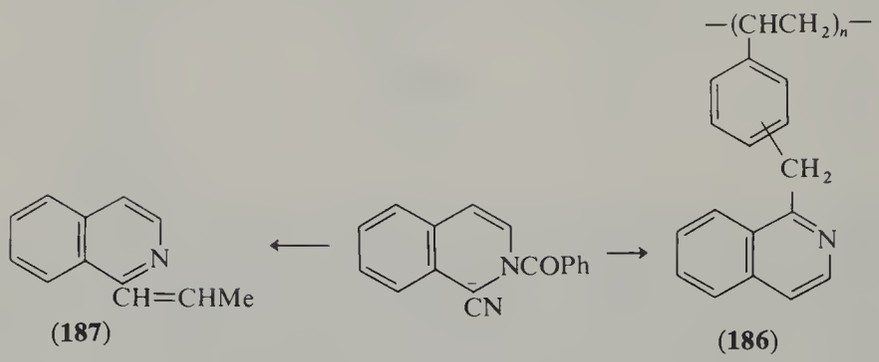


i, NaH, DMF; ii, KOH, EtOH, H_2O; iii, MeI, MeOH; iv, $NaBH_4$, MeOH, H_2O

Scheme 118

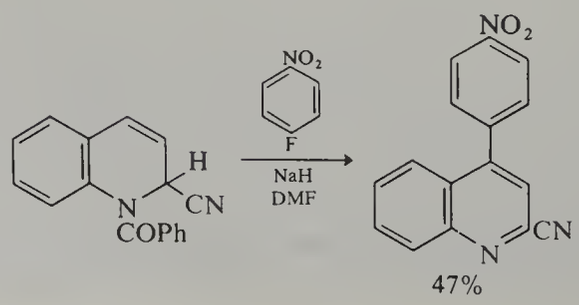


(120)



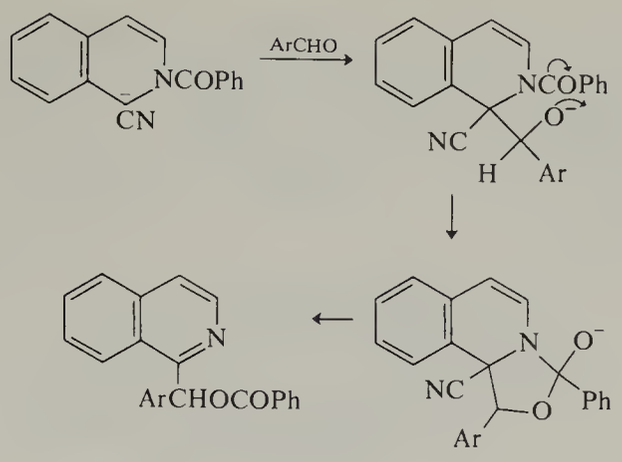
(187) **(186)**

Scheme 119

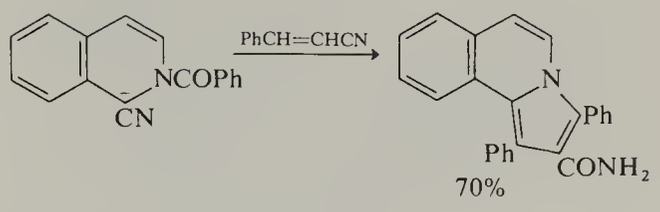


47%

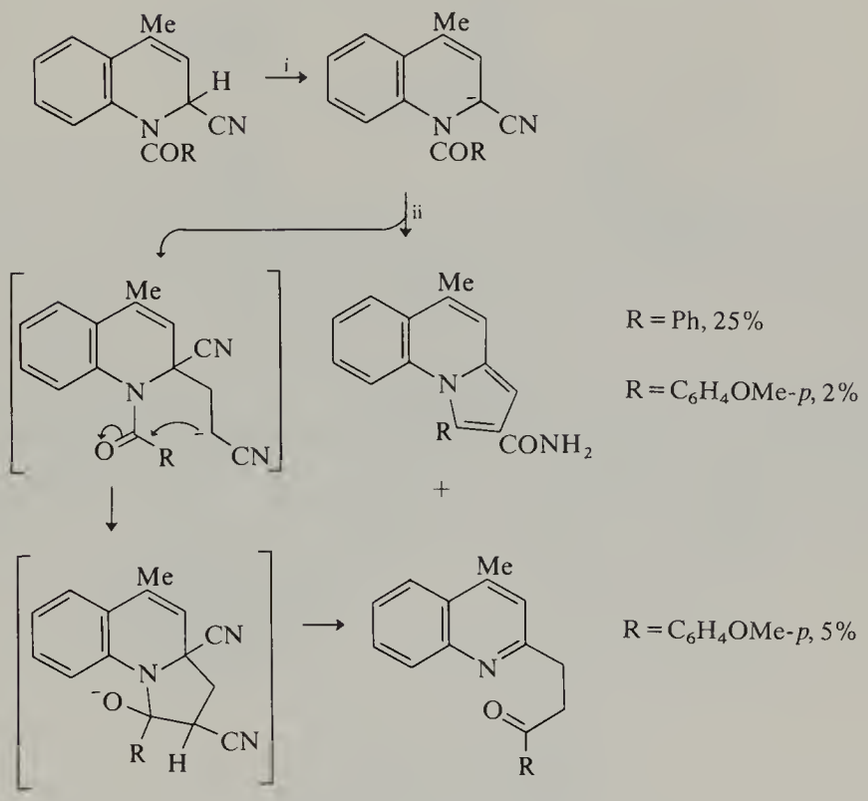
(121)



Scheme 120



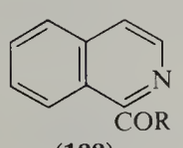
(122)



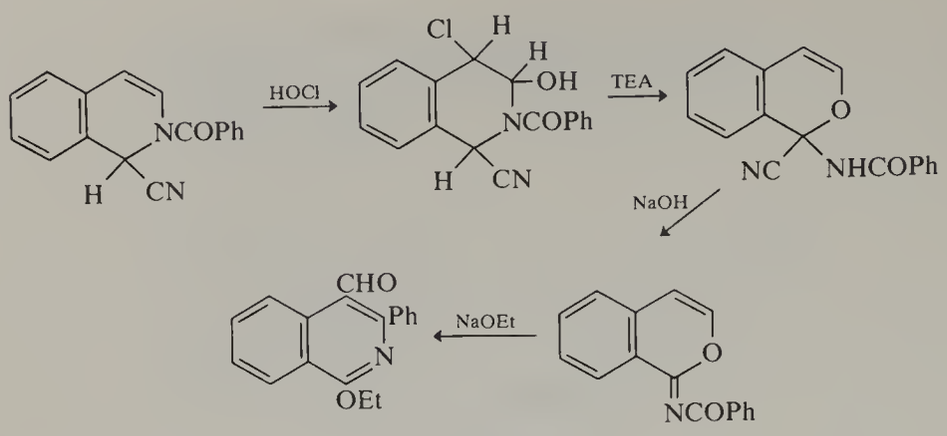
i, NaH, DMF, −30 °C; ii, CH_2=CHCN

Scheme 121

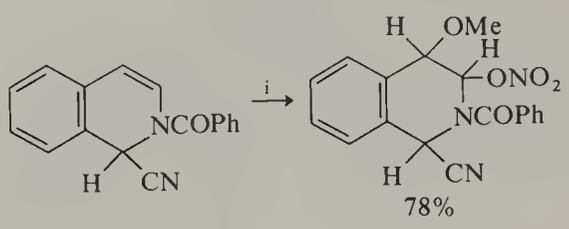
benzoyl group. The difference in behavior was attributed to the effect of an electron-donating group attached at C-7 which favors coordination of TTN at the double bond in (**189**) and subsequent ring contraction in the former case. Electron donating groups at the 6-position promote the elimination of methyl benzoate and thallium(I) nitrate from (**192**; Scheme 124). The isoquinoline Reissert compound (**193**) undergoes oxidation with molecular oxygen to form a 1-cyanoisoquinoline with preservation of the 3,4-double bond (equation 124) ⟨78H(11)1345⟩.



(**188**)

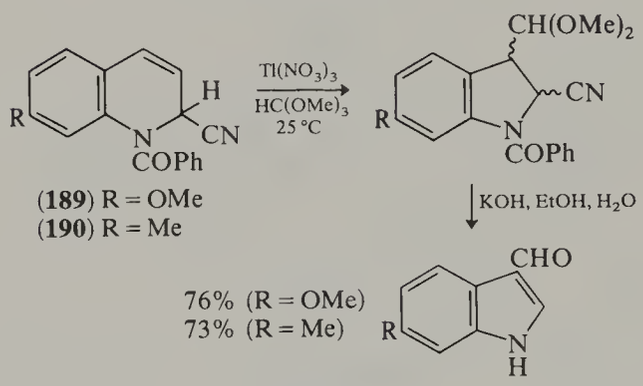


Scheme 122

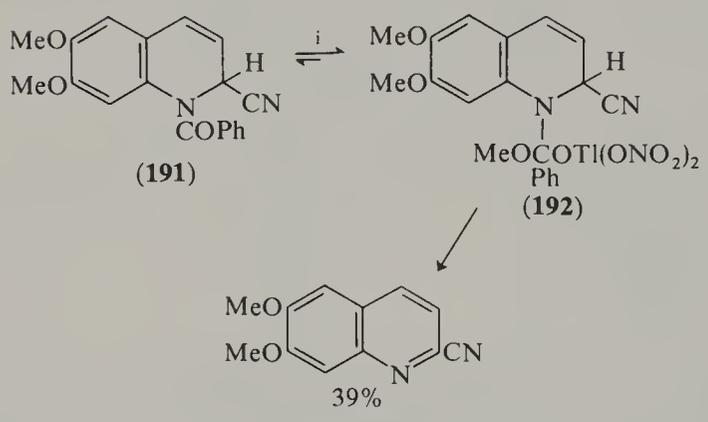


(123)

i, TTN, MeOH, 2–3 h, r.t.



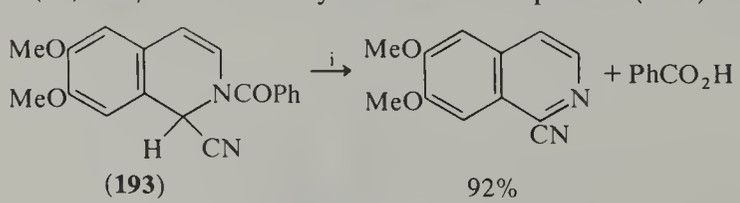
Scheme 123



i, TTN, TMOF, MeOH, 24 h, 50 °C

Scheme 124

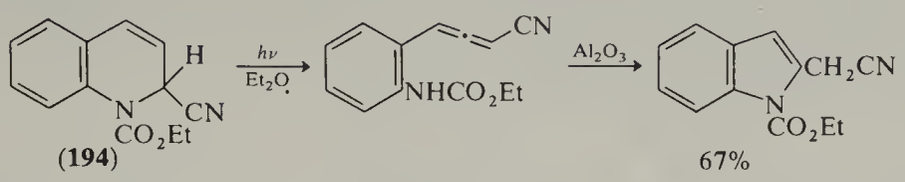
The photochemistry of Reissert compounds truly belongs in Section 2.05.8, but it is discussed here to avoid fragmentation. Irradiation of the cyano ester (**194**) in diethyl ether followed by chromatography on alumina yields ethyl 2-cyanomethylindole-1-carboxylate (Scheme 125) ⟨76JCS(P1)2587⟩. The 1-acetyl Reissert compound (**195**) affords a mixture of



(124)

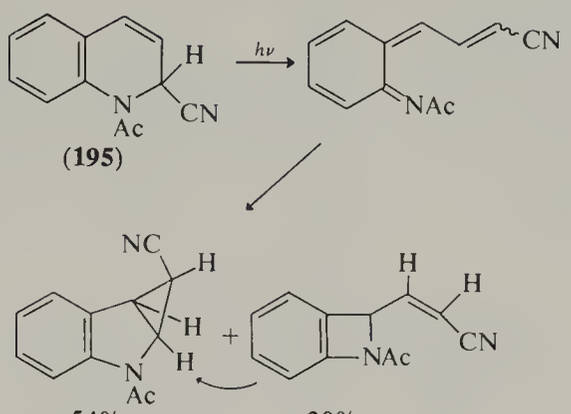
i, O_2, CH_2Cl_2, $PhCH_2\overset{+}{N}Me_3Cl^-$, 50% NaOH aq.

an *N*-acetylbenzoazetidine (**196**) and (**197**) on photolysis in diethyl ether (Scheme 126) ⟨75CC575⟩.



(**194**)

Scheme 125



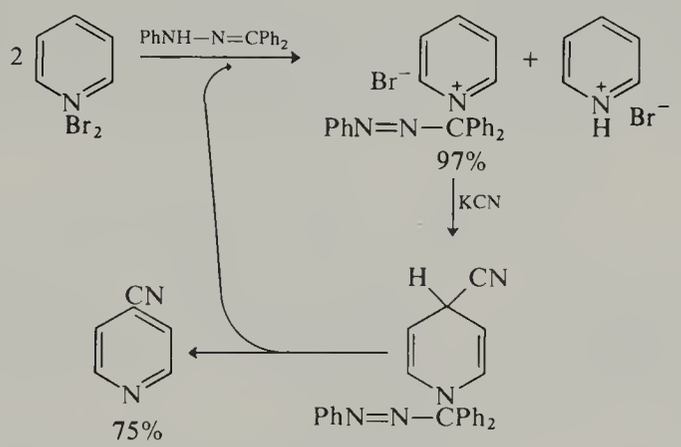
(**195**) (**197**) (**196**)

Scheme 126

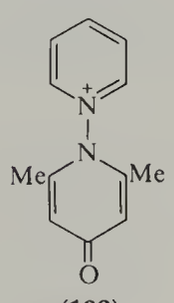
(ii) With alkyl quaternary salts

The reaction of alkyl quaternary salts of pyridine and its benzo analogues with cyanide ion and subsequent loss of the alkyl substituent is known as the Reissert–Kaufmann reaction (Scheme 112). It is not of as much importance for heterocyclic cyanations or alkylations as the other reactions described in this section, chiefly because the *N*-substituent is such a poor leaving group.

Recently, two types of *N*-substituent (a phenylhydrazone and a pyridinone) have been found to be good leaving groups. Benzophenone phenylhydrazone has been employed in a process in which it is recyclable, and which provides a high yield method for regiospecific 4-cyanation (Scheme 127) ⟨80S694⟩. Katritzky's N—N linked heterocycle approach using (**198**) also leads to 4-cyanation ⟨79JCS(P1)1698⟩; see Section 2.05.4.7.3 for a discussion.

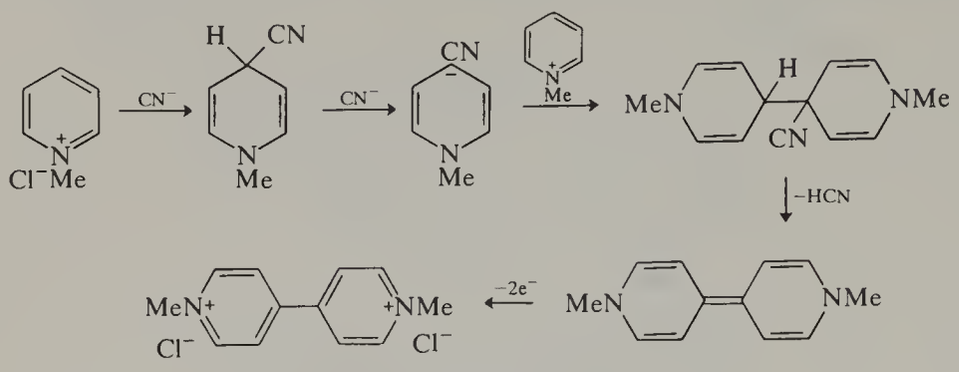


Scheme 127

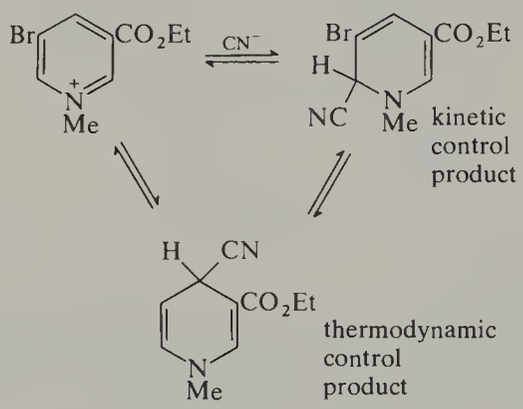


(**198**)

The heterocyclic equivalent of the benzoin condensation offers a route to the important herbicide 'paraquat' (Scheme 128) ⟨73JOC3993⟩ (see also Section 2.05.7). *N*-Alkylnicotinic acid and its derivatives readily undergo addition of cyanide and many other nucleophiles (see Section 2.05.4.8). In the example shown in Scheme 129, 1,2-addition is subject to kinetic, and 1,4-addition to thermodynamic, control.



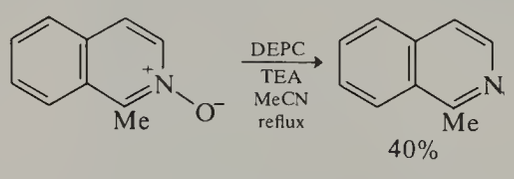
Scheme 128



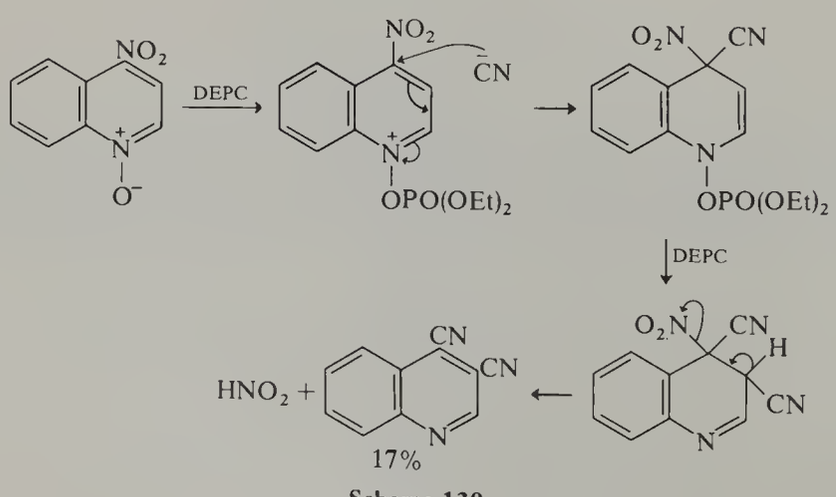
Scheme 129

(iii) With N*-oxides and alkoxy quaternary salts*

The Reissert–Henze and the Feely–Beavers–Tani reactions are considered together in this section because of their similarity. The former involves cyanation of acyloxy (formed *in situ*) (Scheme 113), and the latter alkoxy (Scheme 114), quaternary salts. The Reissert–Henze reaction is a facile, fairly general reaction for quinoline and isoquinoline *N*-oxides (Table 19) with cyanation occurring α to the ring nitrogen. Certain substituents inhibit reaction, for example a 1-methyl group (equation 125), and others undergo replacement (Scheme 130) ⟨81H(15)981⟩. Reaction of 1-methylisoquinoline 2-oxide with benzoyl chloride



(125)



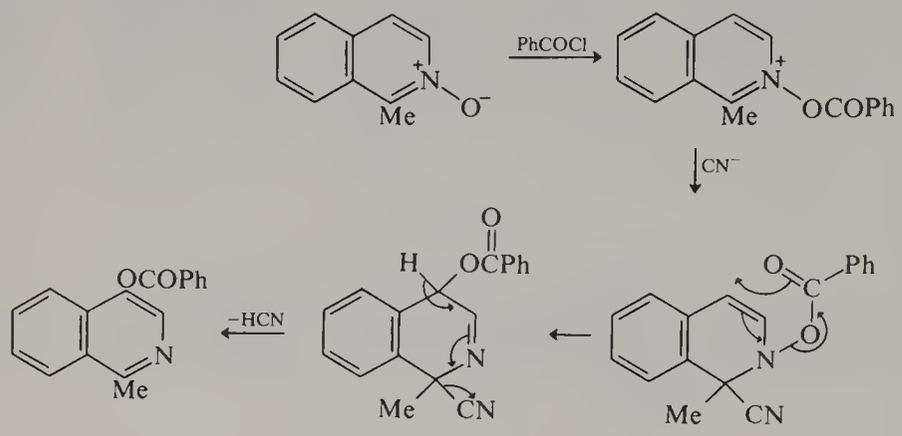
Scheme 130

Table 19 Reaction of *N*-Oxides with Cyanide Ions; Reissert–Henze Reactions

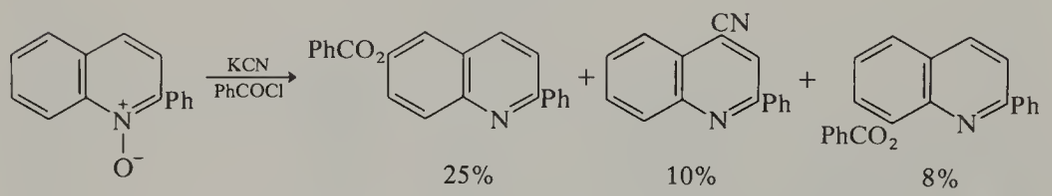
N-Oxide Substituent (mol)	*Acyl halide* (mol)	*Cyanide source* (mol)	*Conditions*	*% Yield of products*[a] *2-CN*	*4-CN*	*6-CN*	*Ref.*
Pyridine							
none (1)	AcCl (1)	Me_3SiCN (1)	CH_2Cl_2, 24 h, r.t.	<10	—	—	81MI20500
none (1)	PhCOCl (1)	Me_3SiCN (1)	CH_2Cl_2, 15 min, r.t.	30	—	—	81MI20500
none (1)	PhCOCl (2)	Me_3SiCN (5)	CH_2Cl_2, 1 h, r.t.	100	—	—	81MI20500
none (1)	EtOCOCl (1)	Me_3SiCN (1)	CH_2Cl_2, 24 h, r.t.	40	—	—	81MI20500
none (1)	Me_2NCOCl (1)	Me_3SiCN (1)	CH_2Cl_2, 48 h, r.t.	100	—	—	81MI20500
none (1)	Ph_2NCOCl (1)	Me_3SiCN (1)	CH_2Cl_2, 4 d, r.t.	79	—	—	81MI20500
none (1)	$(PhO)_2POCl$ (1)	Me_3SiCN (1)	CH_2Cl_2, 4 d, r.t.	27	—	—	81MI20500
none	TsCl	KCN	EtOH aq.	18.3	—	—	60YZ269
none (1)	—	DEPC[b] (3)	MeCN, 18 h, reflux	24.5	—	—	81H(15)981
2-Me (1)	Me_2NCOCl (1)	Me_3SiCN (1)	CH_2Cl_2, 2 d, r.t.	—	—	100	81MI20500
3-Me (1)	Me_2NCOCl (1)	Me_3SiCN (1)	CH_2Cl_2, 2 d, r.t.	91	—	6	81MI20500
4-Me (1)	Me_2NCOCl (1)	Me_3SiCN (1)	CH_2Cl_2, 2 d, r.t.	100	—	—	81MI20500
4-Cl	PhCOCl	KCN aq.	—	63	—	—	45YZ7
4-NO_2	PhCOCl	KCN aq.	—	—[c]	—	—	45YZ7
4-OEt	PhCOCl	KCN aq.	—	—[c]	—	—	45YZ7
2-CF_3	PhCOCl	KCN aq.	$CHCl_3$, 3 h, r.t.	63	—	—	69CPB510
3-CF_3	PhCOCl	KCN aq.	$CHCl_3$, 6 h, r.t.	17	—	48	69CPB510
4-CF_3	PhCOCl	KCN aq.	$CHCl_3$, 7 h, r.t.	72	—	—	69CPB510
Quinoline							
none	PhCOCl	KCN aq.	—	60–90	—	—	B-71MI20500
— (1)	—	DEPC[b] (3)	MeCN, TEA (1), 18 h, reflux	57	—	—	81H(15)981
2-Cl (1)	PhCOCl	DEPC[b] (3)	MeCN, TEA (1), 18 h, reflux	40	—	—	81H(15)981
6-Cl	PhCOCl	KCN aq.	—	77	—	—	B-71MI20500
7-Cl	PhCOCl	KCN aq.	—	75	—	—	B-71MI20500
6-OEt	PhCOCl	KCN aq.	—	70	—	—	B-67MI20501
5-NO_2	PhCOCl	KCN aq.	—	65	—	—	B-71MI20500
6-NO_2	PhCOCl	KCN aq.	—	77	—	—	B-71MI20500
Isoquinoline							
none (1)	—	DEPC[b] (3)	MeCN, TEA (1), 18 h, reflux	81[d]	—	—	81H(15)981
5-OH	PhCOCl	KCN	—	53[d]	—	—	62JOC4571

[a] Cyano compounds produced were sometimes isolated as the corresponding amide or carboxylic acid.
[b] DEPC, diethyl phosphorocyanidate.
[c] Starting *N*-oxide recovered.
[d] 1-CN.

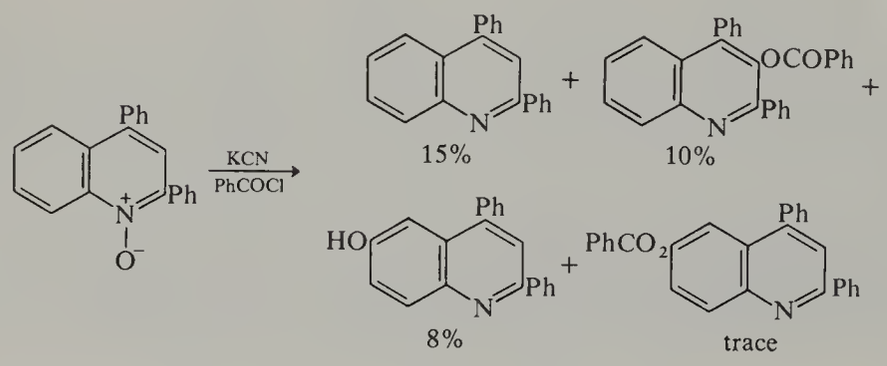
and potassium cyanide can result in a rearrangement (Scheme 131) ⟨79H(12)837⟩. When the 2-position of quinoline 1-oxide is blocked by a substituent that is a poor leaving group, cyanation occurs at C-4; however, rearrangements of the *N*-benzoyloxy group are also known (equation 126) ⟨66YZ59⟩. 2,4-Diphenylquinoline 1-oxide, where the 2- and 4-positions are blocked, does not undergo cyanation; instead, rearrangements of the benzoyloxy group take place (equation 127) ⟨60CPB487⟩. Treatment of phenanthridine 5-oxide with benzoyl chloride and aqueous potassium cyanide affords mainly phenanthrid-6-one, presumably by pseudobase involvement. This competitive pathway may be eliminated by using DEPC under non-aqueous conditions (Scheme 132) ⟨81H(15)981⟩, and 6-cyanophenanthridine is formed in good yield.



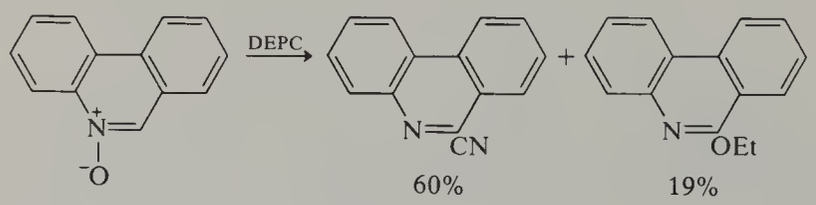
Scheme 131



(126)



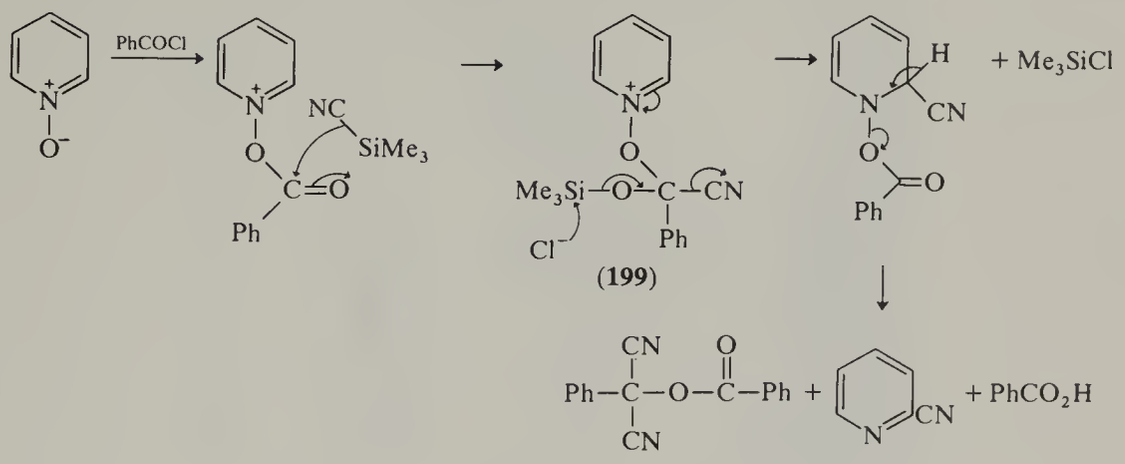
(127)



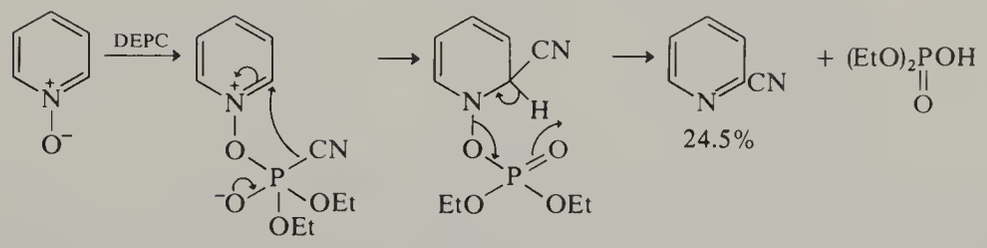
Scheme 132

4-Chloropyridine 1-oxide was found to give quite a good yield of 2-cyano-4-chloropyridine on reaction with benzoyl chloride and aqueous potassium cyanide. On the other hand, 4-nitro- and 4-ethoxy-pyridine 1-oxide, and pyridine 1-oxide itself, did not cyanate under these conditions ⟨45YZ7⟩. Until recently, it was widely held ⟨74HC(14-S2)1⟩ that with few exceptions (Table 19) pyridine 1-oxides did not normally undergo Reissert–Henze reaction. This seemed strange as the closely related Feely–Beavers–Tani reaction is general for *N*-alkoxy (instead of *N*-acyloxy) quaternary pyridinium salts. However, pyridine 1-oxides have recently been found to undergo the Reissert–Henze reaction very readily, and sometimes in quantitative yield, when the reaction is carried out in a non-aqueous medium (Scheme 133) ⟨81MI20500⟩. The salt (**199**), formed by silylation of the *N*-benzoyloxy intermediate, decomposes in the presence of chloride ions. The cyanide which is displaced

probably attacks the α-position intramolecularly, as no γ-cyanation has been found. The dicyano ester is formed as a byproduct by dimerization of benzoyl cyanide (formed in the reaction) and subsequent rearrangement. When TEA is added to facilitate the last step, these reactions proceed faster and in some cases quantitatively. Pyridine 1-oxide may also be cyanated in lower yield by either tosyl chloride and potassium cyanide, or DEPC. DEPC acts as both acylating agent and cyanide source, and cyanation almost certainly takes place intramolecularly (Scheme 134). Only two examples of the cyanation of 3-substituted pyridine 1-oxides appear in Table 19. 3-Methylpyridine 1-oxide quite predictably undergoes substitution predominantly at C-2, whereas the 3-trifluoromethyl analogue reacts preferentially at C-6 to ultimately afford the amido derivative. It will be seen later (Table 20) that the 3-cyano-1-methoxypyridinium salt gives almost as much C-2 as C-6 product in the Feely–Beavers–Tani reaction. Further examples of the cyanation of 3-substituted precursors by the two methods should prove interesting.

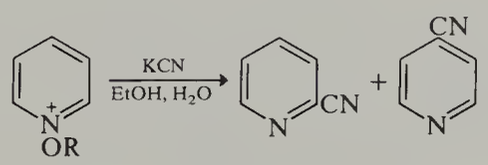


Scheme 133



Scheme 134

Okamoto and Tani ⟨59CPB130⟩ and Feely and Beavers ⟨59JA4004⟩ independently discovered that *N*-alkoxy quaternary salts give α- and γ-cyano derivatives and an alcohol, on reaction with cyanide ion. These reactions are usually carried out by adding an aqueous solution of the quaternary salt to an excess (*ca.* three-fold) of sodium or potassium cyanide dissolved in water (or ethanol, aqueous ethanol or dioxane) at *ca.* −5 °C. The reaction mixture (pH ~ 11) is allowed to come to room temperature and stirred for a further 3 h (or more) at room temperature (or higher). The reaction conditions have a critical bearing on the orientation of substitution. In general, higher reaction temperature or a more polar solvent raises the amount of 4-substitution. Increase in the size of the *N*-alkoxy group also promotes 4- at the expense of 2-cyanation (Scheme 135).



4 : 1 20 °C, 30 min	%	%
R = Me	72	17
R = Et	20.5	58
R = Bu^n	23	50

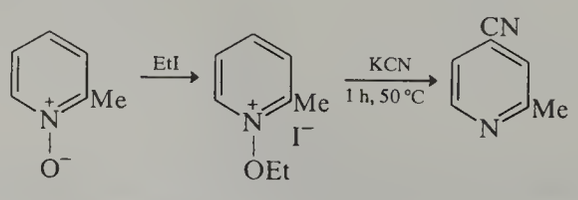
Scheme 135

Recently, these principles have been put to good use in the synthesis of 4-cyano-2-methylpyridine in 60% yield from 1-ethoxy-2-methylpyridine (Scheme 136) ⟨81JHC1349⟩.

Table 20 Reaction of *N*-Methoxy Quaternary Salts with Cyanide Ions

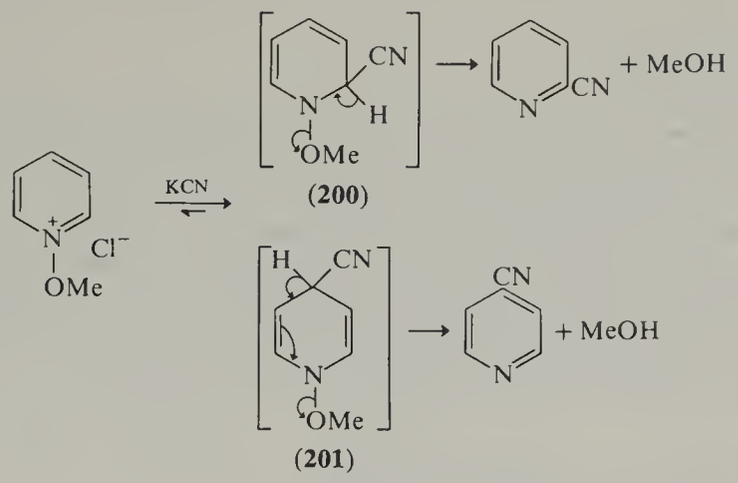
Salt *Substituent*	*Yield of products* (%) 2-*CN*	4-*CN*	6-*CN*
Pyridinium			
none	48–49	24–32	—
2-Me	—	10–18	45–48
3-Me	30–36	6–15	6
4-Me	40	—	—
2,4-Me_2	73	—	—
2,6-Me_2	(6-CH_2CN)33	15	0
2-Et	—	10.6	19.2
4-Et	30	—	—
2-Cl	—	—	47
4-Cl	56	—	—
3,5-Br_2	70	—	—
2-CN	84	—	—
3-CN	28	—	18
4-CN	54–70	—	—
2-OMe	—	—	15
3-OMe	68	—	—
4-OMe	40	—	—
2-COMe	—	—	50
4-COMe	69	—	—
2-CO_2Me	50	—	—
3-CO_2Me	19	32	—
3-CO_2Et	19	32	—
4-CO_2Me	69	—	—
4-NO_2	54	—	—
2-Me-4-NO_2	—	—	54
3-Me-4-NO_2	86	—	—
5-Et-2-Me-4-NO_2	82	—	—
Quinolinium			
none	71	trace	—
2-Me	—	7	—
4-Me	65	—	—
Isoquinolinium			
none	(1-CN) 49	—	—

This compares with a 15% yield of the same compound from the methoxy quaternary salt at room temperature (Table 20). A high pH (>11) is essential for success in these reactions, to ensure proton loss in the last (rate determining) step (Scheme 137). Note that the dihydro intermediates (**200**) and (**201**) are formed in a reversible first step. Results for related cyanations are listed in Table 20. Electron-withdrawing substituents attached at C-2 or C-4 facilitate reaction and electron-donating groups have the opposite effect. A substituent at C-3 (with the exception of a 3-carboxylic ester) directs the incoming cyanide ion predominantly to the 2-position, although as already pointed out the 3-cyano salt gives an appreciable amount of 6-substitution. A problem with the *N*-alkoxy quaternary salt approach is competition from path **A** (*vide supra*) under the very basic conditions used for cyanation. Path **A**, in principle, could be suppressed by replacing active hydrogens in the alkoxy substituent by alkyl groups. However, such quaternary salts are hard to make, and in these salts steric effects would tend to direct cyanation to C-4 rather than to C-2 or C-6. Difficulties of the above nature have been circumvented by employing more reactive halo esters and halo acids as alkylating agents. For instance, the salt (**202**) gives a good yield of 2-cyanopyridine (equation 128) on reaction with aqueous potassium cyanide. Replacement of just one active hydrogen, by phenyl, is not sufficient as the carboxylic ester group increases



Scheme 136

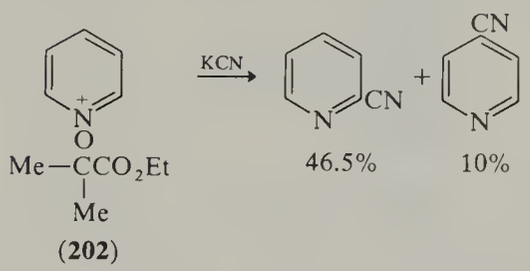
the acidity of the remaining hydrogen and thus facilitates path **A** (equation 129). Betaine formation under the basic conditions of reaction can reduce yields of cyano products in the case of acid derivatives.



(200)

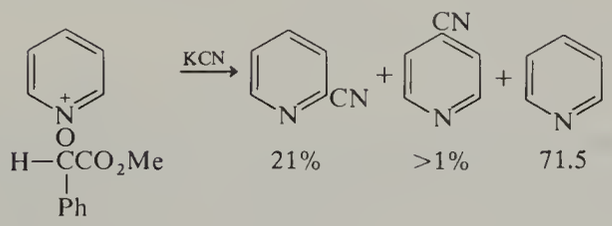
(201)

Scheme 137



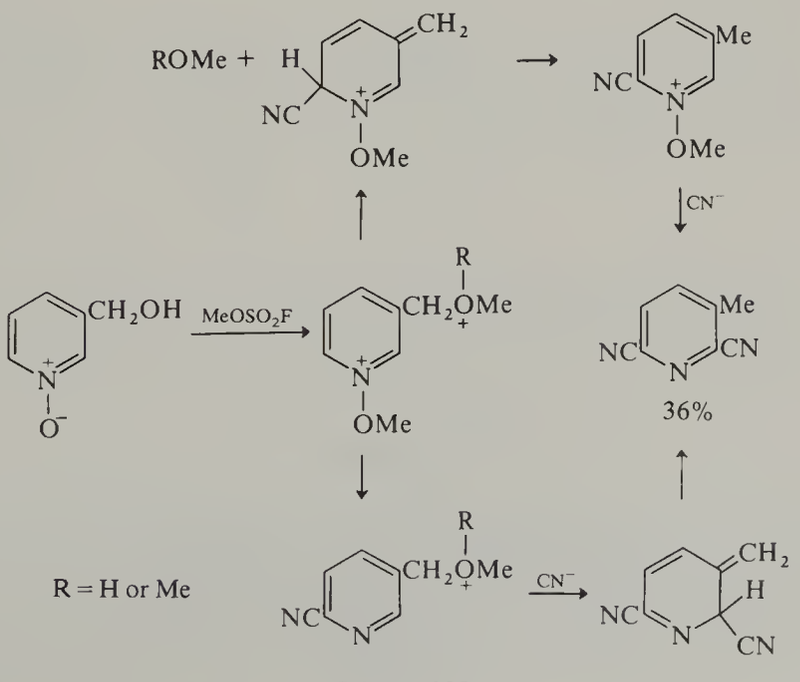
(128)

(202)



(129)

The reaction of 3-hydroxymethylpyridine 1-oxide with methyl fluorosulfonate and potassium cyanide provides a direct method for 2,6-dicyanation ⟨75JOC2092⟩. However, the generality of this method is limited by the need for a 3-substituent that can form an anhydrobase. In this example (Scheme 138) the anhydrobase is formed by methylation of the 3-hydroxymethyl group followed by elimination either during or subsequent to attack by the second mole of cyanide. The use of such a powerful methylating agent overcomes



Scheme 138

the reluctance of a methyl group at C-3 (compared with C-2 or C-4) to give an anhydrobase by proton loss.

2.05.4.7.2 Organometallics

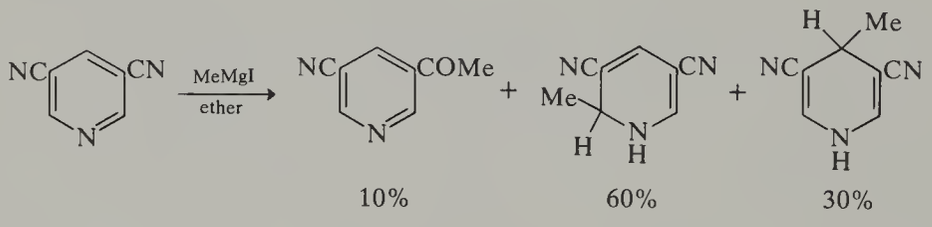
Pyridine and quinoline undergo alkylation by Grignard reagents chiefly at the α-position, although there appear to be some exceptions (Table 21) ⟨B-74MI20503⟩. Yields with pyridines are low, but reaction is facilitated by the attachment of two electron-withdrawing groups (equation 130) ⟨66AHC(6)229⟩ or benzene ring annelation. Alkylation of quinoline with allylmagnesium chloride affords 2-allylquinoline in good yield, but this product is accompanied by 2-*n*-propylquinoline, formed by bond isomerization (Scheme 139) ⟨59JA4000⟩.

Table 21 Reaction of Pyridines with Grignard Reagents

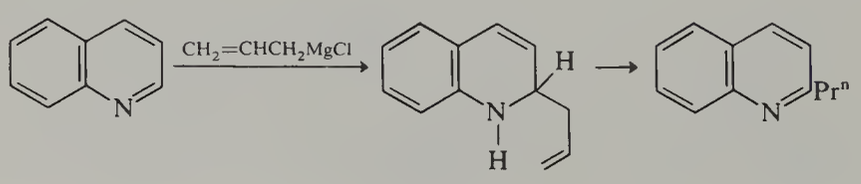
Heterocycle	*Reagent (RMgHal)*	*Yield of products (%)* 2-*R*	4-*R*
Pyridine	EtMgBr	45	—
	Bu^nMgI	18	—
	Bu^sMgBr	6	3
	$CH_2{=}CHCH_2MgBr$	—	9
	$PhCH_2MgCl$	1.5	6.5
	PhMgBr	44	—
3-CN	Pr^nMgBr	—	22[a]
Quinoline	$CH_2{=}CHCH_2MgBr$	80[b]	—
	PhMgBr	66	—

[a] 4-*n*-Propyl-3-pyridyl *n*-propyl ketone.
[b] Contaminated with 2-*n*-propylquinoline.

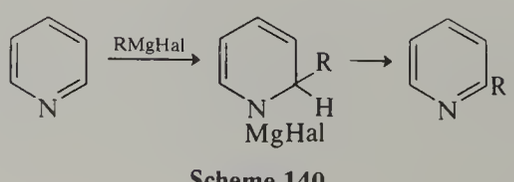
These and other results ⟨66AHC(6)229⟩ gave a confusing picture regarding 2- *versus* 4-alkylation, but the situation has been clarified ⟨76JCS(P1)1977⟩. Pyridine reacts with ether-free alkylmagnesium halides in the absence of free metals to give 2-alkylpyridines by a mechanism similar to that of the Chichibabin reaction (Scheme 140). However, if free metals are present some 4-alkylation is observed as well. When the reaction is carried out with pyridine and *n*-butylmagnesium iodide (which contains no excess magnesium) in toluene a 22% yield of *n*-butylpyridines (2-:4- >100:1) can be obtained. Under comparable conditions, but in the presence of free magnesium (100 atom %), the predominance of the 2-product over the 4- drops to 3:1. The effect of free magnesium has been used to obtain almost regiospecific 4-alkylation.



(130)

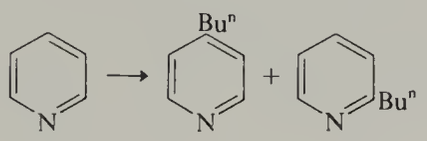


Scheme 139



Scheme 140

4-*n*-Butylpyridine (containing <0.5% of the 2-isomer) can be prepared (57% yield) by reaction of *n*-butyl chloride and magnesium in boiling pyridine (equation 131). The chloride is preferred as it quaternizes the pyridine nitrogen less readily than the other halides. Other metals (lithium, sodium, calcium, zinc and aluminum) are able to help effect this reaction. A plausible mechanism for these 4-alkylation reactions is illustrated in Scheme 141, by reference to the reaction of pyridine with *n*-butyl chloride and lithium. The first stage is composed of two competing reactions in which a radical anion (**202**) and *n*-butyllithium are formed. This radical anion could react with *n*-butyllithium to give the dihydro intermediate, which yields 4-*n*-butylpyridine on oxidation following hydrolysis. Two other explanations are feasible. The radical anion might react with *n*-butyl chloride, although 4-butylation takes place even in the absence of *n*-butyl chloride. The third possibility is that the radical anion (**202**) might couple with the radical anion of *n*-butyl chloride at the metal surface. This might involve an intermediate that resembles (**203**), indeed all three processes described above may be accommodated by selective breaking of the bonds depicted by the dotted lines.

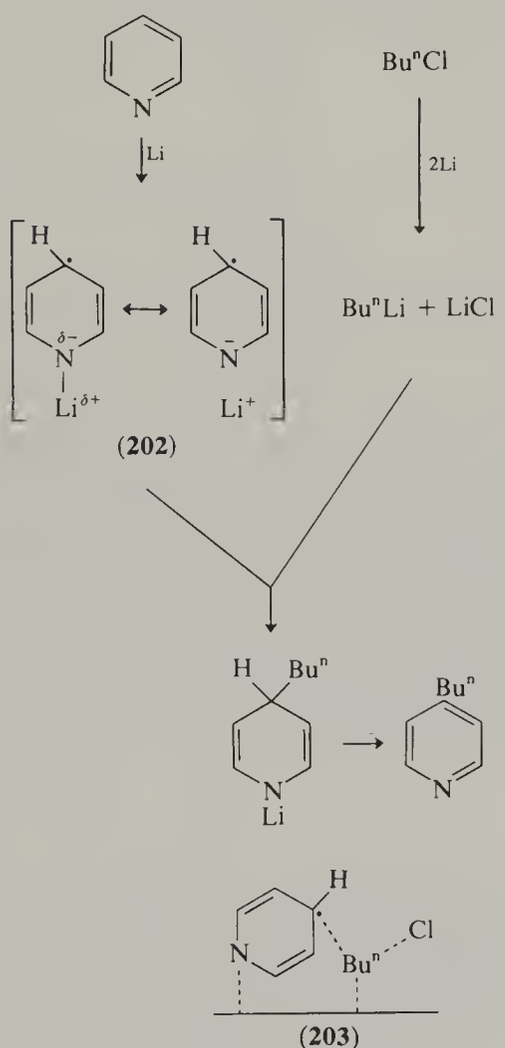


100 : ≪1

57%

i, Bu^{n}Cl 1.65 : 1 Mg, 3 h, 122 °C

(131)

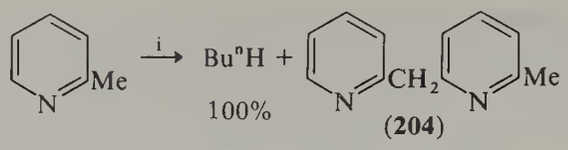


(**202**)

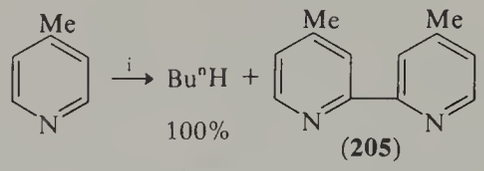
(**203**)

Scheme 141

Treatment of 2-methylpyridine with magnesium and *n*-butyl chloride gives a 1 : 5 mixture of 2-*n*-pentylpyridine (*via* metallation) and 4-*n*-butyl-2-methylpyridine. Similar treatment of the 4-isomer gives only 4-*n*-pentylpyridine. These methylpyridines behave quite differently when treated with the preformed Grignard reagent. 2-Methylpyridine gives *n*-butane and (**204**; equation 132), and the 4-isomer yields (**205**) and *n*-butane (equation 133).

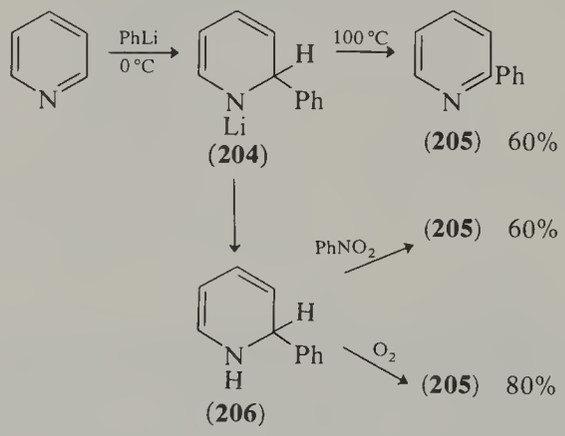


i, Bu^{n}MgI (ether free) (132)



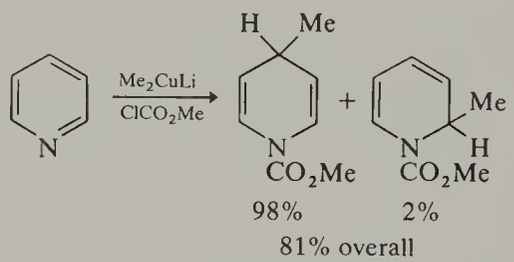
i, Bu^{n}MgI (ether free) (133)

Pyridines are alkylated more easily by organolithium than by Grignard reagents. The mechanism of reaction (Scheme 142) and the orientation of substitution (at C-2, with rare exceptions) resemble that of the Chichibabin reaction ⟨B-74MI20503⟩. Pyridine forms an isolable addition complex (**204**), with phenyllithium at 0 °C ⟨69CC142⟩. This complex has to be heated to form 2-phenylpyridine (**205**) ⟨30CB1847⟩. Hydrolysis of (**204**) gives a dihydro compound (**206**), which is readily oxidized to 2-phenylpyridine ⟨46JOC741, 53CJC457⟩. Some examples of alkylations and arylations with organolithium compounds are presented in Table 22.



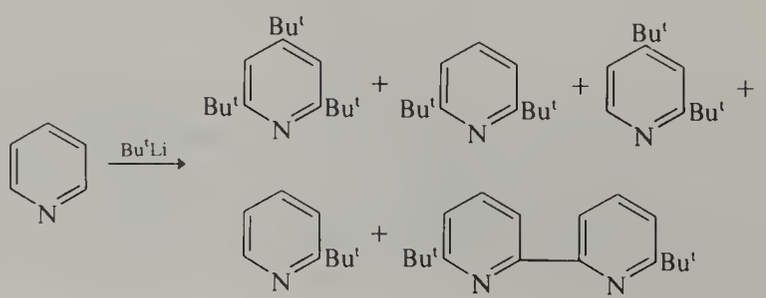
Scheme 142

4-Substitution is rare and usually a low yield pathway, except with benzyllithium ⟨69JCS(B)901⟩, although more examples are emerging. 2-Lithio-1,3-dithiane reacts with pyridine to give a 69% yield of 2-(4-pyridyl)-1,3-dithiane ⟨73CL1307⟩. Reaction of pyridine with lithium dialkylcuprates and a suitable electrophile gives the 1,4-dihydro product almost free of the 1,2-isomer (equation 134) ⟨74CJC3563⟩.



81% overall (134)

Treatment of pyridine with *t*-butyllithium affords mainly the symmetrical tri-*t*-butyl product under optimum conditions (equation 135) ⟨71JOC2541⟩. Other workers ⟨71CC1420⟩ have shown that when this alkylation is carried out at room temperature, addition of the



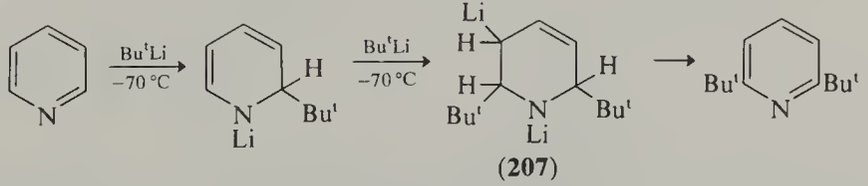
(135)

Table 22 Reactions of Alkyl- and Aryl-lithium Compounds (RLi) with Pyridines and Some 2- or 4-Substituted Derivatives[g]

Heterocycle Substituent		*R*	*Yield of substituted pyridines (%)* 2-*R*	4-*R*	2,4-R_2	2,6-R_2	2,4,6-R_3	*Others*
Pyridine								
none		Me	35.8	—	—	—	—	—
none		Et	—	trace	—	90	—	—
none		Pr^i	35–50	—	—	—	—	—
none		Bu^n	—	trace	—	89	—	—
none	1:10	Bu^t [a]	9	7	22	58	—	—
none	1:10	Bu^t [b]	—	—	1	5	80	—
none	1:20	Bu^t [c]	4	—	11	5	55	15[d]
none		—	40–60	—	—	—	—	—
2-Me		—	—	—	—	—	—	2-(2-methylpyridyl)lithium
2-Bu^n		Bu^n	—	—	—	67	—	—
2-Bu^t		Bu^t	—	—	—	50	—	—
4-Me		Ph[e]	39	—	—	36	—	—
4-Me		Ph[f]	—	—	—	—	—	4-(4-methylpyridyl)lithium
4-OEt		Bu^t	45–50	—	—	—	—	—
4-SMe		Bu^t	40–45	—	—	—	—	—
Quinoline								
		Bu^n	50–93	—	—	—	—	—
Isoquinoline								
		Bu^n	—	—	—	—	—	1-*n*-butylisoquinoline (70)
Acridine								
		Ph	—	—	—	—	—	9,10-dihydro-9-phenylacridine (61)
Phenanthridine								
		Bu^n	—	—	—	—	—	6-*n*-butylphenanthridine (90)
Phenanthridine								
		Ph	—	—	—	—	—	6-phenylphenanthridine

[a] In heptane at r.t. ⟨71CC1420⟩.
[b] In heptane at reflux ⟨71CC1420⟩.
[c] No heptane at reflux, overall yield 90% ⟨71JOC2541⟩.
[d] 6,6′-Di-*t*-butyl-2,2′-bipyridine.
[e] 4-Methylpyridine added to phenyllithium.
[f] 4-Phenyllithium added to 4-methylpyridine.
[g] ⟨66AHC(6)229, B-74MI20503⟩.

third *t*-butyl group does not take place; heating is required. 2,6-Di-*t*-butylpyridine was found to be formed *via* the 1,3-lithio derivative (**207**; Scheme 143). 4-Alkylation predominates when reaction is carried out in the presence of free lithium, but a different mechanism is believed to be operative here (Scheme 141). Pyridines that bear methyl groups attached at C-2 or C-4 undergo metallation at the substituent rather than attack at a ring carbon.



(207)

Scheme 143

The effect of a 3-substituent on the orientation of the addition of alkyl- and aryl-lithium compounds is interesting and salient results appear in Table 23. Attack at C-2 is favoured over that at C-6 unless either, or both, the C-3 substituent and the attacking alkyl group are very large. Reaction of isopropyllithium with 3-methylpyridine does not follow this trend. Benzyllithium is anomalous in that it attacks preferentially at C-4. A study of the relative rates of these alkylations revealed the remarkable fact that a 3-methyl or 3-ethyl group activates the 2-position (but not the 6-) towards attack by phenyllithium but not methyllithium. However, a 3-isopropyl and 3-cyclohexyl group deactivates C-2 relative to

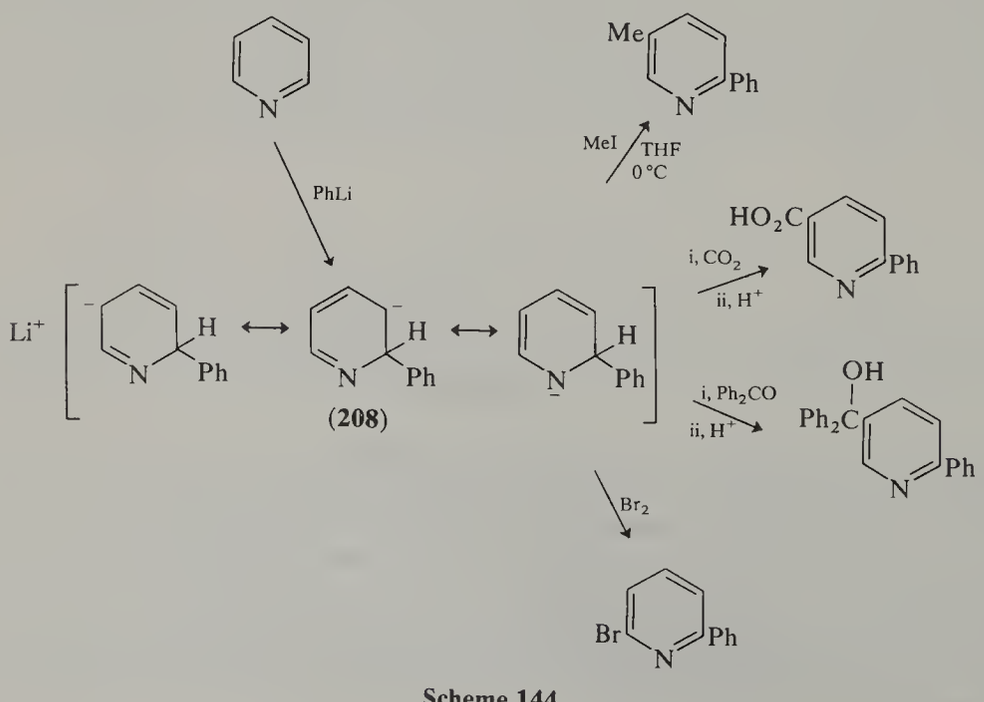
pyridine. It has been suggested that there is an attractive force between phenyllithium and the 3-substituent attributable to London dispersion forces or electron deficient bonding that lowers the activation energy for attack at C-2. This subject has been comprehensively reviewed ⟨74HC(14-S1)1⟩. Regiospecific attack at C-2 observed in the phenylation of 3-amino- and 3-methoxy-pyridines is more easily understood as a consequence of the coordination of phenyllithium with the substituent heteroatom.

Table 23 Reaction of Alkyl- and Aryl-lithium Compounds (RLi) with 3-Substituted Pyridines

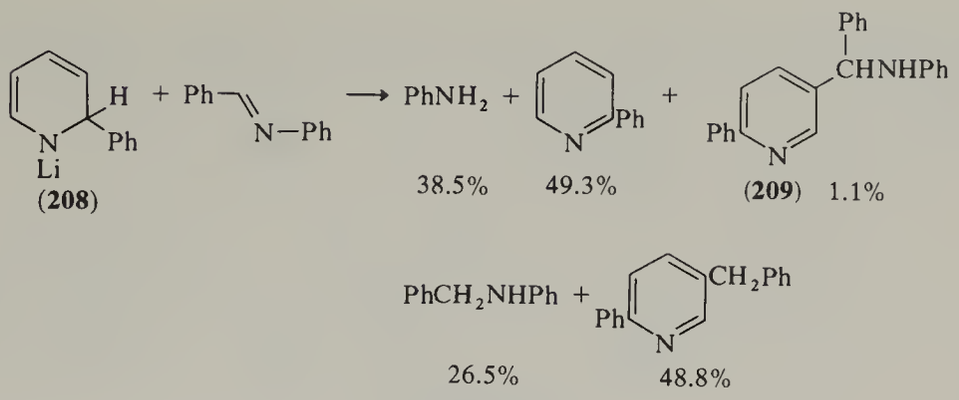
Substituent	*R*	% *Yield*[a]	% *Composition* 2,3-	2,5-
Me	Me	27.8	84.4	15.6
Me	Pr^i	[b]	20.5	79.5
Me	$PhCH_2$	41[c]	—	—
Me	Ph	48	94	6
Et	Ph	42	87	13
Pr^i	Ph	32	76	24
Bu^t	Me	61	1	99
Bu^t	Ph	24	4.5	95.5
C_6H_{11}	Ph	[b]	65	35
Ph	Ph	35	16.5	83.5
OMe	Ph	21	100	0
NH_2	Ph	24.5	100	0

[a] ⟨66AHC(6)229, 74HC(14-S1)1⟩.
[b] Not quoted.
[c] 4-Benzyl-3-methylpyridine.

The *N*-lithio-2-phenyl-1,2-dihydro adduct (**208**) is a useful synthetic intermediate that reacts with alkyl halides, bromine ⟨70CC478⟩, carbon dioxide ⟨70TL3371⟩ and benzophenone ⟨70CC921⟩ to give 2,5-disubstituted derivatives (Scheme 144). The intermediate (**208**) reacts with Schiff bases to give a mixture of products rather than the anticipated high yield of β-alkylamino derivative (**209**; Scheme 145) ⟨75CJC2305⟩. Ambident behaviour has been observed in the addition of acid chlorides to (**208**). Acetyl chloride gives mainly *N*-acylation, whereas trifluoroacetyl chloride adds preferentially at C-5 (Scheme 146) ⟨74JOC3565⟩. The ratio of *N*/*C*-substitution drops with increase in the reactivity of the electrophile. The same pattern holds for additions of isocyanates to (**210**; Scheme 147) ⟨78CJC1913⟩. In a search for new routes to pharmacologically interesting heterocycles, the cyclic dienamine (**211**) was found to undergo 1,3-dipolar cycloaddition with cyanogen azide (Scheme 148) ⟨78CJC1026⟩.

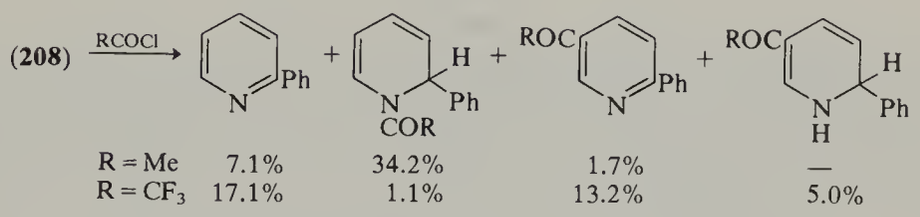


Scheme 144

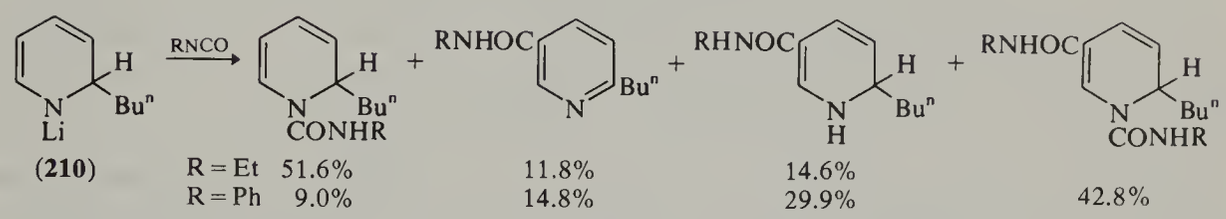


(208)

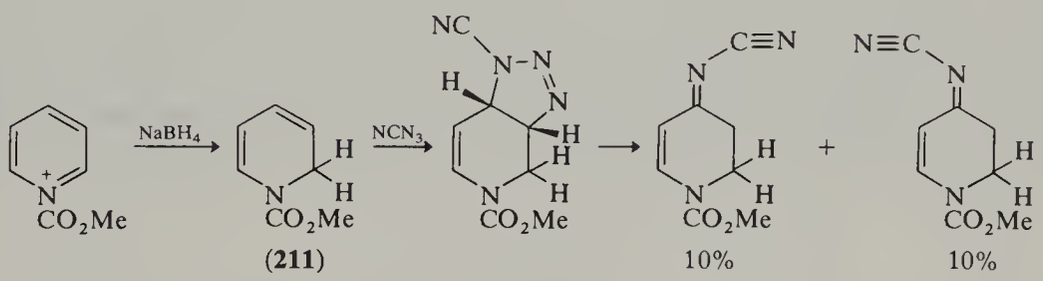
Scheme 145



Scheme 146

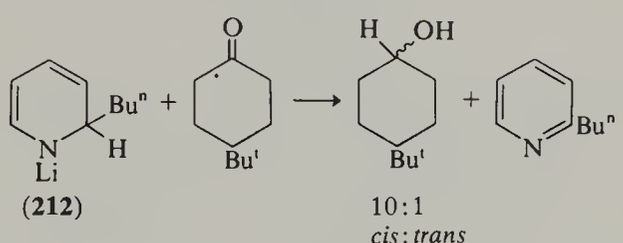


Scheme 147



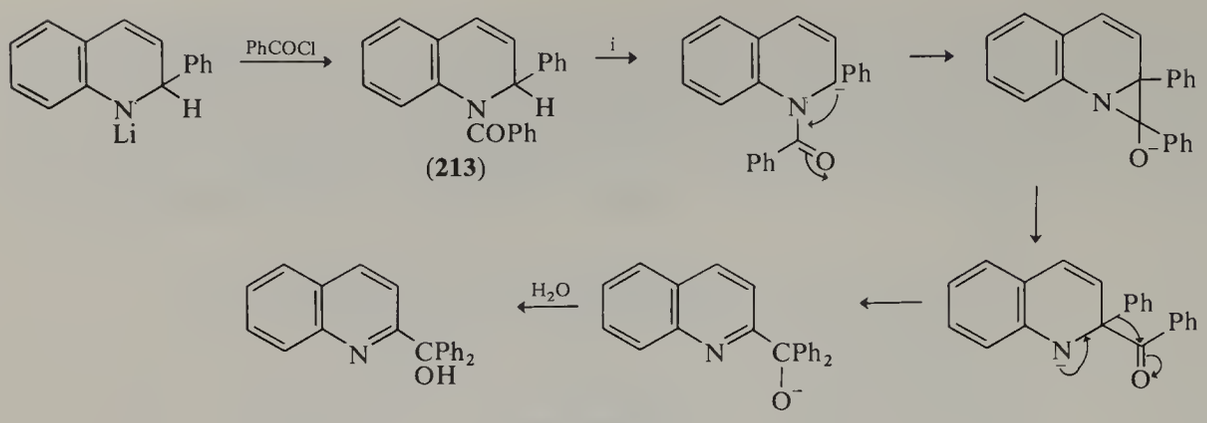
Scheme 148

The *N*-lithio-*n*-butylpyridine-1,2-dihydro adduct (**212**) has found use as a reducing agent, for example in the conversion of 4-*t*-butylcyclohexanone to a mixture (*cis* : *trans*, 10 : 1) of 4-*t*-butylcyclohexanols (equation 136) ⟨65CJC2631⟩.



(136)

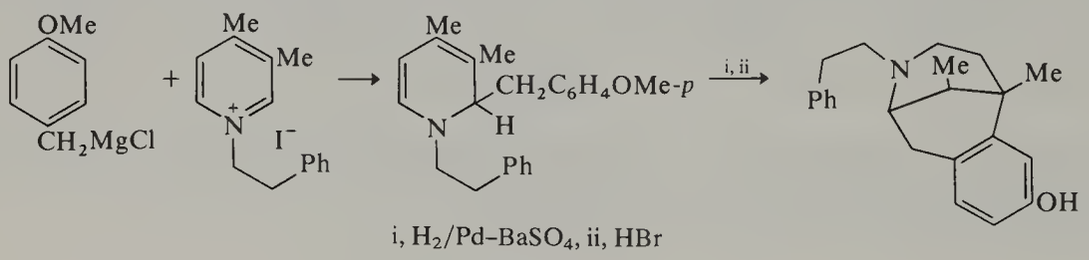
The question of 1,2- *versus* 1,4-addition to quinoline was resolved in favor of the former by two research groups at about the same time ⟨72JCS(P1)2807, 72JCS(P1)2810⟩. Furthermore, the suggestion ⟨71BCJ520⟩ that the 1,2-adduct arises by initial 1,4-addition followed by rearrangement was disproved. *N*-Lithio-1,2-dihydroquinoline adducts have a blocked 5-position so they are not as versatile as their pyridine analogues. Nevertheless, treatment of such an adduct with benzoyl chloride gives (**213**; Scheme 149), which reacts with *n*-butyllithium to give a Reissert-like intermediate that undergoes rearrangement to yield ultimately a carbinol ⟨72CC865⟩. When a quinoline already bears a 2-substituent, such as 2-phenylquinoline, reaction with phenyllithium gives 2,2-diphenyl-1,2-dihydroquinoline ⟨47JA877⟩.



i, Bu^nLi, Et_2O, 35 °C

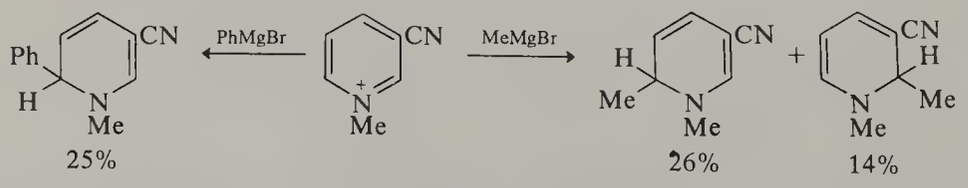
Scheme 149

The reaction of Grignard reagents with *N*-alkylpyridinium salts offers a useful approach to 1,2-dihydropyridines. The example shown in Scheme 150 illustrates how a benzomorphan can be obtained from a simple pyridine precursor ⟨60JOC984⟩. In this case nucleophilic attack takes place at the 2- rather than the 6-position. The reaction of the *N*-alkyl salts of 3-cyanopyridine results in alkylation at both α-positions, but arylation is confined to C-6 (Scheme 151) ⟨71JOC772⟩. The orientation of nucleophilic addition may be changed by increasing the size of the *N*-substituent. The *N*-phenoxycarbonyl salt of 3,4-dimethylpyridine was found to undergo highly regioselective phenylation at C-6 with phenylmagnesium bromide (Scheme 152) ⟨76JOC3250⟩. Rearomatization was achieved by heating with sulfur rather than by using *n*-butyllithium. 4-Alkylation and -arylation of N—N linked pyridinium salts (**214**), in which attack at C-2 is sterically hindered, is usually a good yield reaction that is fairly general (Scheme 153) ⟨80JCS(P1)2480⟩. Addition of phenylmagnesium bromide in THF to (**214**) gave, after stirring at room temperature for 70 h and water work-up, an unstable crude intermediate oil (**215**). The oil could be converted to product either by heating at 200 °C for 5 min, or by extraction into acid, basification and chloroform extraction. Recently, almost quantitative regiospecific 4-alkylation of (**216**) was observed on treatment with a Grignard reagent, a copper salt and boron trifluoride etherate (Scheme 154) ⟨82TL429⟩. Aromatization of the dihydro intermediates was accomplished with oxygen. When the *N*-substituent is a good leaving group, C-2 substitution occurs very easily by path **B**, with only a little competition from path **A** (equation 137) ⟨60CI(L)1482⟩.

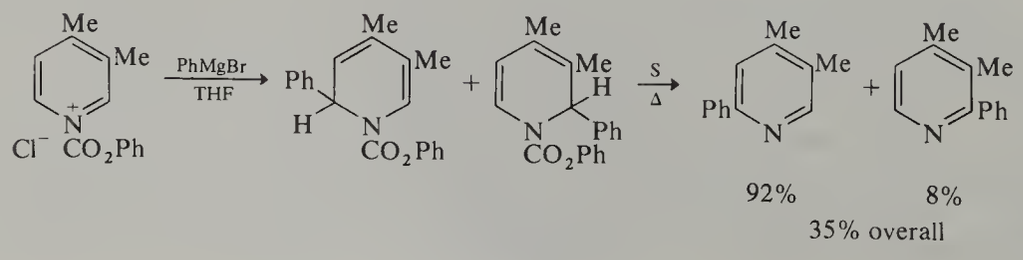


i, H_2/Pd–$BaSO_4$, ii, HBr

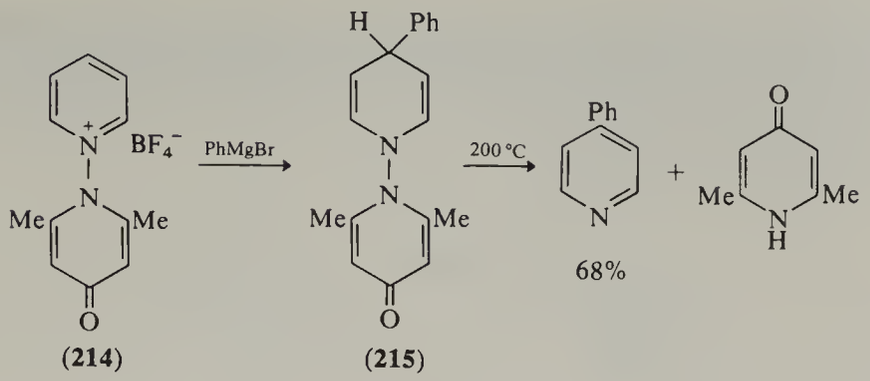
Scheme 150



Scheme 151

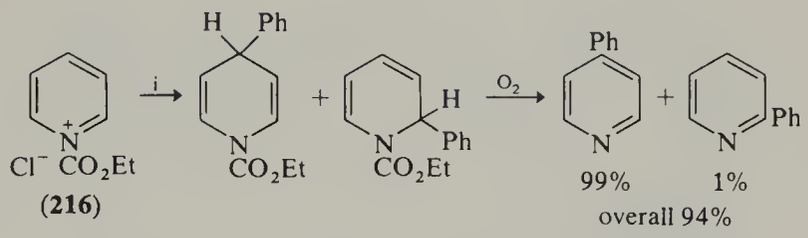


Scheme 152



(214) (215)

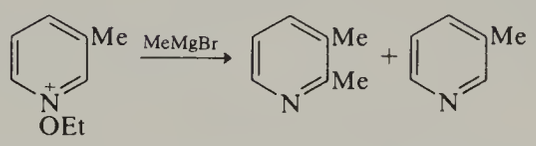
Scheme 153



(216)

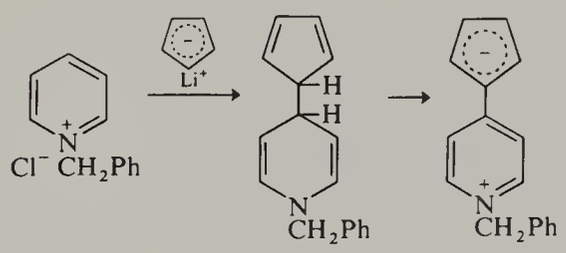
i, CuI, PhMgBr, Mg, $BF_3{\cdot}OEt_2$, THF, −78 °C, added to (**216**)

Scheme 154

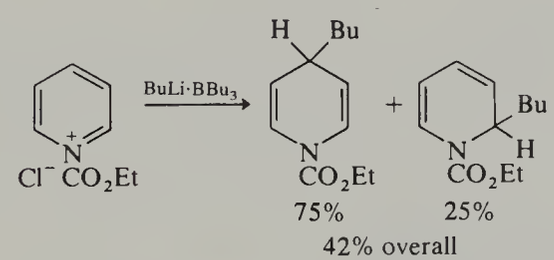


(137)

Organolithium compounds usually add 1,2 to quaternary pyridinium salts but these reactions have been found to be of less synthetic value than those with Grignard reagents ⟨B-74MI20503⟩. Polymerization of the dihydro intermediates often occurs under the highly basic reaction conditions. Cyclopentadienyllithium, a less reactive reagent, adds 1,4 to *N*-benzylpyridinium salts (equation 138). This reaction is probably favoured by the stability of the product formed. There are several other examples of 1,4-additions to pyridinium salts, by carboranyllithium ⟨70ZOB125⟩ and butyllithium–tributylborane (equation 139) ⟨82TL429⟩.



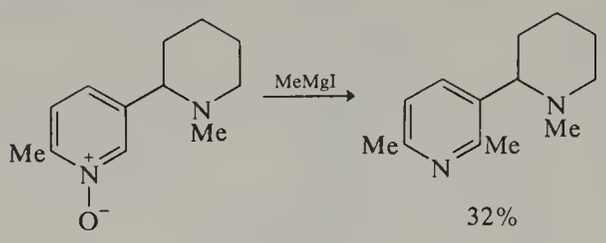
(138)



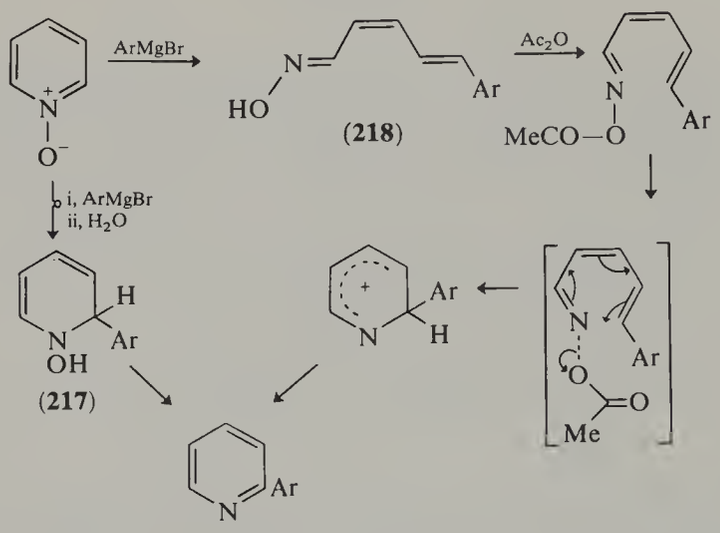
(139)

Reactions of pyridine 1-oxides with Grignard reagents are more complex than those with quaternary salts. A typical reaction is α-alkylation with deoxygenation, as for example in the reaction of *N*-methylanabasine *N'*-oxide with methylmagnesium iodide (equation 140). The analogous 2-arylation of pyridine 1-oxide has been shown not to proceed *via* the dihydro intermediate (**217**), but rather by a ring opening–ring closure sequence (Scheme 155) ⟨71JOC1705⟩. The all *trans*-pentadienal oximes (**218**) were isolated, with difficulty, and characterized spectroscopically. The reaction of quinoline 1-oxide with phenylmagnesium bromide was reported ⟨53G58⟩ to yield 2-phenylquinoline (**219**; 30%) when carried out in ether. More recent work ⟨65JOC910⟩ has shown that several products may be obtained when

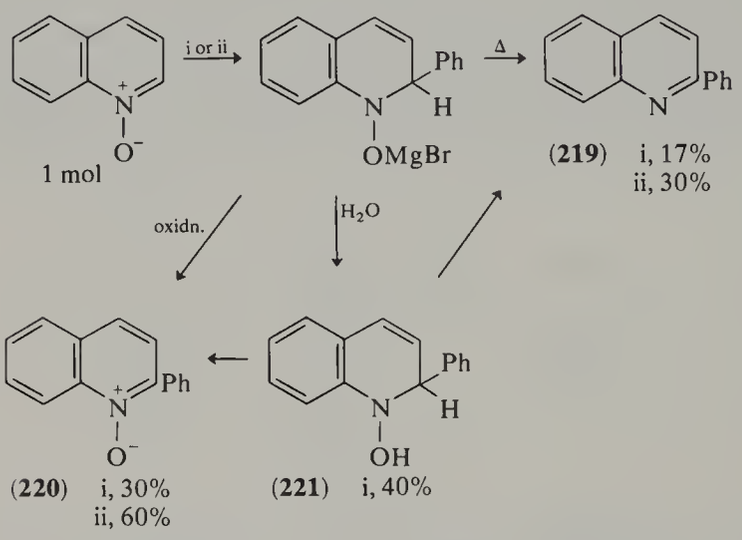
THF is used as solvent for this reaction (Scheme 156). Indeed, THF is the solvent of choice for the alkylation of *N*-oxides by Grignard reagents. The following references ⟨B-71MI20500, 74HC(14-S2)1⟩ should be consulted for a more comprehensive coverage of these reactions. Reactions of the above type with organolithium compounds are less successful as metallation becomes a major pathway (*vide infra*).



(140)



Scheme 155



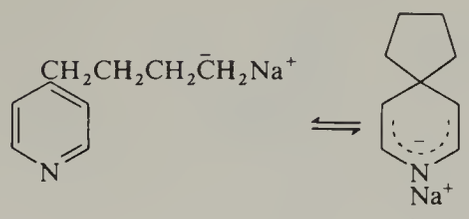
i, PhMgBr (2 mol), THF, 7 h, 10–15 °C; ii, PhMgBr (2 mol), THF, 5 h, reflux

Scheme 156

2.05.4.7.3 Active hydrogen compounds

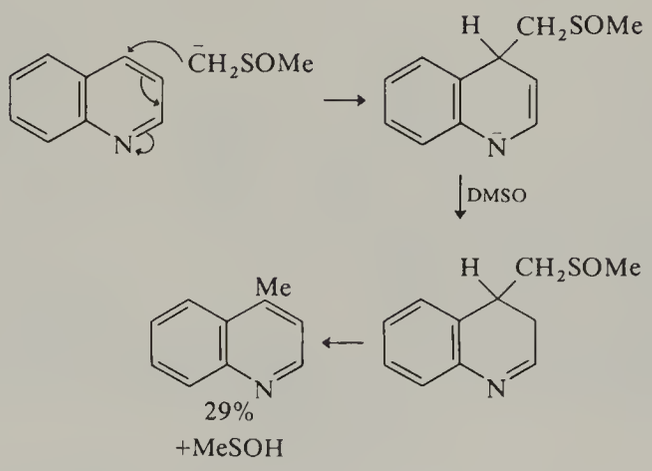
Pyridines that are not activated by quaternization usually do not undergo nucleophilic attack by active hydrogen compounds. An exception to this statement is provided by the observation that 4-(4-pyridyl)butylsodium (and potassium, lithium and magnesium chloride) exist in the 4,4′-spirodihydropyridine structure (**222**) rather than the open-chain form (equation 141) ⟨72JA4732⟩. However, quinoline is more reactive (effect of an annelated benzene ring) and is attacked at C-4 by the dimsyl anion to yield 4-methylquinoline (Scheme 157) ⟨66TL1123⟩. Acridine reacts more readily still with such nucleophiles. It gives 9-methylacridine (60% yield) on treatment with phenyl sulfone in HMPA, presumably by

a similar mechanism to that shown in Scheme 157. Addition of nitromethane has been observed under basic conditions (Scheme 158) ⟨B-78MI20501⟩.

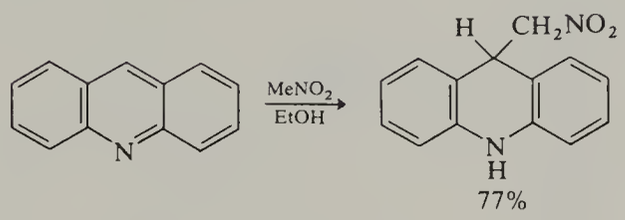


(141)

(222)

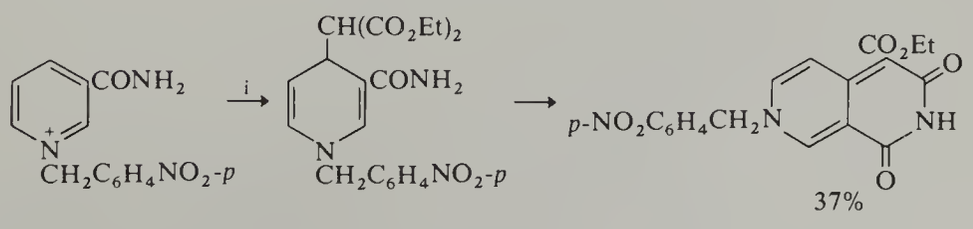


Scheme 157



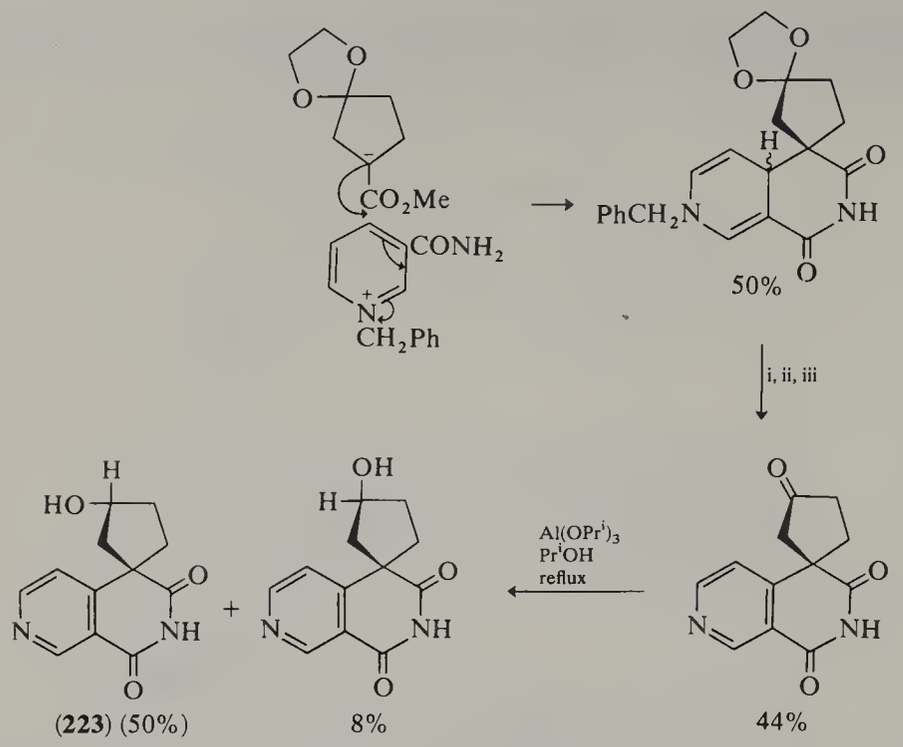
Scheme 158

Pyridinium salts react with active hydrogen compounds much more readily than the parent systems. The literature is rich in examples of reactions that lead to products (resulting from C-4 alkylation) of interest, particularly in the pharmaceutical field. Enolate anions can add to pyridinium salts at C-2 and C-4 ⟨51JA2104⟩, but recently some important regiospecific C-4 alkylations have appeared. A method for the preparation of 2,7-naphthyridones is based on nucleophilic attack by acetate and malonate anions at C-4 (Scheme 159) ⟨74JCS(P1)57⟩, and subsequent ring-closure of the product on to the 3-substituent. This method has been developed further to permit the introduction of a spiro centre at C-4, and make available a simple high yield route to the cytotoxic alkaloid (±)-sesbanine (**223**; Scheme 160) ⟨81H(15)377⟩. This compound was first isolated from extracts of the seeds of *Sesbania drummondii* that have potent antileukemic activity. The morphine analogue (**224**) may be prepared in very high yield from the salt (**225**) (synthesized by an improved method); in this case the spiro centre was established by intramolecular carbanion attack (Scheme 161) ⟨81TL4381⟩. The easy reversal of this reaction by acid is also noteworthy. Regiospecific γ-alkylation is a key step in a synthesis of pseudo-yohimbine (**226**; Scheme 162) ⟨79JA5370⟩.



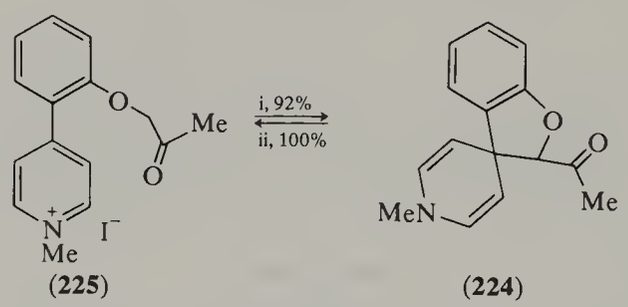
i, $CH_2(CO_2Et)_2$, Et_3N, pH 9–10, 3 h, r.t.

Scheme 159



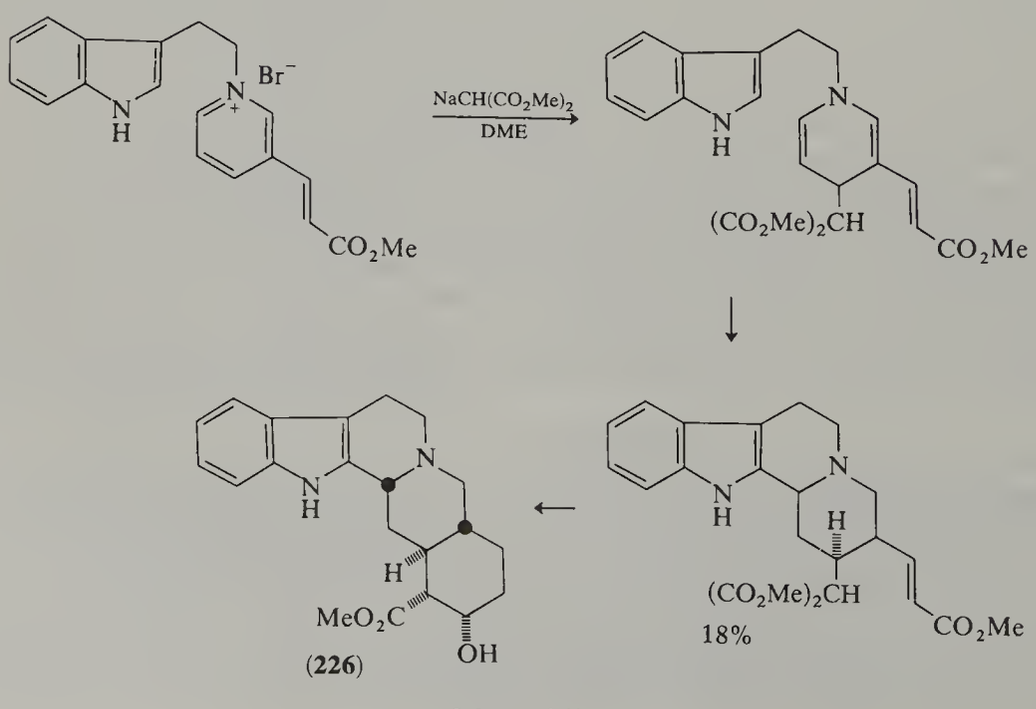
i, *N*-benzylquinolinium bromide, MeCN, 2 d, r.t.; ii, 235 °C/0.01 mmHg, *in vacuo*, 1 h; iii, deprotection

Scheme 160

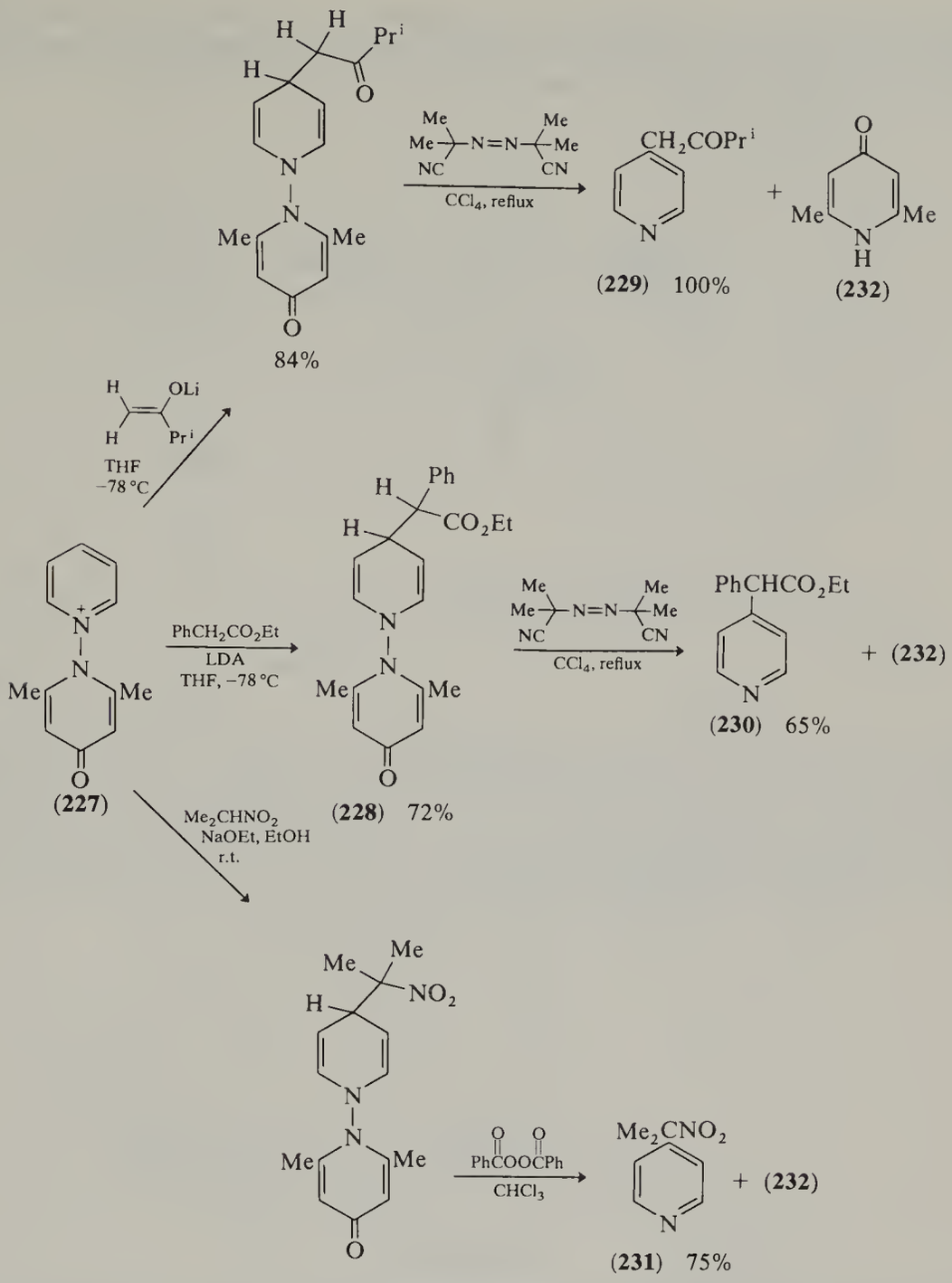


i, 4N NaOH, PhH, DMSO; ii, conc. HI, EtOH

Scheme 161



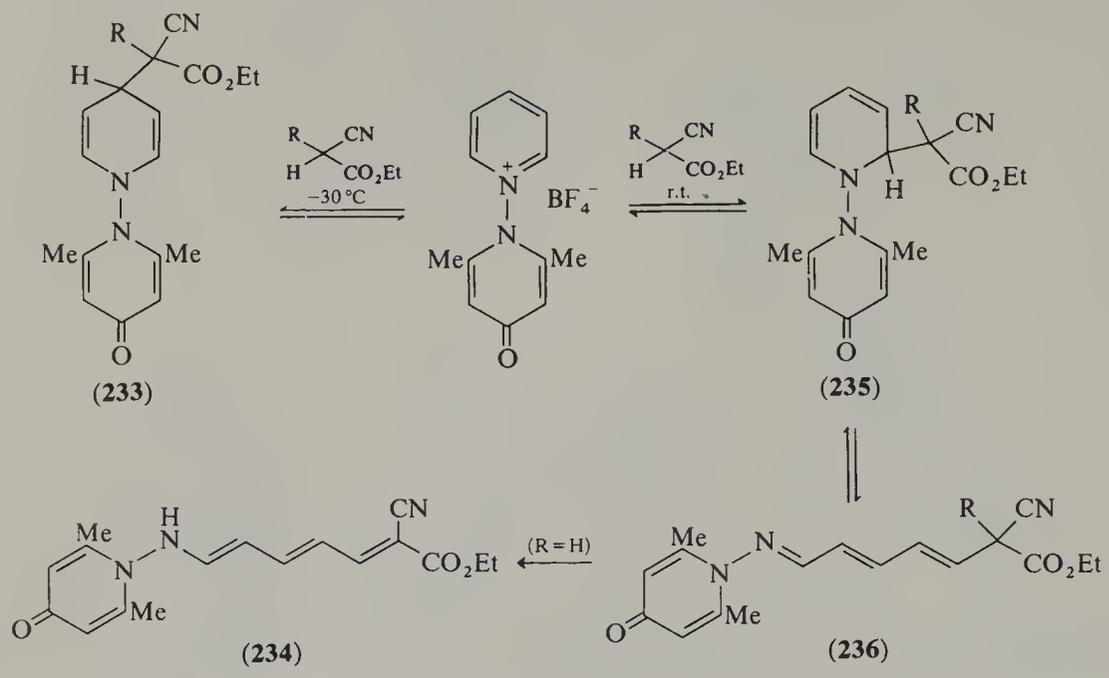
Scheme 162



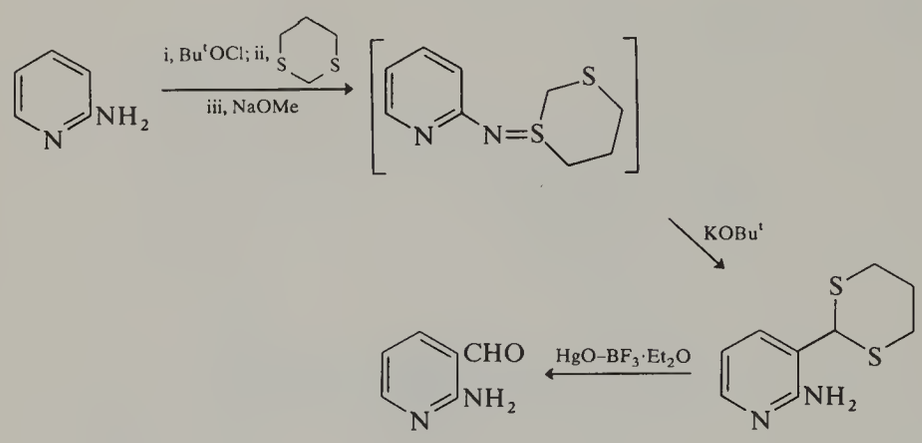
Scheme 163

Another means of directing nucleophilic attack to C-4 rather than C-2 is based on N—N linked quaternary pyridinium salts (**227**). These have great potential as synthetic intermediates for the introduction of many nucleophiles at C-4. They may be prepared easily in high yield ⟨77JCS(P1)327⟩; the γ-position is activated towards nucleophilic attack, whilst the α-positions are sterically hindered. Furthermore, the *N*-substituent may be removed readily ⟨81JCS(P1)2835⟩. The generality of the application of the procedure to carbanion reactions is illustrated in Scheme 163. The stability of the 1,4-dihydro intermediates varies from extremely unstable, for those prepared from Grignard reagents (Scheme 153), to (**228**) which can survive heating at reflux for 6 hours in chloroform. The last step, conversion of the 1,4-dihydro intermediates to the 4-alkyl products (**229–231**) and 2,6-dimethylpyridin-4-one, is promoted by free radical initiators. Lithium enolates of ketones (pK_a 16–20) gave the desired reaction in high yield, whereas lithium derivatives of esters and nitriles (pK_a *ca.* 24) gave poor results. This was attributed to competing deprotonation of the pyridinone methyl group in the starting salts. Incursion of 1,2-addition was found with the anions derived from malononitrile and ethyl cyanoacetate. The cyano ester gave mainly the 1,4-adduct (**233**) (kinetic control) at −30 °C, but this rearranged to the ring-opened product (**234**) (thermodynamic control) at room temperature when R = H. It is not surprising that (**235**) undergoes electrocyclic ring opening to relieve steric strain. However, when R = Me

and prototropic, shift is not possible, only 1,4-adducts are formed; therefore (**236**) is apparently less stable than (**233**). The reaction sequence in Scheme 165 shows how a carbanion, generated at a substituent, may attack the 3-position ⟨74CC685⟩.

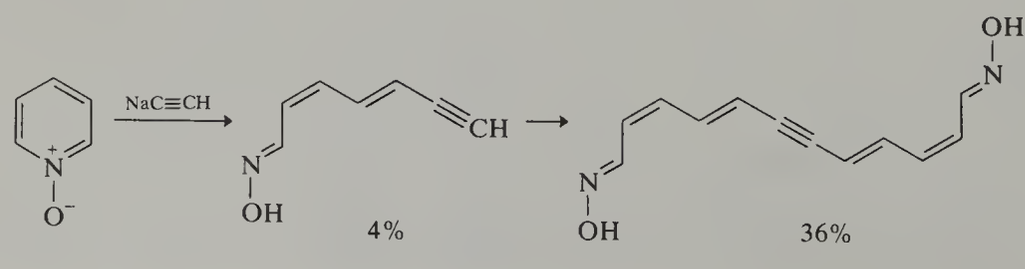


Scheme 164

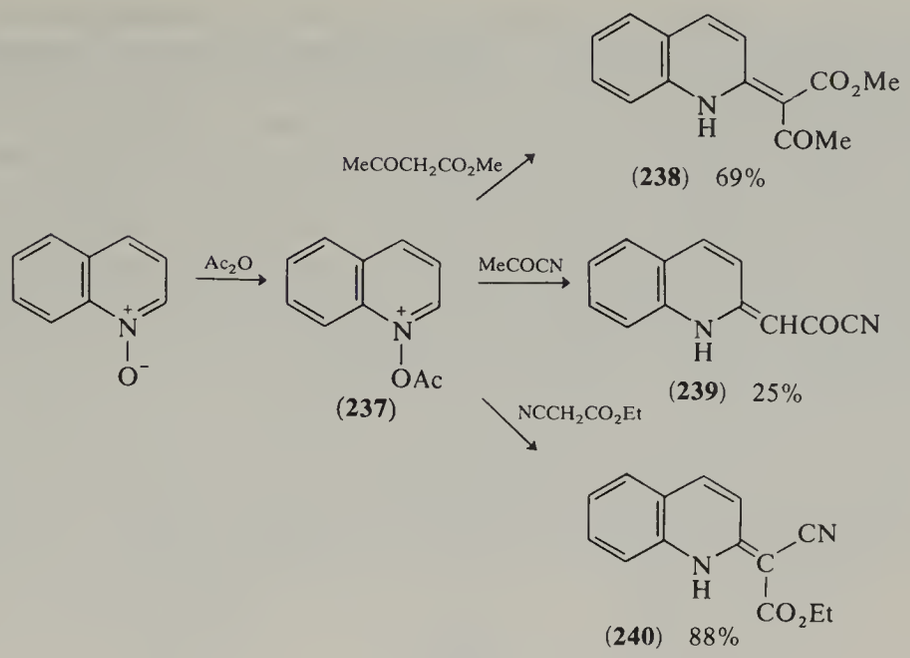


Scheme 165

N-Oxides react with active hydrogen compounds under various conditions, but reaction with free *N*-oxide is rare. Sodium acetylide reacts with pyridine 1-oxide to give ring-opened products (Scheme 166) ⟨74LA1407⟩, and not 2-ethynylpyridine 1-oxide as previously reported. Attachment of a group at oxygen to form a quaternary pyridine nitrogen is usually required to promote reaction. Thus, quinoline 1-oxide reacts with various active hydrogen compounds in the presence of acetic anhydride *via* the intermediate (**237**) to give the α-substituted products (**238–240**; Scheme 167) ⟨78JHC1425⟩. The corresponding reactions are less effective with pyridine 1-oxide. Similarly, 1-methoxypyridinium failed to react with ketones, whereas the 1-methoxyquinolinium analogue gave 2-quinolyl ketones ⟨B-71MI20500⟩.



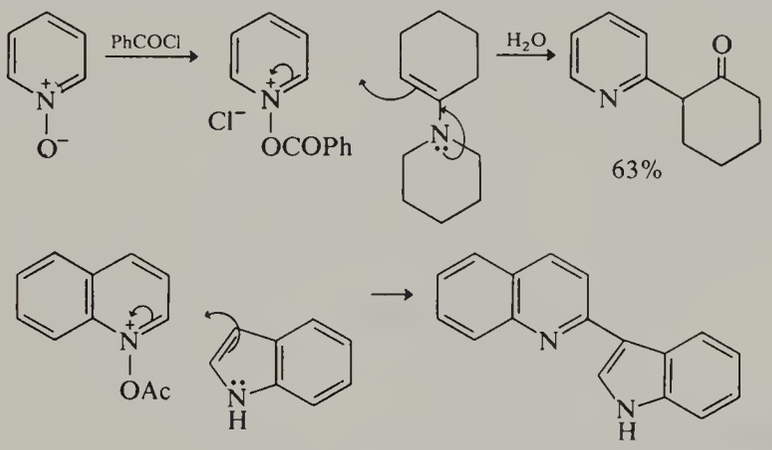
Scheme 166



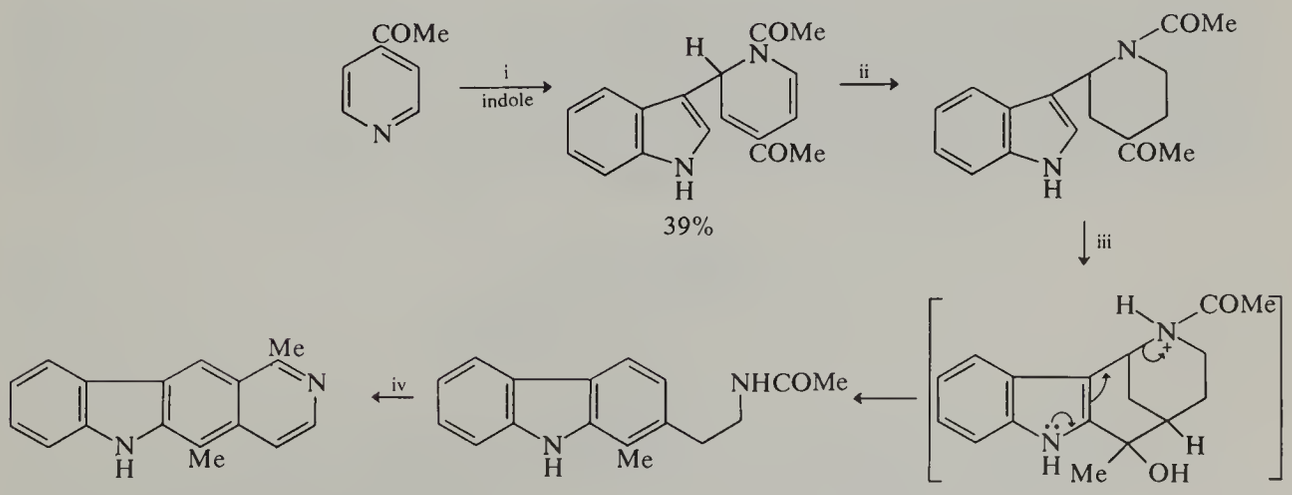
Scheme 167

2.05.4.7.4 Enamines

Pyridines and their *N*-oxides undergo attack by enamines under acylating conditions (Scheme 168), and the results for reactions of *N*-oxides have been surveyed ⟨B-71MI20500⟩. A modification of this heteroarylation reaction has been employed in the first step of a new synthesis of the antitumor alkaloid olivacine (**241**; Scheme 169) ⟨81CC44⟩. Electron-withdrawing groups attached at C-4 in the pyridine nucleus appear to facilitate this reaction.



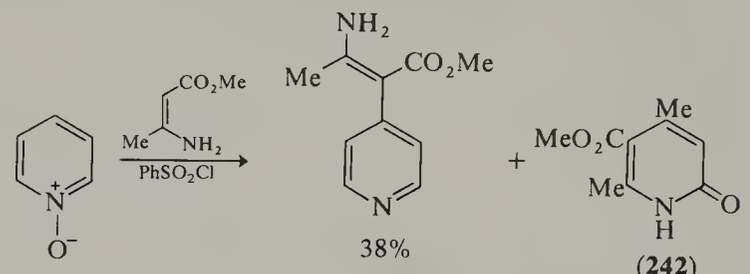
Scheme 168



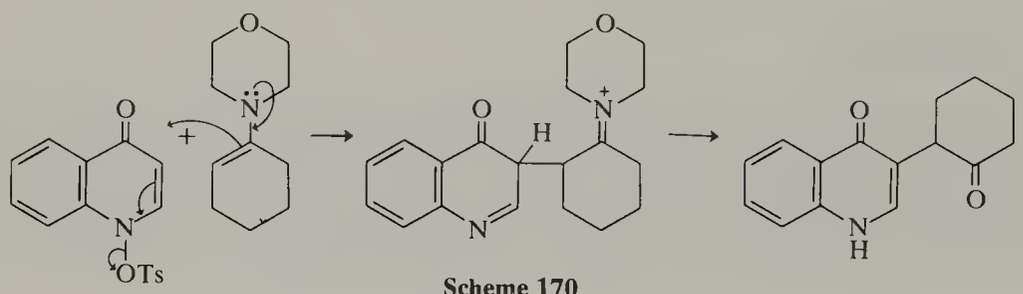
i, MeCOCl, CH_2Cl_2, 0–25 °C, 8 h; ii, H_2/PtO_2; iii, $BF_3{\cdot}Et_2O$, $CHCl_3$; iv, $POCl_3$, Pd–C

Scheme 169

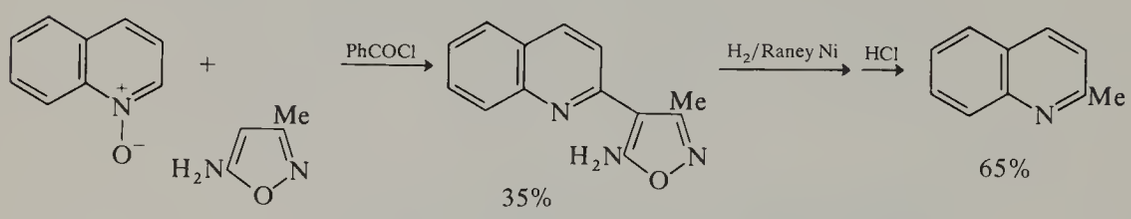
The reaction of *N,N*-dimethylaniline with pyridine (equation 55) should also be considered in this category. Enamines usually attack acylated *N*-oxides at position 2 unless it is blocked, as in 2-methylquinoline 1-oxide, when attack takes place at C-4. Methyl β-aminocrotonate attacks quinoline and isoquinoline *N*-oxides at the position α to the *N*-oxide function in the presence of tosyl chloride ⟨78JHC1425⟩. However, pyridine and 2-methylpyridine 1-oxides react at the 4-position (equation 142). A low yield of by-product (**242**) is formed in each case, probably as a result of self-condensation of methyl β-aminocrotonate. 4-Hydroxyquinoline 1-oxide is exceptional in that it reacts with an enamine in the presence of tosyl chloride at the β-position (Scheme 170) ⟨B-71MI20500⟩. 5-Amino-3-methylisoxazole reacts with quinoline 1-oxide at the α-position, and the product can be degraded, to afford ultimately 2-methylquinoline (Scheme 171) ⟨78CPB2759⟩.



(142)



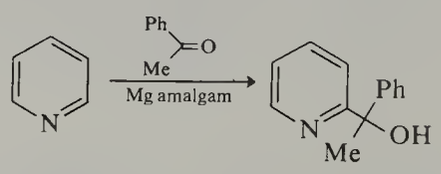
Scheme 170



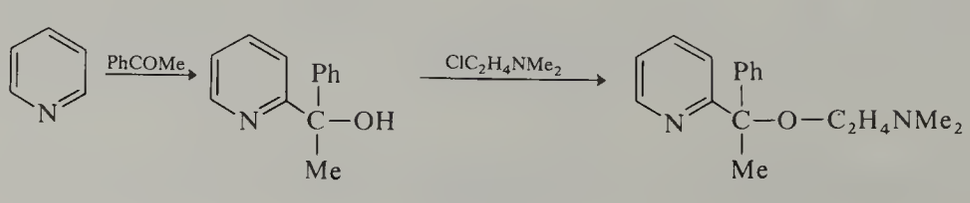
Scheme 171

2.05.4.7.5 Emmert reaction

Emmert and Asendorf found that pyridine can undergo condensation with a ketone on heating in the presence of magnesium amalgam to give a pyridyl alcohol (equation 143) ⟨39CB1188⟩. This reaction appears to be quite general for pyridines and quinolines with aldehydes and ketones although yields are variable. It has proved a useful method for the preparation of some pyridyl alcohols that are precursors of pyridyl dimethylaminoethyl ethers, a number of which are histamine antagonists (Scheme 172) ⟨48JA4001⟩.

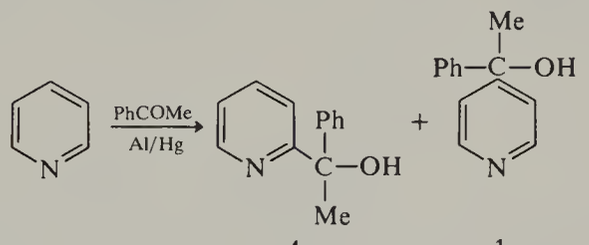


(143)



Scheme 172

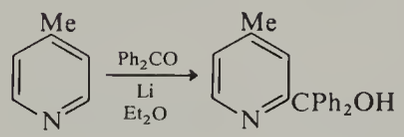
Several metals have been used for the reaction apart from magnesium amalgam. Magnesium metal turnings and mercury(II) chloride in the presence of a little mercury were found to be effective. Use of aluminum amalgam with aromatic ketones also gave some 4-substituted product (**243**; equation 144) ⟨48JA4001⟩. More recently, lithium wire or LDA have been used to effect the reaction. When a mixture of 4-methylpyridine, benzophenone and lithium wire was heated under reflux in ether a good yield of the 2-carbinol (**244**) was obtained (equation 145) ⟨70CC1406⟩. Use of these conditions also gave the corresponding 2-carbinol (31.8%) with quinoline (and the 1-carbinol with isoquinoline), and another product (**245**) which was suggested to arise by a single electron transfer mechanism (Scheme 173). A similar mechanism is also favored for the reaction of pyridine, a ketone and LDA (Scheme 174) ⟨82JOC599⟩. The dimerization of pyridine to 2,2′-bipyridyl with LDA (an extension of the Emmert reaction) may also proceed by a mechanism like that shown in Scheme 174. ESR signals, attributable to the benzylidenemethylamine radical, have been observed in the reaction of pyridine with a Schiff's base in the presence of sodium (Scheme 175) ⟨78JOU2341⟩. Acridine reacts with acetophenone in the presence of aluminum and a mercury(II) salt to give 9-phenacylmethylacridine rather than the appropriate carbinol (equation 146) ⟨70JOU1611⟩.



(144)

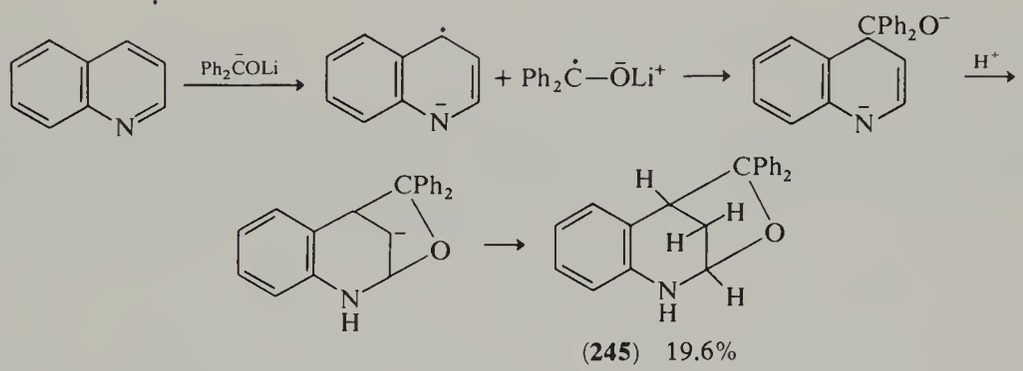
4 **1**

(**243**)



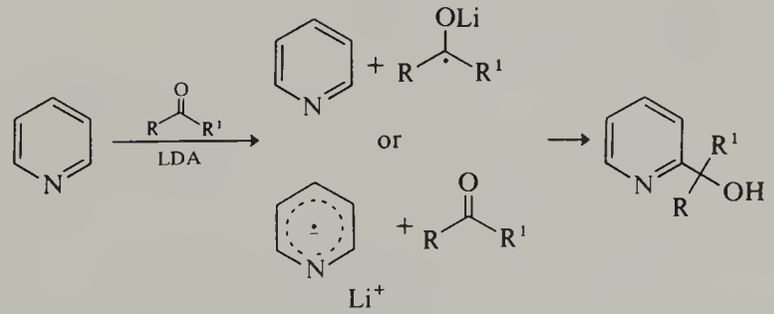
(145)

(**244**) 47%

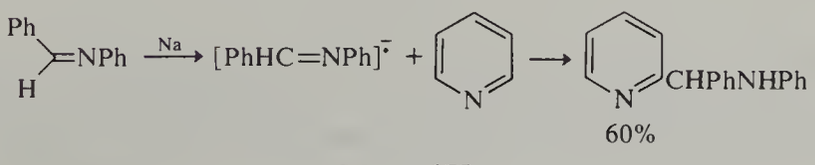


(**245**) 19.6%

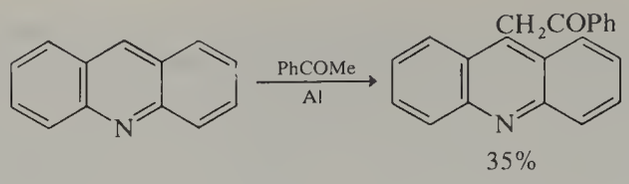
Scheme 173



Scheme 174



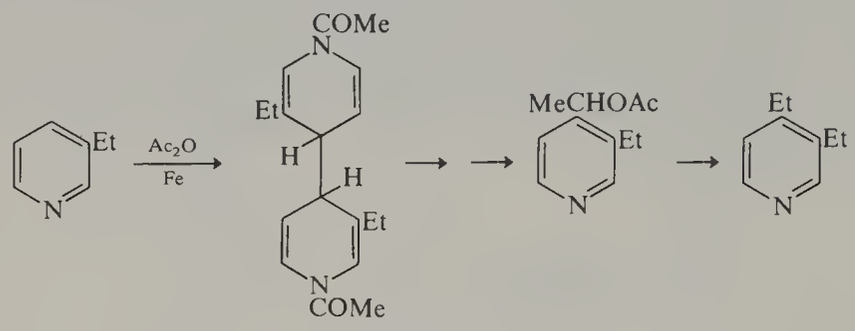
Scheme 175



35% (146)

2.05.4.7.6 Wibaut–Arens procedure

The Wibaut–Arens procedure ⟨41RTC119⟩ is a useful, but seldom used, method for the 4-alkylation of pyridines. 3,4-Diethylpyridine can be obtained (55% yield) by heating 3-ethylpyridine with iron and acetic anhydride for several hours (Scheme 176) ⟨65JOC3229⟩.



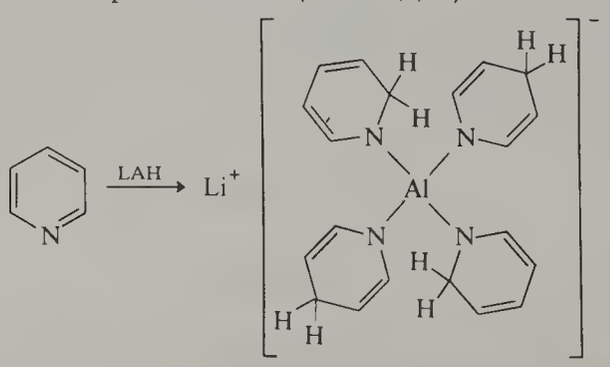
Scheme 176

2.05.4.8 Chemical Reduction (hydride equivalents and free electrons)

Pyridines are reduced more easily than the corresponding benzenoid compounds. The greater the electron-withdrawing power of the substituents attached to the pyridine ring the easier is reduction by nucleophilic reducing agents.

2.05.4.8.1 With lithium aluminum hydride

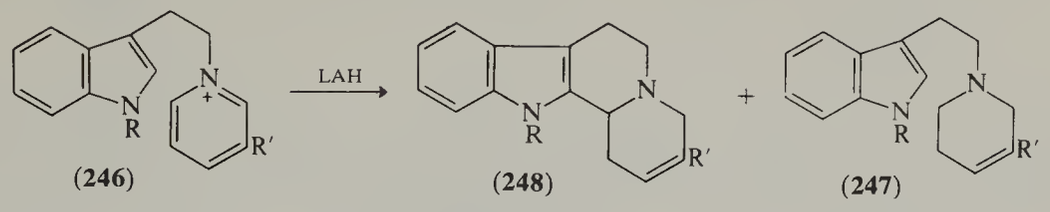
Dihydropyridines have been prepared by reduction of the corresponding pyridines or pyridinium salts with complex metal hydrides. Several general reviews have appeared ⟨66AHC(6)45, 72CR1⟩, and also one on dihydropyridines in synthesis and biosynthesis of alkaloids ⟨77H(6)583⟩. Pyridine itself forms a complex with LAH which contains 1,2- and 1,4-dihydropyridine rings, but dihydropyridines have not been isolated (equation 147) ⟨63JA2236⟩. An aged solution of this complex can act as a selective reducing agent for the reduction of ketones in the presence of carboxylic acids. When pyridine is treated with LAH and aluminum chloride, mixtures of tetrahydropyridines and piperidines are obtained ⟨66AHC(6)45⟩. Reduction of quinoline with LAH affords the 1,2-dihydro derivative. Acridine is readily reduced in high yield by this reagent to 9,10-dihydroacridine and the product is slowly oxidized to acridine on exposure to air ⟨66AHC(6)45⟩.



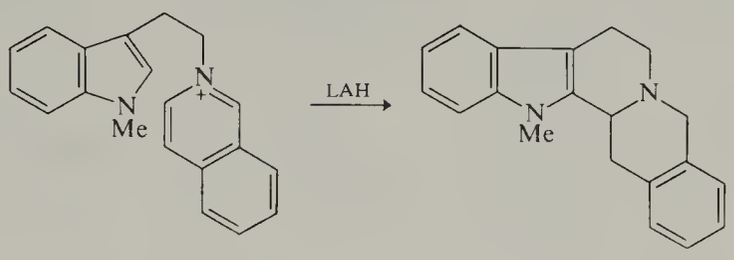
(147)

Pyridinium salts are reduced much more easily than pyridines by LAH. Reactions of quaternary salts have received much attention as they have found use in alkaloid synthesis. When the pyridinium salt (**246**; R = H) was treated with LAH the major product was the 1,2,3,6-tetrahydropyridine (**247**) rather than the desired indoloquinolizine (**248**). It was

suggested ⟨57JOC1376⟩ that this anomalous product was formed by reduction of the 1,2-dihydro intermediate by an LAH complex bonded to the indole nitrogen. This was supported by the observation that when R = Me the indoloquinolizine (R = Me) was the only product. Similarly, LAH is effective for the reductive cyclization of an isoquinolinium salt (equation 149) ⟨66AHC(6)45⟩.



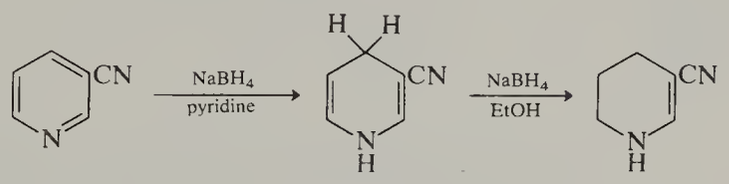
(148)



(149)

2.05.4.8.2 With sodium borohydride

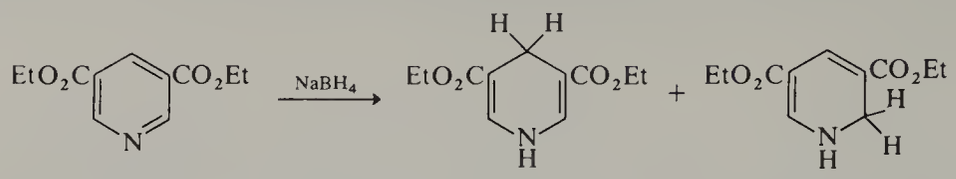
Pyridine is not reduced by sodium borohydride, but di- and tetra-hydropyridines can be obtained when the ring bears an electron-withdrawing substituent (Scheme 177). Sodium borohydride is often a more satisfactory reagent than LAH as it does not reduce substituents as readily. Pyridines that bear 3- and 5-electron-withdrawing groups can be reduced to dihydropyridines by both reagents without undergoing substituent reduction, as they are so reactive. The products of reaction are mixtures of 1,2- and 1,4-isomers, and the ratio of these isomers is solvent dependent (equation 150) ⟨72CR1⟩. The ester (**249**) gives a mixture of the 1,2- and 1,4-dihydro isomers on reaction with sodium borohydride, but it yields the pure 1,4-isomer with sodium cyanoborohydride (equation 151). Bromopyridines give unstable dihydropyridines. Reduction of monosubstituted pyridines with sodium borohydride usually stops at the dihydropyridine stage, unless a protic solvent is used (Scheme 177). On the other hand pyridinium salts are reduced by sodium borohydride to yield unstable dihydro intermediates which undergo further reduction to 1,2,5,6-tetrahydropyridines (equation 152). This is in contrast to unquaternized pyridines which yield 1,2,3,4-tetrahydropyridines on further reduction (Scheme 177).



Scheme 177

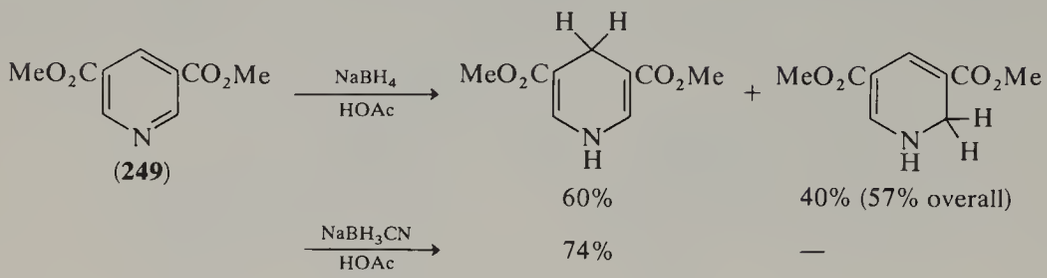
Borohydride reduction of alkylpyridinium salts produces a mixture of dihydro- and 1,2,5,6-tetrahydro-pyridines, unless alkali or cyanide is present, in which case a mixture of 1,2- and 1,6-dihydropyridines is obtained (equation 153). The pathways leading to reduction products of pyridinium salts with sodium borohydride are outlined in Scheme 178 ⟨55JCS2586⟩. The presence of an electron-withdrawing 3-substituent stabilizes dihydro intermediates. The dihydropyridines formed by borohydride reduction of *N*-phenyl quaternary salts are resistant to further reduction and can be isolated. This has been attributed to orbital overlap of the nitrogen lone pair of electrons with those of the phenyl substituent. The effect of ring substituents on the nature of the dihydropyridines formed in the reduction of 1-methyl-3-nitropyridinium ions is interesting. For example, 1-methyl-3-nitropyridinium yielded (**250**) (1,4-reduction), the 1,2-dimethyl-5-nitro salt gave (**251**) (1,2-reduction), and the 4-methoxy-1-methyl-3-nitro derivative afforded (**252**) (1,6-reduction) ⟨70CB1⟩. 2-Substituted-1-methylpyridinium salts, as expected, are reduced to 1,2,3,6-tetrahydropyridines (Scheme 179). 1,4-Disubstituted pyridinium salts also give 1,2,3,6-tetrahydropyridines on treatment with sodium borohydride, but in this case there is no possibility

of isomeric intermediates. The dihydropyridines obtained by reduction of 1,3,5-trisubstituted pyridinium salts are useful intermediates in benzomorphan synthesis (Scheme 180) ⟨66AHC(6)45⟩.



(150)

pyridine 87% 13% (74% overall)
MeCN 37% 63% (58% overall)

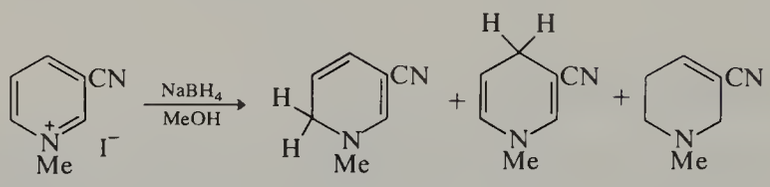


(151)

(**249**)

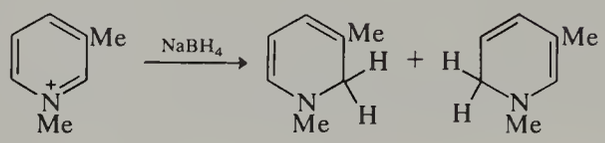
60% 40% (57% overall)

$NaBH_3CN$, HOAc: 74% —

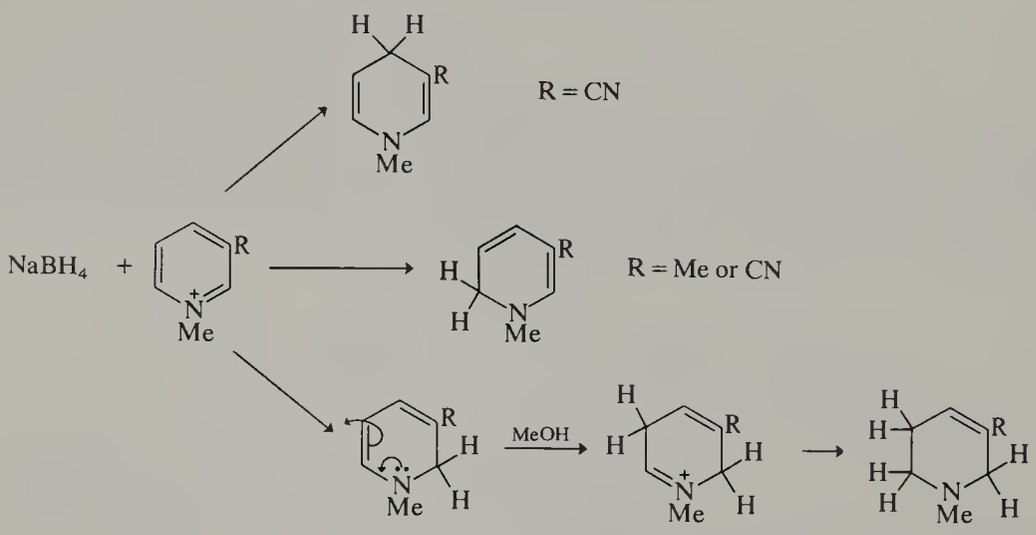


(152)

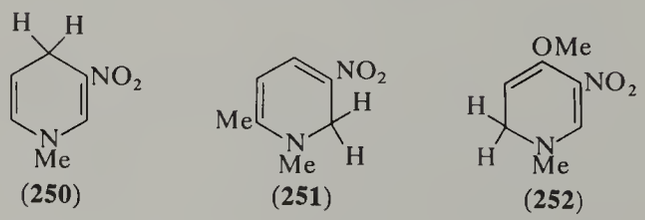
7% 14% 34%



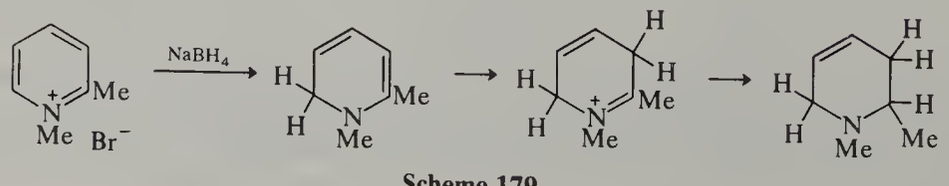
(153)



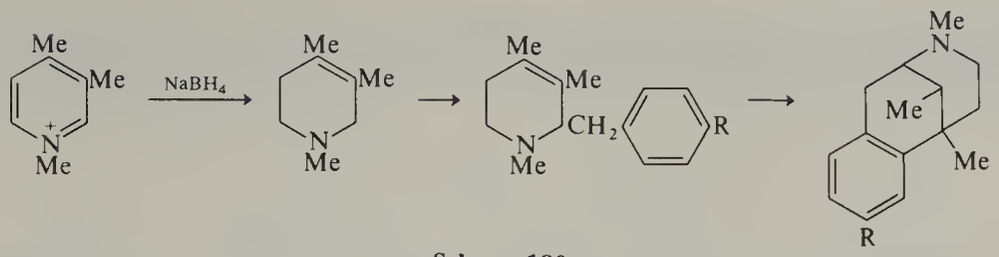
Scheme 178



(**250**) (**251**) (**252**)

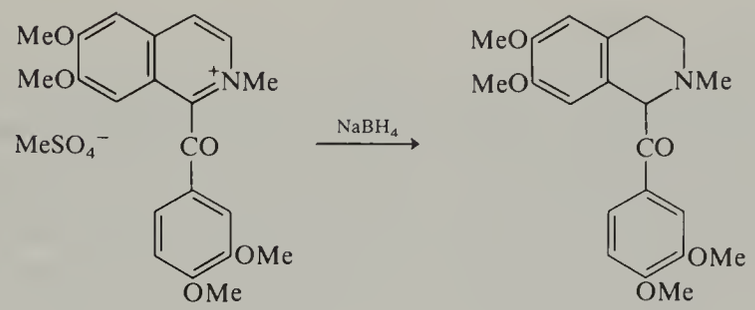


Scheme 179

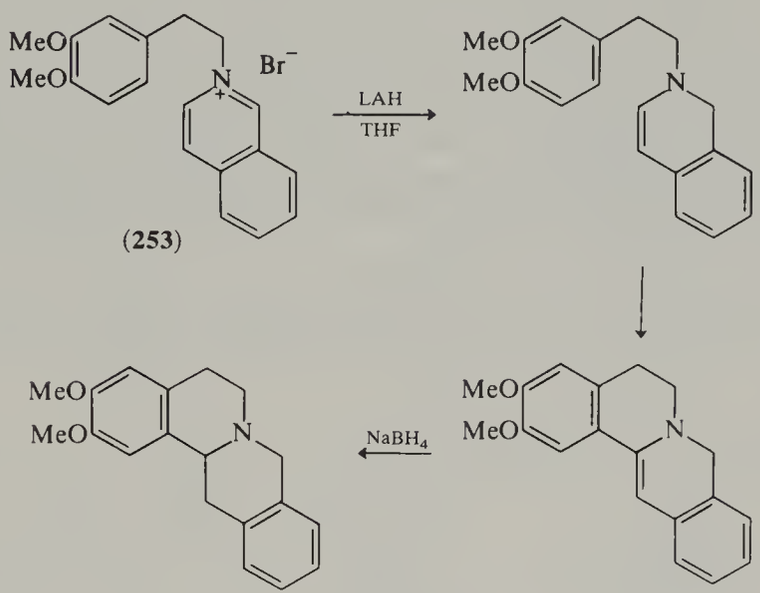


Scheme 180

Sodium borohydride is the reagent of choice for the reduction of the pyridine ring in isoquinolinium salts. It reacts so rapidly that even the carbonyl group of a 1-aroyl substituent can survive (equation 154) ⟨63JCS2487⟩. A 1,2-dihydro intermediate has been isolated during the cyclization of (**253**) to 2,3-dimethoxyberbine by sodium borohydride, which suggests that a similar mechanism to that described above is operative here (equation 155) ⟨60JOC90⟩.



(154)

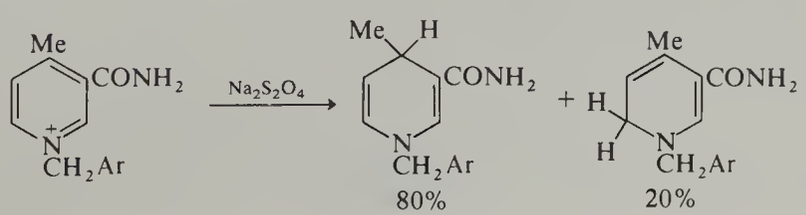


(253)

(155)

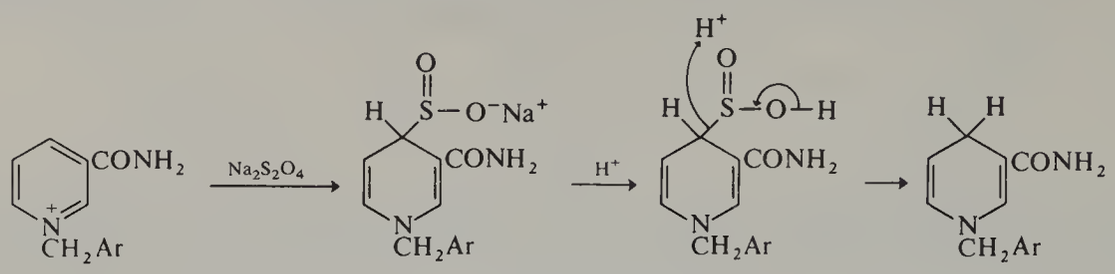
2.05.4.8.3 With sodium dithionite

Sodium dithionite attracted attention as a reducing agent quite a long time ago when it was found that it could be used to convert NAD to NADH ⟨35MI20500⟩. Many 3- and 3,5-disubstituted pyridinium salts subsequently were found to be reduced by this reagent, particularly NAD models bearing alkyl, benzyl and carbohydrate groups attached to nitrogen. Reduction to 1,4-dihydropyridines is overwhelmingly favoured over 1,2- or 1,6-reduction, contrary to some earlier reports ⟨72CR1⟩. However, small amounts of 1,2- or 1,6-dihydro isomers are found as products of the reduction of nicotinamide and nicotinonitrile salts that carry a substituent at C-4 (equation 156) ⟨68BSF1159⟩.



(156)

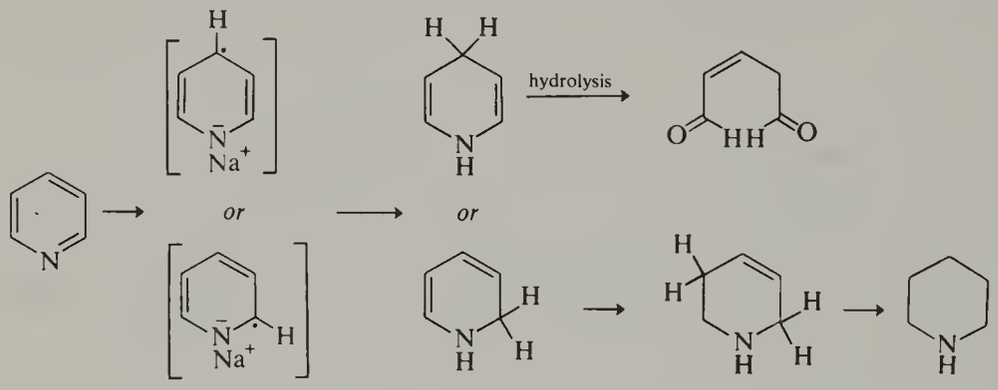
The mechanism of this reduction involves initial formation of a sodium sulfinate intermediate, which is stable in alkaline solution and can be isolated. In acid or neutral solution it decomposes as shown (Scheme 181) to yield the 1,4-dihydropyridine product.



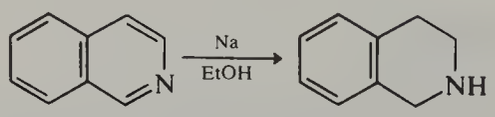
Scheme 181

2.05.4.8.4 One-electron reduction

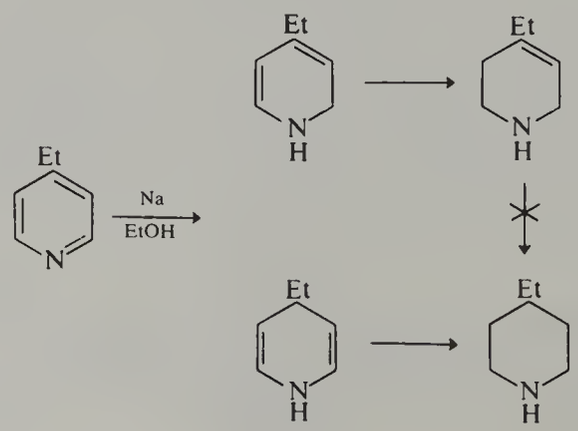
Reduction of pyridines with sodium in ethanol (Ladenburg reduction) usually gives the corresponding piperidines (Scheme 182) ⟨70AHC(12)43⟩. Hydrolysis of the reaction mixture gives some glutaconic dialdehyde. Isoquinoline yields a tetrahydro product on similar treatment (equation 157), but quinoline is only reduced to the 1,2-dihydro derivative by sodium in liquid ammonia. Some 4-substituted pyridines are also more difficult to reduce than pyridine, and tetrahydro derivatives accompany piperidine formation (Scheme 183). Addition of the first mole of hydrogen can take place 1,2 or 1,4, and the 1,4-dihydro derivative is easily reduced further. Only one more mole of hydrogen can be added to the 1,2-dihydro intermediate to form 4-ethyl-3-piperideine, which is stable to the reaction conditions and can be isolated ⟨70AHC(12)43⟩. Pyridin-4-one may be converted to 4-piperidinol by Ladenburg reduction. Reduction of 2,4,6-trimethylpyridine yields a mixture of *cis*-2,4,6-trimethyl-3-piperideine and three isomeric 2,4,6-trimethylpiperidines ⟨69CCC1985⟩. Treatment of pyridine with sodium in an aprotic solvent results in dimerization of the initially formed pyridinyl radical rather than further reduction (Scheme 184).



Scheme 182

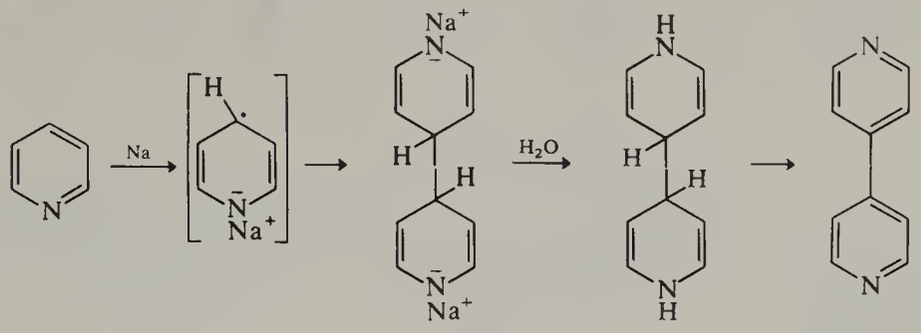


(157)



Scheme 183

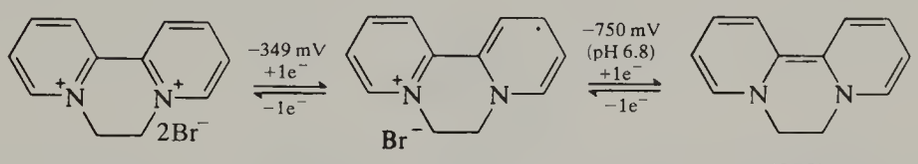
Bipyridyls are by-products in the Chichibabin reaction. The dimerization of methylpyridinium salts has been patented, as it provides a route to the important herbicide paraquat ⟨69USP3478042⟩. Pyridine may undergo reduction in the presence of other metals as mentioned in Sections 2.05.4.7.5 and 2.05.4.7.6.



Scheme 184

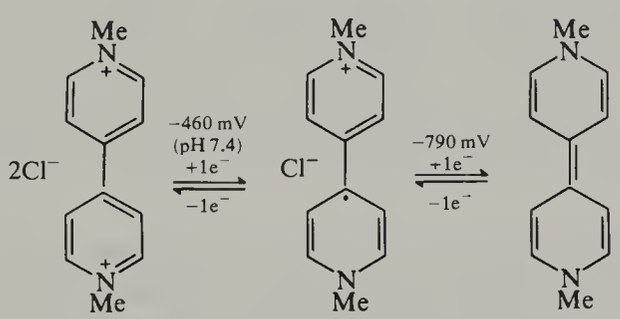
Pyridine was first found to undergo reduction to piperidine at a lead cathode in 10% sulfuric acid late last century ⟨1895MI20500⟩. There has been a reawakening of interest in the electrochemistry of organic compounds in recent years. Pyridine electrochemistry has been no exception to this trend. Several reviews have appeared, portions of which are devoted to the electrochemistry of pyridines ⟨70AHC(12)213, 77CJC3392, B-80MI20504⟩. Substituents attached to the pyridine nucleus exert a similar effect to that in chemical reductions. Electron-withdrawing substituents make the nucleus more susceptible to reduction, whereas electron-donating groups make oxidation easier. The redox reactions of quaternary bipyridinium salts, and of NAD^+ and its analogues, are the two areas that have received most attention.

Some bipyridinium salts are remarkable herbicides. They rapidly desiccate all green plant tissue with which they come into contact, and they are inactivated by adsorption on to clay minerals in the soil. This potent herbicidal activity is found only in quaternary salts, *e.g.* diquat (**254**) and paraquat (**255**), with redox potentials for the first reduction step between −300 and −500 mV (equations 158 and 159) ⟨B-80MI20504⟩. The first reduction step, which is involved in herbicidal activity, involves a completely reversible, pH independent, one-electron transfer to yield the resonance stabilized radicals (**256**) and (**257**). The second reduction step, (**256** → **258**) and (**257** → **259**), is pH dependent and the *p*-quinoid species formed are good reducing agents that may readily be oxidized to diquaternary salts.



(158)

(**254**) (**256**) (**258**)

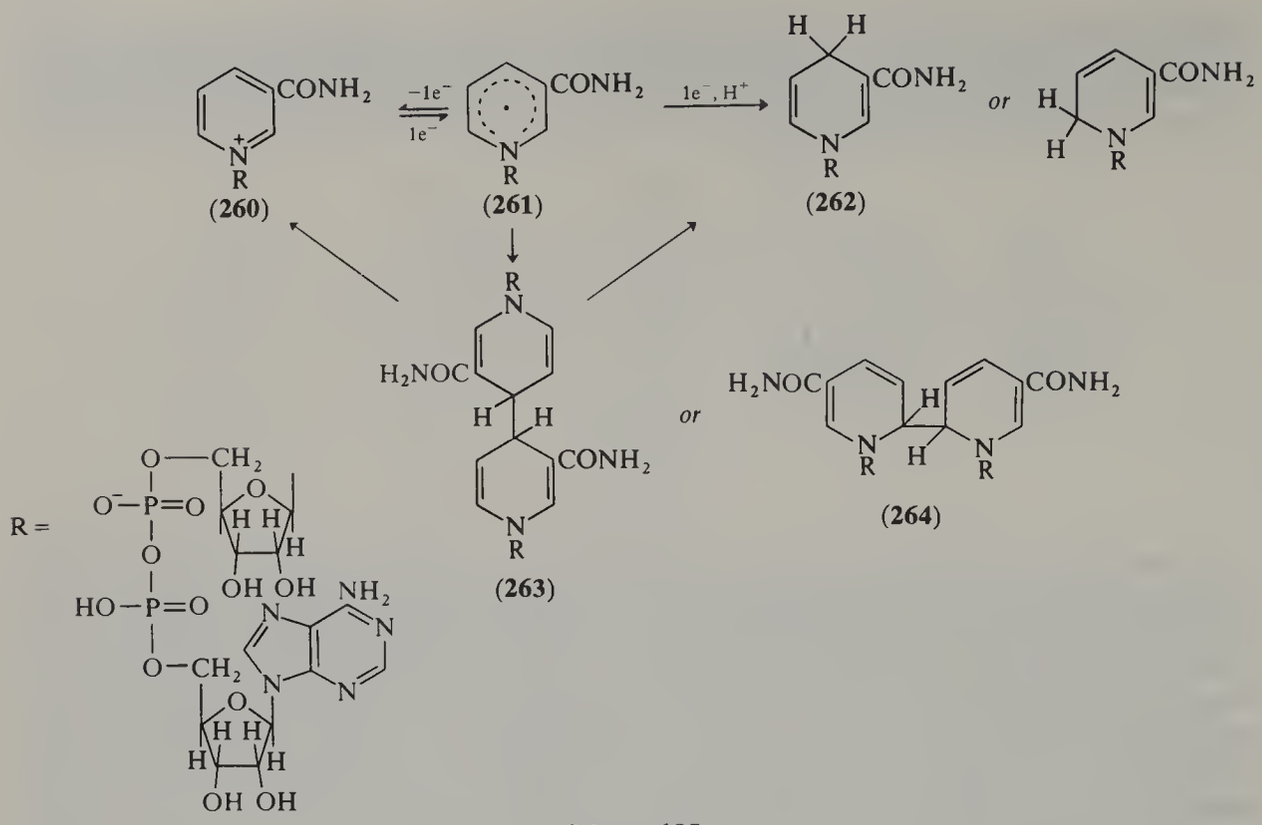


(159)

(**255**) (**257**) (**259**)

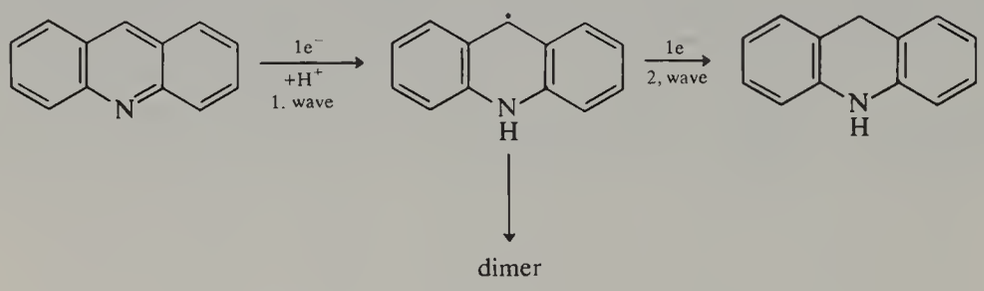
A simplified picture of the electrochemical reduction of NAD^+ (**260**) to NADH (**262**) and other products is illustrated (Scheme 185) ⟨75JA5083⟩. The first reduction of NAD^+ to the radical (**261**) is pH independent, and this free radical rapidly dimerizes to (**263**) or (**264**). At more negative potential, NAD^+ is reduced to a dihydropyridine by one-electron reduction of (**261**), but the dimer is not reduced at this potential.

Quinoline and isoquinoline undergo reduction in a similar way to pyridine but with greater ease. Acridine may be polarographically reduced in both acid and alkaline solution.

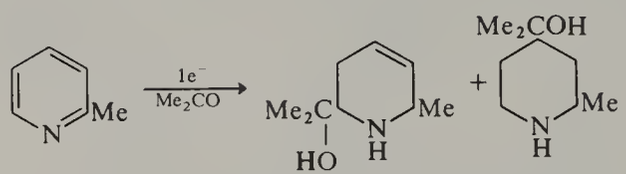


Scheme 185

A single one-electron wave was found in strong acid solution, but in weaker acid or alkaline solution two one-electron waves were observed (Scheme 186). Pyridine and acetone undergo Emmert reaction and further reduction on electrolysis in dilute sulfuric acid using lead electrodes (equation 160) ⟨69CCC2108⟩.



Scheme 186

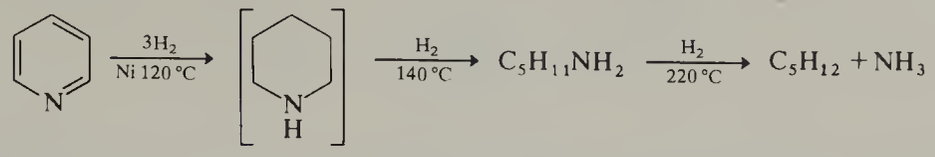


(160)

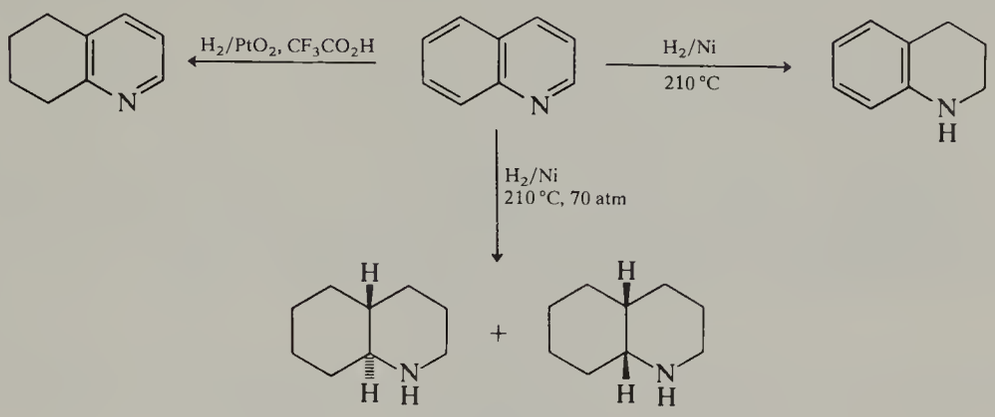
2.05.4.9 Hydrogenation

Platinum oxide or rhodium on a carrier are the most effective catalysts for the low-pressure hydrogenation of pyridine to piperidine. Raney nickel requires higher temperatures and pressures for success. Three notable reviews of the hydrogenation of pyridines have appeared ⟨63MI20500, B-67MI20502, B-71MI20503⟩. Pyridines are usually reduced in acidic solution to avoid poisoning of the catalyst by the pyridine nitrogen atom. Pyridinium chloride can be reduced readily to piperidine in absolute alcohol or glacial acetic acid, but the presence of water causes serious inhibition of reaction. Cracking may occur when higher temperatures are used (Scheme 187). High temperature hydrogenations in alcohols can lead to *N*-alkylation of the piperidines formed. Attachment of an α-methyl substituent to pyridine resulted in an increased rate of hydrogenation compared with pyridine when hydrogen and ruthenium dioxide were employed. The effect is even greater for 2,6-dimethylpyridine. The pyridine ring of quinoline undergoes hydrogenation before the benzene ring on hydrogena-

tion over nickel at 210 °C, but more severe conditions give a mixture of *cis*- and *trans*-decahydroquinolines (Scheme 188). The pyridine ring of isoquinoline is also hydrogenated first; however, hydrogenation of the benzene ring is more difficult than in quinoline.

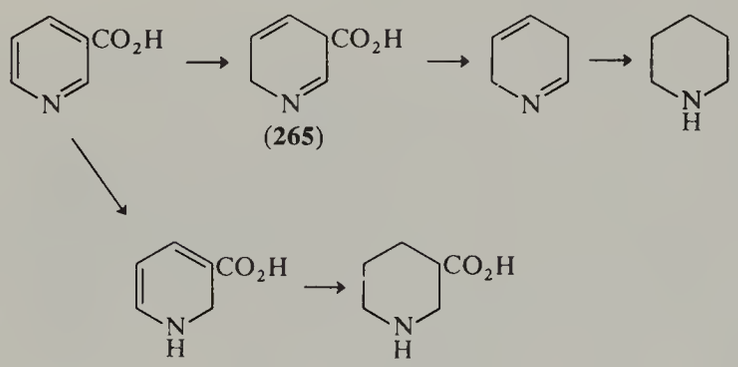


Scheme 187



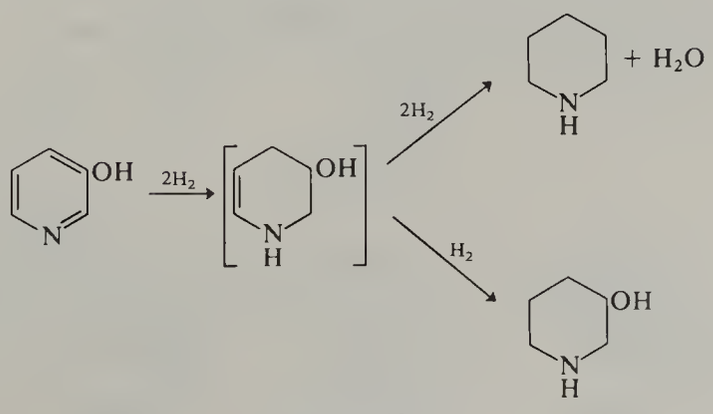
Scheme 188

Nicotinic acid forms some piperidine as well as nipecotic acid when it is reduced with hydrogen over ruthenium, rhodium or platinum oxide; presumably decarboxylation involves the intermediate 3,6-dihydro compound (**265**), which behaves like a β-keto acid (Scheme 189).



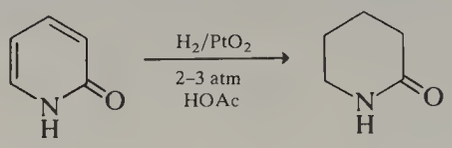
Scheme 189

Decarboxylation can be avoided by employing dilute hydrochloric acid as solvent. On the other hand, hydrogenation with retention of the carboxyl group may be achieved using rhodium on alumina in an aqueous solution that contains a slight excess of ammonia. Some loss of a hydroxy substituent was observed in the hydrogenation of 3-pyridinol (Scheme 190). Hydrogenation of pyridin-2-one gives piperid-2-one (equation 161) and pyridin-4-one yields 4-hydroxypiperidine under the conditions indicated (equation 162). 3-Aminopyridine is readily hydrogenated to 3-aminopiperidine, but 4-aminopyridine undergoes this reaction

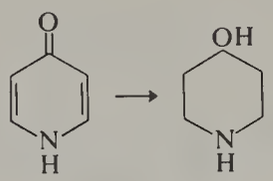


Scheme 190

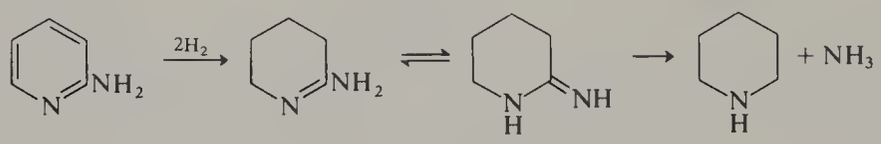
less readily. 2-Aminopyridine is initially reduced to the tetrahydro derivative which undergoes further hydrogenation to piperidine and ammonia (Scheme 191).



(161)



(162)



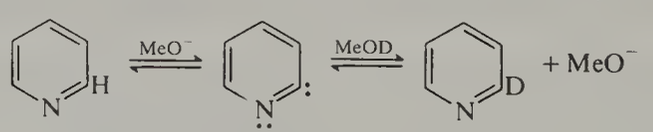
Scheme 191

Pyridinium salts can be reduced more easily than the corresponding pyridines, and yields are higher because the resulting *N*-methylpiperidines do not poison the catalyst.

2.05.5 NUCLEOPHILIC ATTACK AT HYDROGEN

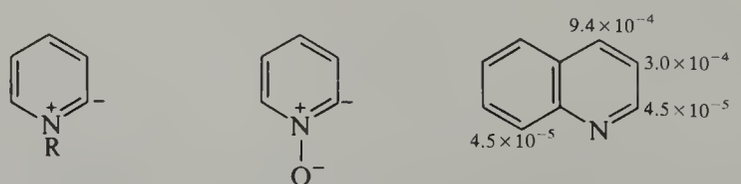
2.05.5.1 Base-catalyzed Hydrogen–Deuterium Exchange

Pyridine undergoes base-catalyzed hydrogen–deuterium exchange much more readily than benzene. The reactivity order $\gamma > \beta > \alpha$ is found for exchange in NaOMe–MeOD at 164.6 °C, NaOD–D_2O at 200 °C and $NaND_2$–ND_3 at −25 °C. The apparent anomalously low reactivity of the 2-position has been attributed to the unfavorable lone pair–lone pair interaction in the intermediate carbanion (**266**; Scheme 192). Pyridinium salts and *N*-oxides undergo exchange most easily at C-2 *via* the ylides (**267**) and (**268**) where no unfavorable interaction exists. In aqueous solution, base-catalyzed hydrogen–deuterium exchange of pyridine is believed to involve the pyridinium ion (Scheme 193) ⟨74AHC(16)1⟩. Quinoline undergoes hydrogen–deuterium exchange in NaOMe–MeOD, at 190.6 °C at the 2-, 3-, 4- and 8-positions (**269**) ⟨73JA3928⟩. Isoquinoline exchanges at C-4 more easily than at C-1 with KOMe–MeOD at 160 °C. Attachment of an electron-withdrawing group at C-4 in a pyridine ring accelerates exchange at C-3. Similar substitution at C-3 promotes exchange at C-4. In both of these cases, exchange is slowest at C-2. 4-Amino- and 4-dimethylaminopyridine undergo exchange at the α- and β-positions, but α-exchange predominates in less basic solution. Treatment of 3-chloropyridine with strong base yields 3,4-pyridyne rather than the 2,3-isomer. The fact that the rate of hydrogen–deuterium exchange of this compound at C-2 is immeasurably slower than at C-4 has been taken as evidence that the 3,4-pyridyne is formed *via* the carbanion (Scheme 194) ⟨66JA4766⟩.

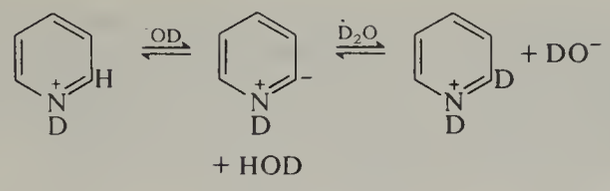


(**266**)

Scheme 192

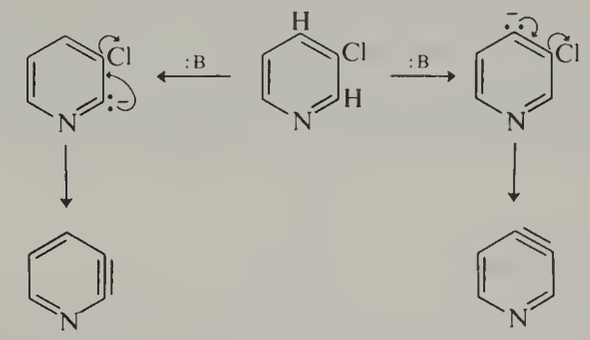


(**267**) (**268**) (**269**)

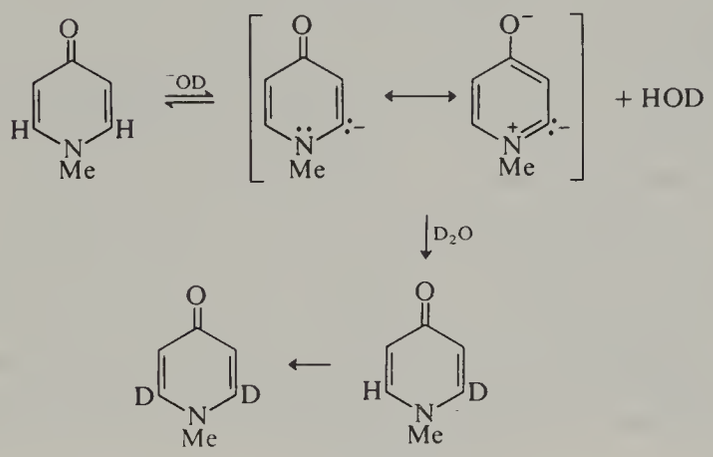


Scheme 193

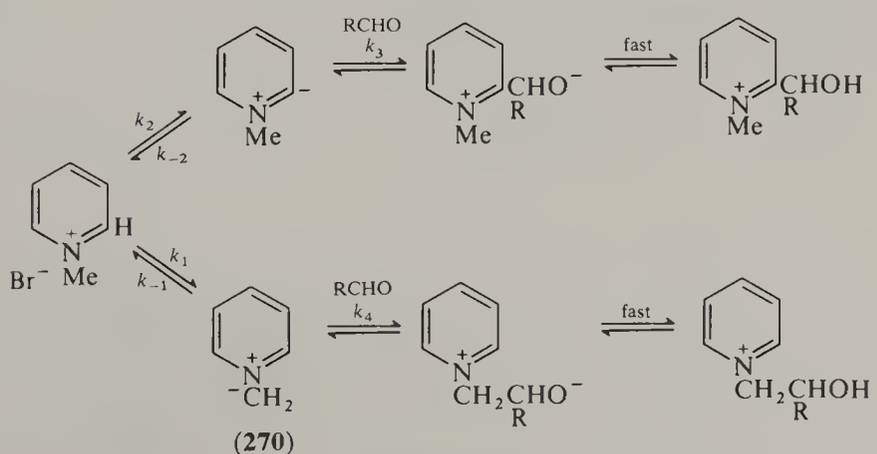
1-Methylpyridin-4-one (and 1-methylpyridin-2-one) undergoes H–D exchange at the 2- and 6-positions in basic D_2O at 100 °C (Scheme 195) ⟨65JA3365⟩. Hydrogen isotope exchange is most facile at the α-position in pyridinium salts. 3-Methyl- and 3-cyano-pyridinium methiodides undergo exchange in the order $2 > 6 \gg 4,5$ in 0.1M NaOD–D_2O. The relative rates of H–D exchange for the α-, β- and γ-positions in 1-methylpyridinium chloride in phosphate-buffered D_2O are 3400:3:1. An electron-withdrawing group at C-3 activates exchange at the α-positions; the 1-methylnicotinamide cation exchanges faster than 1-methylpyridinium in sodium carbonate–D_2O at 100 °C ⟨69JA6115⟩. Exchange also takes place at the *N*-methyl group *via* the ylide (**270**), but this is some 300 times slower than at the α-position. Rather surprisingly, condensation of 1-methylpyridinium bromide with aldehydes in the presence of base occurs exclusively at the *N*-methyl position. This has been accounted for by the relative rates of the equilibria (Scheme 196): $k_1 \ll k_{-1}$, $k_2 \ll k_{-2}$, $k_2 > k_1$, and $k_4/k_{-1} > k_3/k_{-2}$.



Scheme 194



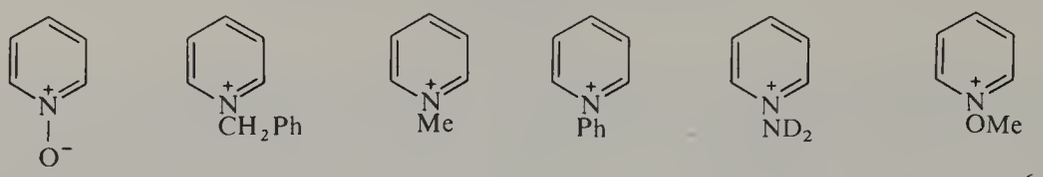
Scheme 195



(270)

Scheme 196

The rates of H–D exchange at the α-positions have been determined for a series of *N*-substituted pyridinium salts and pyridine 1-oxides in D_2O at 75 °C (Scheme 197) ⟨70JA7547⟩. The rates give a good correlation with the Taft inductive parameter σ_I ($\rho_I = 15$). The positively charged nitrogen in a ring has been estimated to activate the α-position towards deprotonation and ylide formation by a factor of 10^{14-16}.

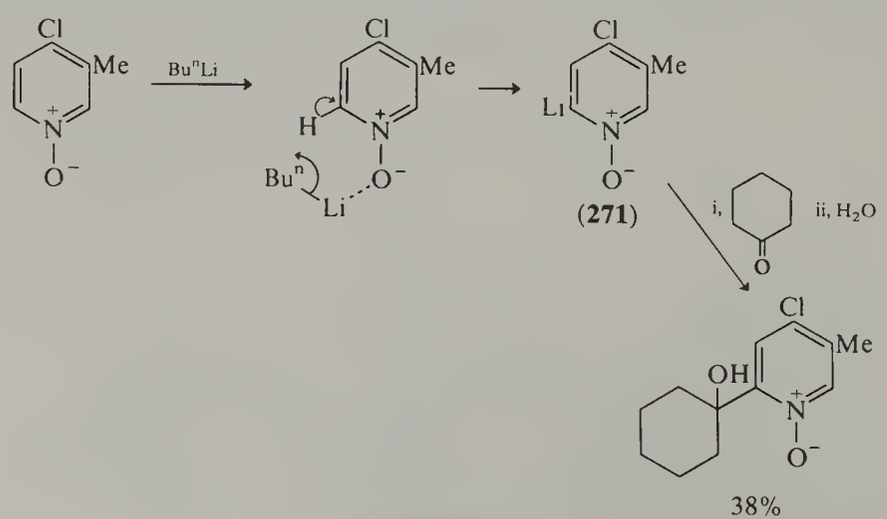


Scheme 197

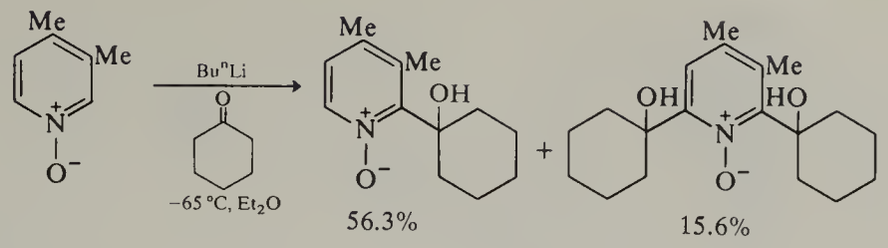
Pyridine *N*-oxides show the same relative positional reactivity towards base-catalyzed H–D exchange as do pyridinium cations. Exchange in 3-bromopyridine 1-oxide with 0.1M $NaOD–D_2O$ follows the order $2 > 6 > 4 \gg 5$ ⟨67CC55⟩. Attachment of an electron-withdrawing group at C-3 or C-4 favours exchange, the effect being greater in the former case. Evidence for ylide intermediacy in pyridine 1-oxide reactions comes from trapping experiments with cyclohexanone in the presence of *n*-butyllithium in non-protic solvents (*vide infra*) ⟨74HC(14-S2)1⟩. Further support was adduced from the fact that the relative rates of exchange in pyridine 1-oxides parallel those for the decarboxylation of *N*-methylpyridinium carboxylates where ylide intermediates are well documented (see Chapter 2.06) ⟨37JCS1724⟩. Exchange next to the heteroatom is favored for quinoline and isoquinoline *N*-oxides. The positional selectivity $1 \gg 3 \gg 4$ is observed for exchange (KOMe–MeOD) in isoquinoline 2-oxide. Quinoline 1-oxide undergoes exchange only at C-2.

2.05.5.2 α-Lithiation of *N*-Oxides

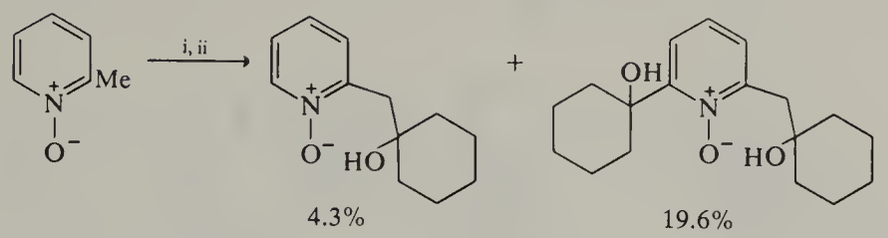
α-Lithio derivatives (**271**) can be generated in non-protic conditions by treating pyridine 1-oxides with *n*-butyllithium. These may be intercepted by various electrophiles (path **E** behaviour) such as cyclohexanone (Scheme 198). When two equivalents of butyllithium are employed, some disubstitution is observed (equation 163) ⟨72JOC1690⟩. This reaction is fairly general, but yields are variable ⟨74HC(14-S2)1⟩. 2-Methylpyridine 1-oxide also undergoes attack at the α-methyl group (equation 164). Extension to trapping with other electrophiles has met with mixed success. Use of an ester yields a ketone (equation 165), but reaction with epoxides only gives vinyl polymer and no alcohols ⟨74HC(14-S2)1⟩. Treatment of the 6-lithio derivative of 3,4-dimethylpyridine 1-oxide with *N*,*N*-dimethylacetamide ultimately affords (**272**; Scheme 199) ⟨74HC(14-S2)1⟩. Reaction of substituted lithio *N*-oxide derivatives with carbon dioxide gives mono- or di-carboxylic acids (equation 166) ⟨67JA1537⟩. Other reactions of lithio derivatives with sulfur, oxygen, bromine and a Schiff's base are illustrated in Scheme 200. 2-Lithiopyridine 1-oxide has been mercurated with mercury(II) chloride to give a mixture of mercury derivatives. The mixture was not resolved, but yielded 2-bromo- and 2,6-dibromo-pyridine 1-oxides on bromination (Scheme 201) ⟨72JOC1690⟩.



Scheme 198

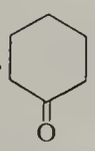


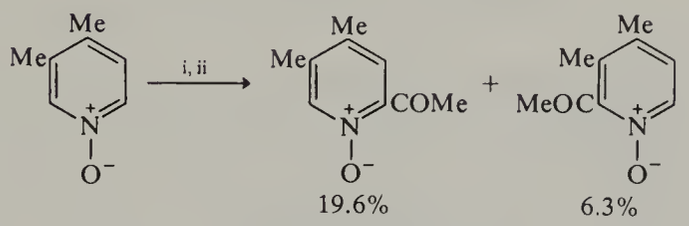
(163)



(164)

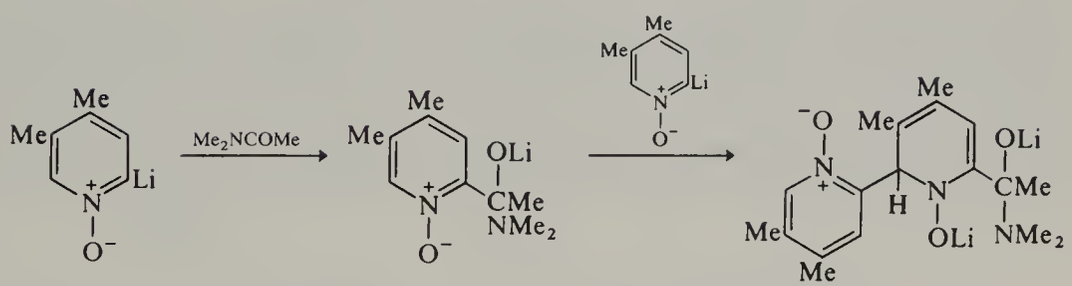
i, Bu^{n}Li, −65 °C, THF; ii,

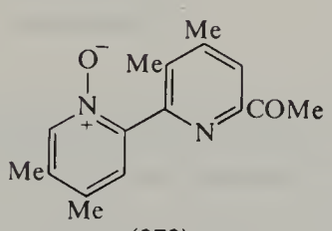




(165)

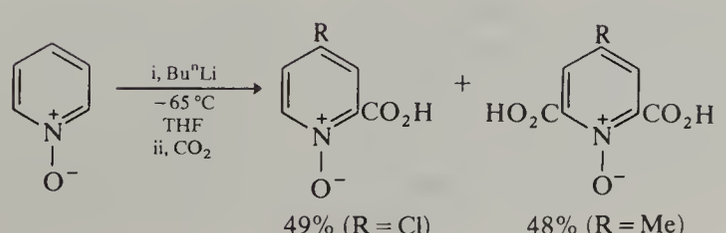
i, Bu^{n}Li, −65 °C, THF; ii, MeCO$_2$Et



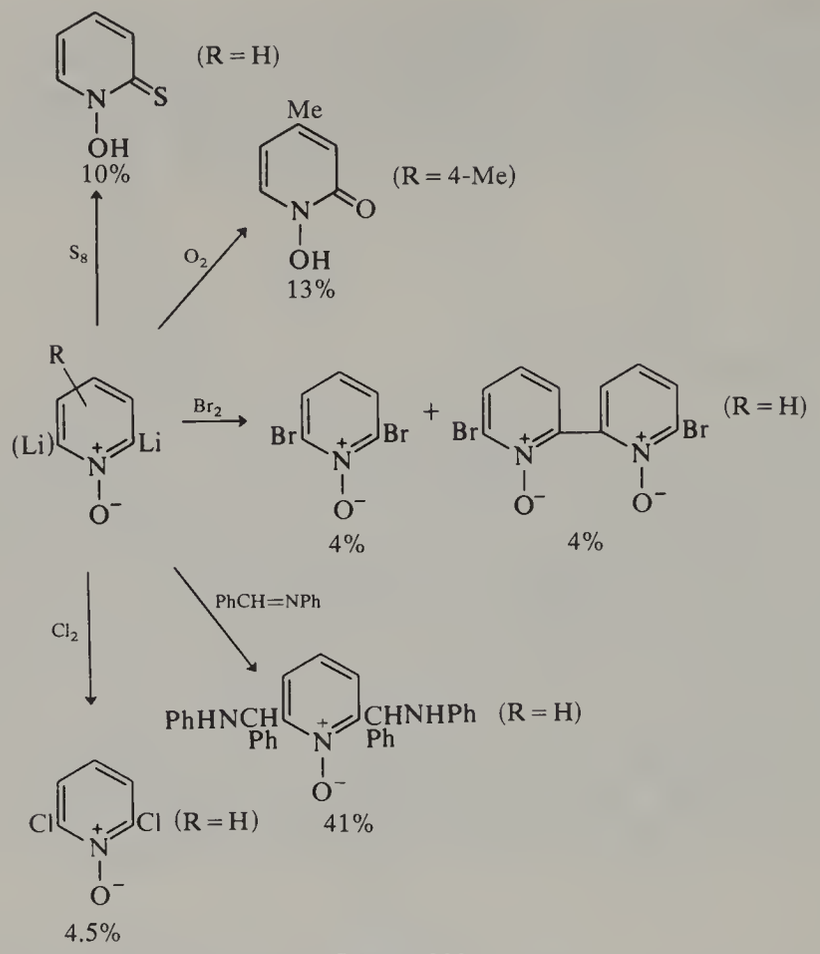


(272)

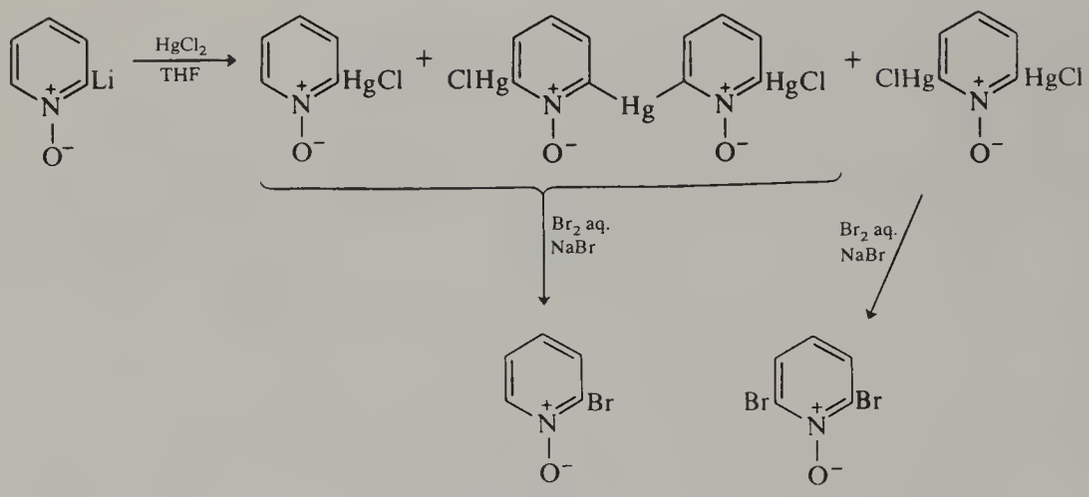
Scheme 199



(166)

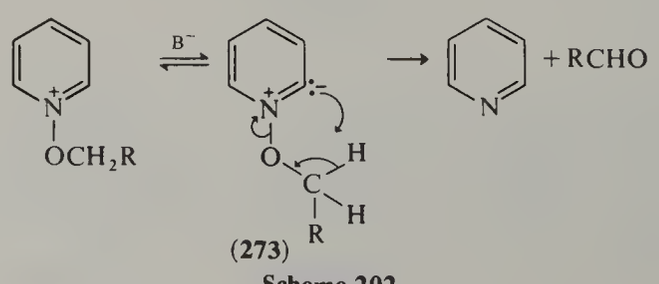


Scheme 200

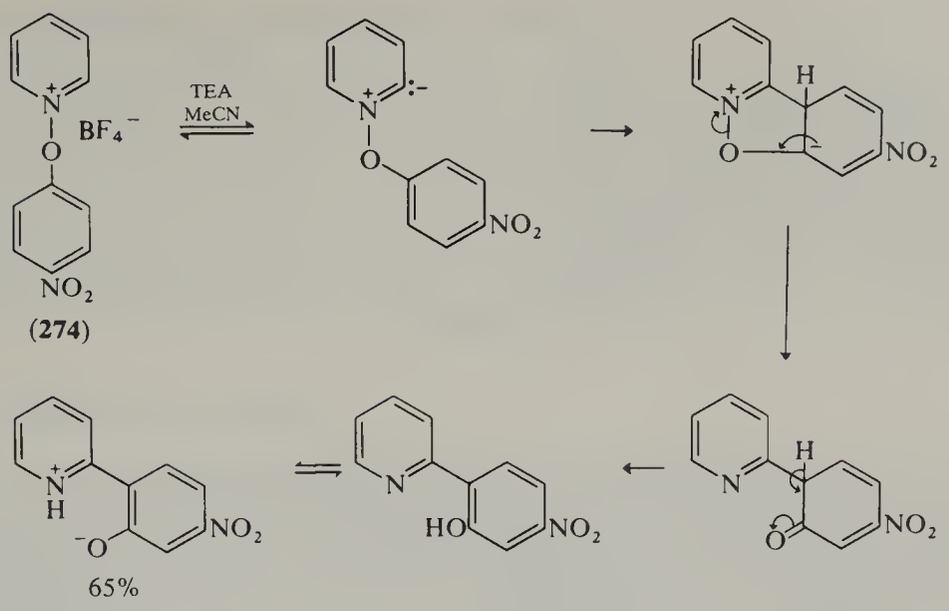


Scheme 201

It has been pointed out ⟨75TL213⟩ that path **A** behavior might be more complex in some instances, and involve initial ylide formation followed by intramolecular proton abstraction (Scheme 202). The aryloxy quaternary salt (**274**), formed by reaction of pyridine 1-oxide with an arenediazonium salt, undergoes an interesting base-catalyzed rearrangement that is believed to take the course (path **E**) indicated (Scheme 203) ⟨71JA3074⟩.



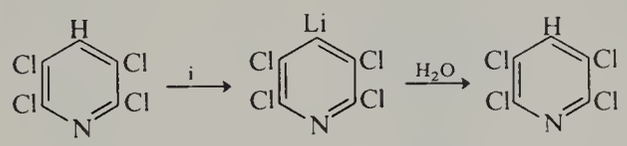
Scheme 202



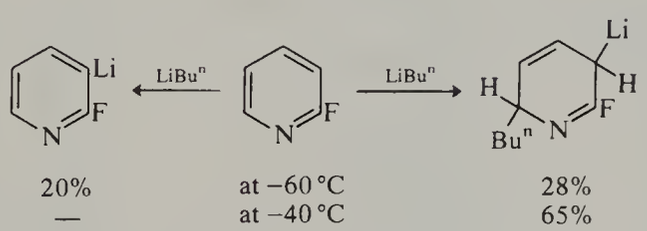
Scheme 203

2.05.5.3 Lithiation of Substituted Pyridines

Metal–halogen exchange may be used to prepare pyridyllithium compounds ⟨B-74MI20503⟩. However, treatment of 2,3,5,6-tetrachloropyridine with *n*-butyllithium in diethyl ether at −75 °C was found to give a solution of tetrachloro-4-pyridyllithium, rather than metal–halogen exchange ⟨69JCS(C)1973⟩. This intermediate could be hydrolyzed back to starting material (Scheme 204). Many more examples of lithiation are now known. Usually pyridyllithium compounds are formed regiospecifically and they are useful for the introduction of certain electrophiles into the pyridine nucleus (Table 24). It is important for success that lithiation is carried out at low temperature (typically *n*-butyllithium at *ca.* −60 °C in diethyl ether or THF has been used) to avoid competing addition reactions. In one instance ⟨78TL227⟩ methyllithium gave quantitative lithiation whereas *n*-butyllithium, *s*-butyllithium, *t*-butyllithium and LDA gave mixtures of the lithio derivative and 1,2-adduct. The effect of temperature upon the competition between addition and metallation has been studied during the reaction of *n*-butyllithium with 2-fluoropyridine (Scheme 205) ⟨81JOC4494⟩.

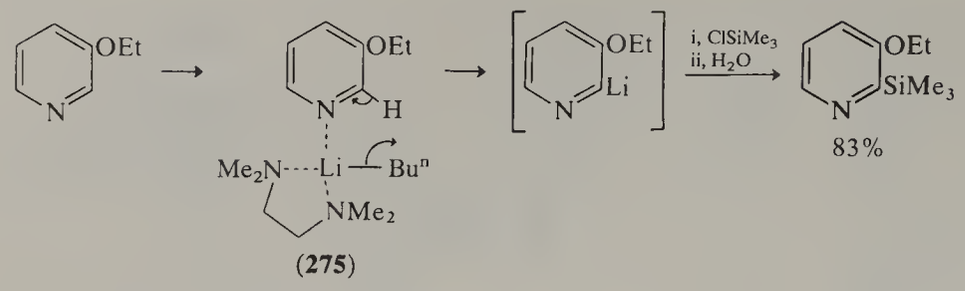


Scheme 204



Scheme 205

2-Substituted pyridyllithiums usually undergo attack by electrophiles at C-3, but the reaction of 2-chloropyridine with pentan-3-one provides an exception, giving 6-substitution ⟨72CR(C)(275)1535⟩. 3-Halo- and 3-oxazinyl-pyridines are lithiated regiospecifically at C-4, although a little 3-chloro-2-pyridyllithium is trapped by propan-3-one. However, 3-alkoxypyridines have been found recently to undergo predominant 2-lithiation. This change in orientation was attributed to stabilization of (**275**) by coordination of the lithium atom by the pyridine nitrogen and TMEDA (Scheme 206) ⟨82S235⟩.



(**275**)

Scheme 206

Table 24 Reaction of Electrophiles with Lithiopyridines

Pyridine	*Electrophile*	*Position of substitution*	*Yield (%)*	*Ref.*
2-F	Et_2CO	3-CEt_2OH	25	72CR(C)(275)1535
2-F	MeCHO	3-CHMeOH	93	81JOM(215)139
2-F	PhCHO	3-CHPhOH	95	81JOM(215)139
2-F	2-$MeOC_6H_4CHO$	3-CH(2-$MeOC_6H_4$)OH	95	81JOM(215)139
2-F	4-$MeOC_6H_4CHO$	3-CH(4-$MeOC_6H_4$)OH	60	81JOM(215)139
2-F	2-$NO_2C_6H_4CHO$	3-CH(2-ClC_6H_4)OH	43	81JOM(215)139
2-Cl	Et_2CO	6-CEt_2OH	10	72CR(C)(275)1535
2-Cl	$ClSiMe_3$	3-$SiMe_3$	74	80TL4137
2-$CONHCH_2Ph$	4-MeC_6H_4COCl	3-COC_6H_4Me-4	89	81S127
2-$CONHCH_2Ph$	PhCOCl	3-COPh	80	81S127
2-$CONHCH_2Ph$	4-ClC_6H_4COCl	3-COC_6H_4Cl-4	84	81S127
2-$CONHCH_2Ph$	4-MeC_6H_4CHO	3-CH(4-MeC_6H_4)OH	64	81S127
2-$CONHCH_2Ph$	Ph_2CO	3-CPh_2OH	72	81S127
2-CONHMe	PhCOCl	3-COPh	56	81S127
2-CONHMe	4-MeC_6H_4COCl	3-COC_6H_4Me-4	49	81S127
2-CONHMe	4-MeC_6H_4CHO	3-CH(4-MeC_6H_4)OH	58	81S127
2-CONHMe	4-$MeOC_6H_4CHO$	3-CH(4-$MeOC_6H_4$)OH	61	81S127
2-CONHMe	Ph_2CO	3-CPh_2OH	66	81S127
3-F	$ClSiMe_3$	4-$SiMe_3$	87	80TL4137
3-F	I_2	4-I	50	80TL4137
3-Cl	$ClSiMe_3$	4-$SiMe_3$	96	80TL4137
3-Cl	I_2	4-I	65	80TL4137
3-Cl	PhSSPh	4-SPh	75	80TL4137
3-Cl	PhCHO	4-CHPhOH	57	80TL4137
3-Cl	Me_2CO	4-CMe_2OH	28	80TL4137
3-Cl	Ph_2CO	4-CPh_2OH	65	80TL4137
3-Cl	Et_2CO	2-CEt_2OH	15	72CR(C)(275)1535
		4-CEt_2OH	35	72CR(C)(275)1535
3-Br	PhSSPh	4-SPh	61	80TL4137
3-OEt	$ClSiMe_3$	2-$SiMe_3$	83	82S235
3-OEt	$IAsMe_2$	2-$AsMe_2$	65	82S235
3-OEt	MeCHO	2-CHMeOH	58	82S235
3-OEt	Et_2CO	2-CEt_2OH	60	82S235
3-OEt	4-$MeOC_6H_4CHO$	2-CH(4-$MeOC_6H_4$)OH	39	82S235
3-OEt	Me_2NCHO	2-CHO	27	82S235
3-OMe	MeCHO	2-CHMeOH	49	82S235
3-OCH_2Ph	$ClSiMe_3$	2-$SiMe_3$	44	82S235
3-oxazinyl	D_2O	4-D	70	78H(11)133
3-oxazinyl	PhCHO	4-CHPhOH	47	78H(11)133
3-oxazinyl	Et_2CO	4-CEt_2OH	52	78H(11)133
4-F	Et_2CO	3-CEt_2OH	65	72CR(C)(275)1535
4-Cl	Et_2CO	3-CEt_2OH	60	72CR(C)(275)1535
4-Cl	$ClSiMe_3$	3-$SiMe_3$	92	80TL4137
4-oxazinyl	D_2O	3-D	80	78TL227
4-oxazinyl	EtI	3-Et	56	78TL227
4-oxazinyl	MeI	3-Me	63	78TL227
4-oxazinyl	CH_2CHCH_2Br	3-CH_2CHCH_2	55	78TL227
4-oxazinyl	PhCHO	3-CHPhOH	83	78TL227
4-oxazinyl	Et_2CO	3-CEt_2OH	76	78TL227
4-oxazinyl	Me_2NCHO	3-CHO	52	78TL227
3-F-4-Cl	Et_2CO	6-CEt_2OH	40	72CR(C)(275)1535

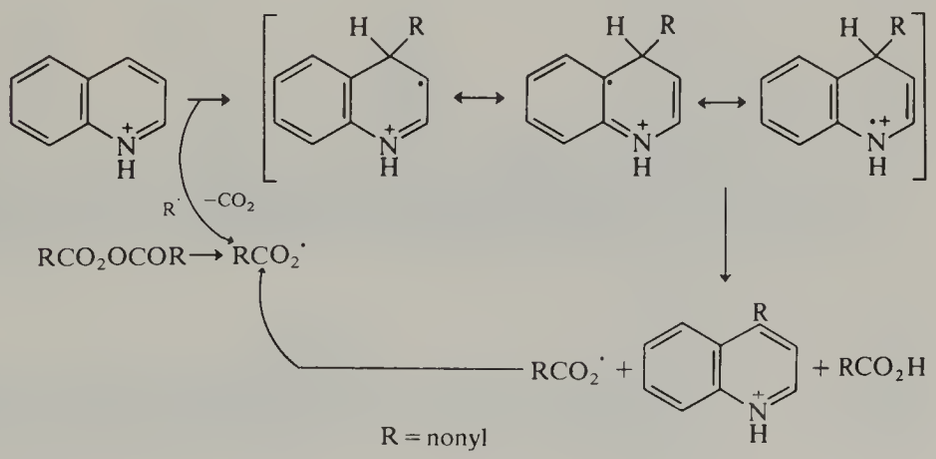
2.05.6 FREE-RADICAL ATTACK AT CARBON

Homolytic substitution in the pyridine series has not been as well studied as heterolytic reactions, because of poor yields, poor selectivity and the less ready availability of suitable radical sources. The chief interest originally was in the use of homolytic substitution to probe aromatic reactivity, which has been reviewed ⟨63AHC(2)131, 66AHC(6)229, 74HC(14-S1)1⟩. The recognition that polar character plays an important part in free radical reactions, particularly of protonated pyridines, has led to the discovery of some potentially useful high yield regiospecific reactions ⟨74AHC(16)123, 76MI20503⟩.

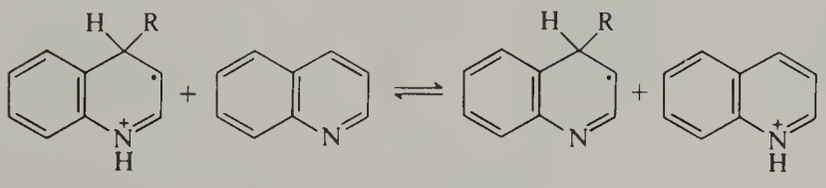
2.05.6.1 Alkylation and Arylation

Free radical substitution of pyridines usually occurs principally at position 2 (Table 25), which is in agreement with theoretical calculations ⟨69CCC1110⟩. 2-Substitution is more favored in methylation than in phenylation of pyridine. This suggests that the methyl has more nucleophilic character than the phenyl radical. Furthermore, methylation of pyridine in acidic solution gives 13-fold excess of 2- over 4-substitution, although the overall yield is low. Alkyl and aryl radicals have been generated from diverse sources (Table 25).

The alkylation of quinoline by decanoyl peroxide in acetic acid has been studied kinetically, and a radical chain mechanism has been proposed (Scheme 207) ⟨72T2415⟩. Decomposition of decanoyl peroxide yields a nonyl radical (and carbon dioxide) that attacks the quinolinium ion. Quinolinium is activated (compared with quinoline) towards attack by the nonyl radical, which has nucleophilic character. Conversely, the protonated centre has an unfavorable effect upon the propagation step, but this might be reduced by the equilibrium shown in equation (167). A kinetic study revealed that the reaction is subject to cross-termination (equation 168). The increase in the rate of decomposition of benzoyl peroxide in the phenylation of the quinolinium ion compared with quinoline is much less than for alkylation. This observation is consistent with the phenyl having less nucleophilic character than the nonyl radical, and so it is less selective. Rearomatization of the σ-complex formed by radicals generated from sources other than peroxides may take place by oxidation by metals, disproportionation, induced decomposition or hydrogen abstraction by radical intermediates. When oxidation is difficult, dimerization can take place (equation 169).



Scheme 207



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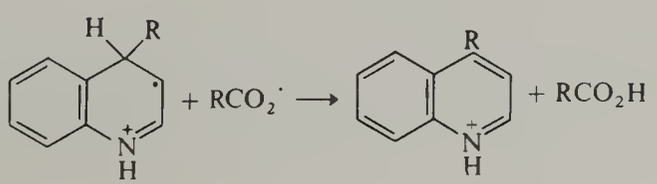


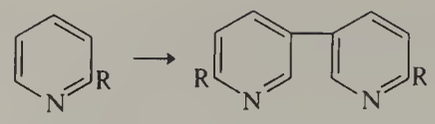
(168)

Table 25 Free Radical Alkylation and Arylation of Pyridines[a]

Heterocycle	*Radical*	*Source*	*Position of substitution (%)* α-	β-	γ-	*Others*	*Yield (%)*
Pyridine	Methyl	Acetyl peroxide	63	20	17	—	35
		LTA	62	21	17	—	10.7
		$(Bu^tO)_2$	62	23	15	—	13.5
		$(Bu^tO)_2$, HOAc	78	2	20	—	28.3
		$(Bu^tO)_2$, HOAc, HCl	93	—	7	—	11.8[b]
		LTA, HOAc	76	3	21	—	12.9[b]
		Electrolysis of HOAc	73	3	27	—	3.5
	Benzyl	$Pb(OCOBz)_4$	83	—	17	—	0.6
		$HgBz_2$, HOAc	77	—	23	—	35
	Phenyl	$(PhCO_2)_2$	54	32	14	—	76[b]
		$Pb(OCOPh)_4$	52	33	15	—	78[b]
		$PhNNCPh_3$	53	31	16	—	61[b]
		$PhN_2^+BF_4^-$	52	32	16	—	—
		$PhN_2^+Cl^-$	51	30	19	—	—
		PhN(NO)Ac	46	43	11	—	47[b]
		$(PhCO_2)_2$, HOAc	82	(3 and 4)	18	—	—
		$(PhCO_2)_2$, HOAc, HCl	65	4	31	—	—
		Electrolysis of BzOH	56	35	9	—	—
	p-MeC_6H_4	$ArN_2^+Cl^-$	56	29	15	—	—
	p-BrC_6H_4	$ArN_2^+Cl^-$	53	34	13	—	—
	p-$MeOC_6H_4$	$ArN_2^+Cl^-$	58	26	16	—	—
	p-$NO_2C_6H_4$	$ArN_2^+Cl^-$	44	43	13	—	—
2-Me	Methyl	$(Bu^tO)_2$, acid	74	—	24	4,6- (2)	—
	Phenyl	$(PhCO_2)_2$	—	31	15	5- (20), 6- (34)	—
	Phenyl	$(PhCO_2)_2$, HOAc, HCl	—	8	41	5- (5), 6- (46)	—
2-OMe	Phenyl	$(PhCO_2)_2$	—	65	5	5- (7), 6- (23)	—
2-CN	Phenyl	$(PhCO_2)_2$	—	33	7	5- (41), 6- (19)	—
3-Me	Methyl	Acetyl peroxide	56	—	20	5- (5), 6- (19)	23.8
	Phenyl	$(PhCO_2)_2$	42	—	26	5- (9), 6- (23)	—
	Phenyl	$(PhCO_2)_2$, HOAc, HCl	42	—	34	5- (2), 6- (22)	—
3-OMe	Phenyl	$(PhCO_2)_2$	59	—	19	5- (8), 6- (14)	—
3-CN	Phenyl	$(PhCO_2)_2$	33	—	25	5- (6), 6- (36)	—
4-Me	Methyl	Acetyl peroxide	64	36	—	—	12.5
	Phenyl	$(PhCO_2)_2$	54	46	—	—	—
	Phenyl	$(PhCO_2)_2$. HOAc, HCl	86	14	—	—	—
4-OMe	Phenyl	$(PhCO_2)_2$	34	66	—	—	—
4-CN	Phenyl	$(PhCO_2)_2$	24	76	—	—	—

Pyridine 1-oxide	Phenyl	$PhNHN_2Ph$, 131 °C	76	8	16	—	27
	Phenyl	$PhNHN_2Ph$, 181 °C	79	8	13	—	28
	Phenyl	$PhNHN_2Ph$, PhOMe, 131 °C	82	4	14	—	45
	Phenyl	$PhN_2^+BF_4^-$, pyridine	66	3	31	2-, 3-, 4-phenylpyridine (66, 11, 23) 6% total yield	0.9
Quinoline	Methyl	$(Bu^tO)_2$	10	—	24	5- (16), 8- (31), 3-+6-+7- (19)	34.7
	Methyl	$Pb(OAc)_4$	9	—	23	5- (18), 8- (32), 3-+6-+7- (18)	19
	Methyl	$(Bu^tO)_2$, acid	49	—	50	—	34.2
	Methyl	Bu^tOOH, acid, Fe^{2+}	42	—	38	2,4- (20)	quant.
	Methyl	HOAc, Ag^{2+}, acid	23	—	25	2,4- (52)	quant.
	Benzyl	$HgBz_2$	33	—	45	2,4- (22)	1.8
		$HgBz_2$, HOAc	50	—	45	2,4- (5)	34.7
	Phenyl	$(PhCO_2)_2$	11	6	18	5- (22), 6- (5.5), 7- (5.5), 8- (32)	—
	Phenyl	$(PhCO_2)_2$, acid	35	—	38	—	—
Isoquinoline	Methyl	$(Bu^tO)_2$	—	—	—	1- (100)	4.5
	Methyl	LTA	—	—	—	1- (100)	6.7
	Methyl	$(Bu^tO)_2$, acid	—	—	—	1- (100)	11.7
	Methyl	LTA, acid	—	—	—	1- (100)	19.3
	Benzyl	$Pb(OCOBz)_4$		3+4- (2)		1- (98)	6.5
	Benzyl	$HgBz_2$, HOAc		3+4- (1)		1- (98)	49.6
Acridine	Methyl	$MeCO_2H$	—	—	—	9- (100)	quant.

[a] The major review references mentioned in the text should be consulted for a more extensive compilation of data.
[b] Yield based on the conversion of radical source.



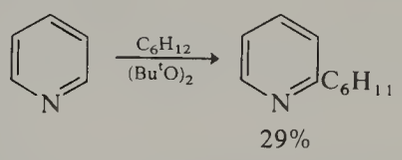
(169)

Methylation is taken as illustrative of alkylation for comparative purposes in Table 25; however, a wide range of other alkylations have been studied ⟨76MI20503⟩. Photolysis of di-*t*-butyl peroxide in a mixture of cyclohexane and pyridine gives cyclohexylation (equation 170) ⟨71CR(C)(272)854⟩. The relative rates for homolytic substitution of pyridines by cyclic alkyl radicals have been obtained ⟨74JCS(P2)1699⟩. A striking contrast can be seen (Table 26)

Table 26 Relative Rates for Homolytic Cyclo-alkylation of Some Pyridiniums

Pyridinium	$C_3H_5\cdot$	$C_6H_{11}\cdot$
4-Me	1	1
4-COMe	6.2	91.6
4-CN	13.9	256

between the relative rates of substitution by cyclopropyl (a radical with a high *s*-character and low nucleophilicity) and cyclohexyl. The hydroxymethylation of pyridine at C-2 and C-4 has been successfully carried out using methanol and ammonium persulfate (equation 171) ⟨71T3575⟩. Photolysis of papaverine in methanol leads to the generation of hydroxymethyl radicals which attack papaverine at C-1, and the adduct fragments (Scheme 208) ⟨68JOC1136⟩.



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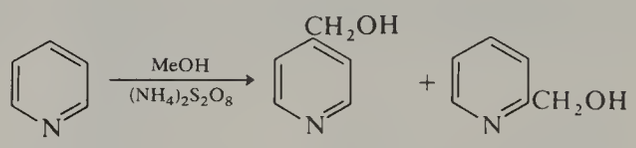

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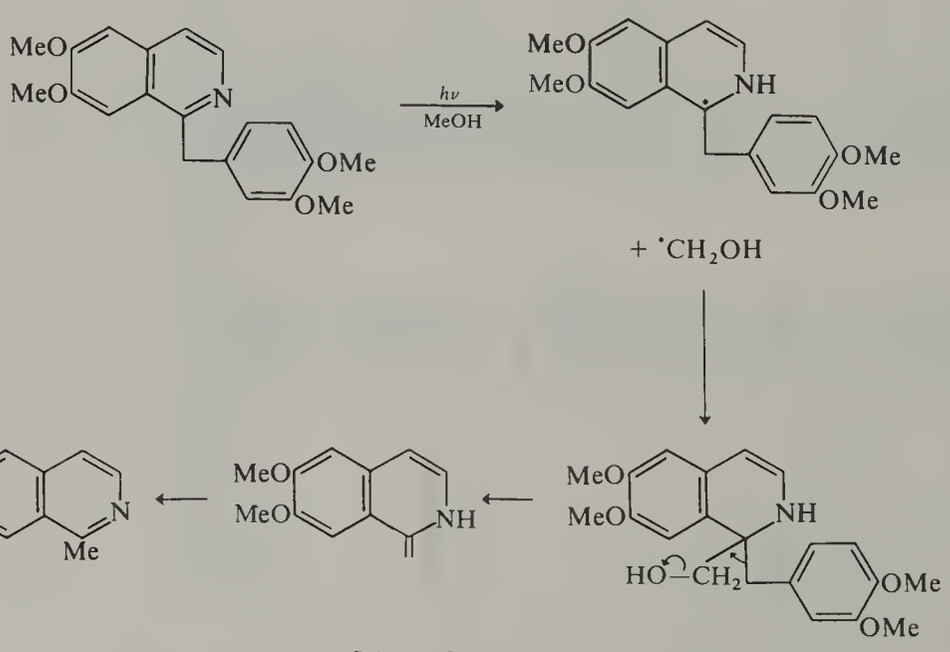
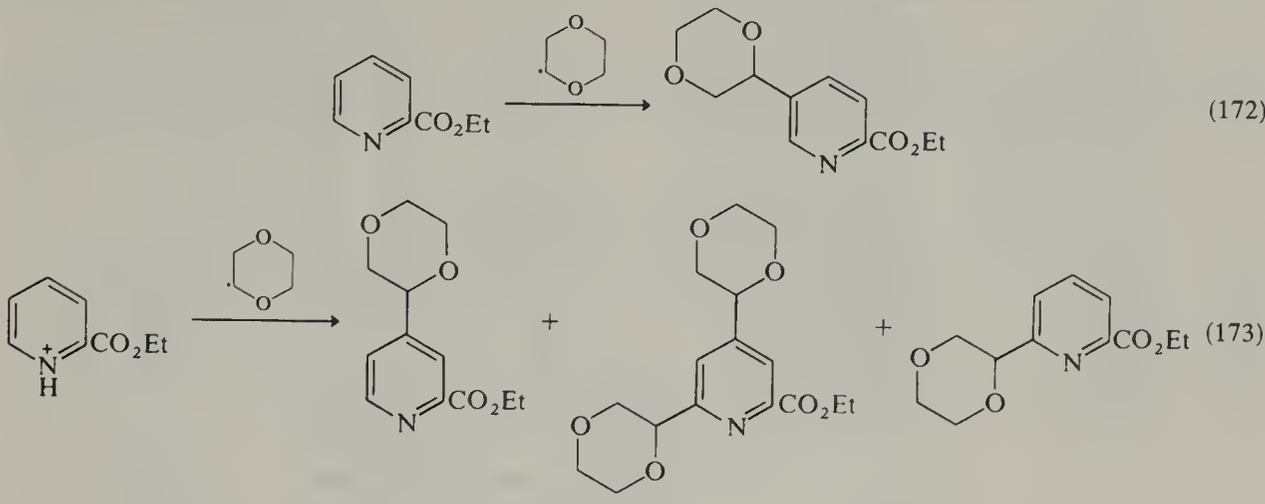


Scheme 208

Recently, some 2-, 3- and 4-substituted pyridines have been found to undergo substitution by cyclohexyl and dioxanyl radicals at different positions depending upon whether they are protonated or not ⟨82T657⟩. Ethyl picolinate undergoes C-5 substitution as the free base (equation 172), but three products are formed under acid conditions (equation 173). No

yields were quoted in the latter case as the reaction was stopped to avoid polysubstitution. 3-Acetylpyridine gives only one product (**276**) on reaction with dioxanyl radicals, whereas under acidic conditions disubstitution also is observed (Scheme 209). The regioselectivity is poor in the reaction of 4-acetylpyridine with cyclohexanyl radicals (equation 174). Under acid conditions β-substitution is not observed (equation 175).



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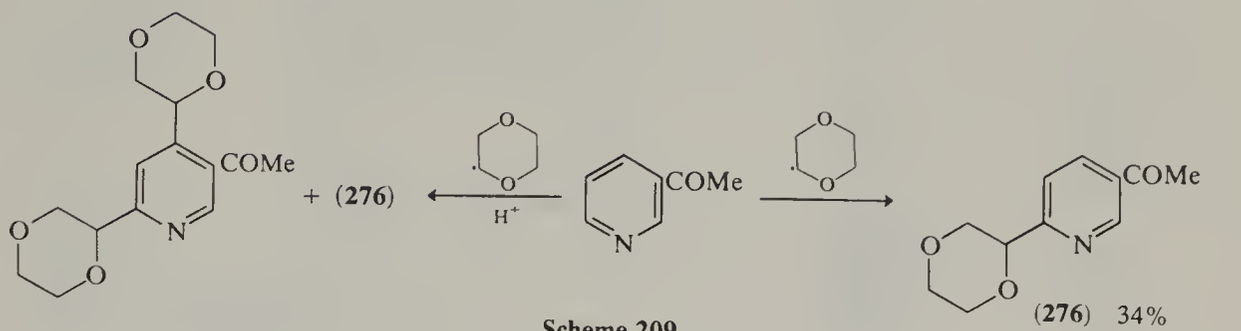
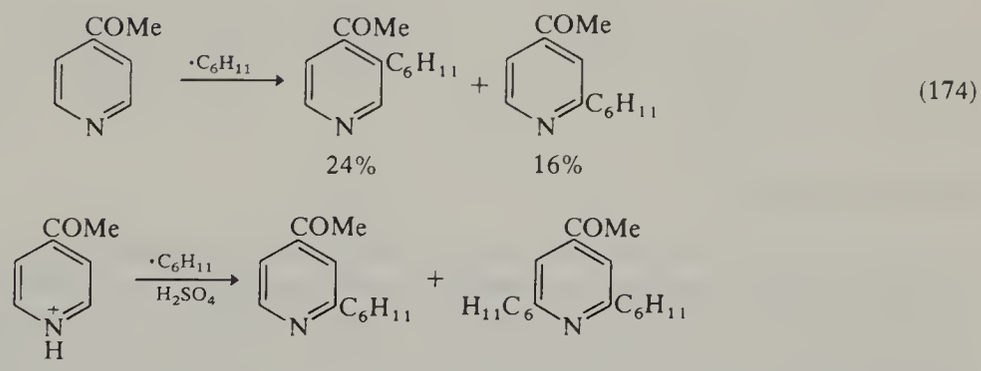


Scheme 209



(174)

Arylation of pyridine and some of its derivatives has been studied quite thoroughly ⟨74HC(14-S1)1⟩. Relative rates and partial rate factors have been obtained by the competition method (Table 27) ⟨66CJC1765⟩. Pyridine is phenylated a little more easily than benzene. However, attack by electrophilic radicals is much less facile. This reactivity pattern is consistent with those for heterolytic reactions. The reactivity of the 2- and 4-positions towards phenylation is increased in pyridinium ions relative to the free bases, consistent with prediction by HMO calculations ⟨72BSF1834⟩. A study of the phenylation of pyridine 1-oxide with benzenediazonium fluoroborate in acetonitrile revealed a total rate ratio of 52, and partial rate factors of $F_2 = 139$, $F_3 = 1.5$, $F_4 = 31.2$. The surprisingly high total rate ratio might be attributable to selective solvation of the diazonium ion by (or formation of a complex with) the *N*-oxide in the competitive experiments ⟨74HC(14-S1)1⟩.

Phenylation of quinoline with benzoyl peroxide is easier ($^{quin}_{Ph}K$ 5.0) than that of pyridine ⟨71BSF2612⟩. Substitution takes place at all carbons, and partial rate factors ($F_2 = 3.3$, $F_3 = 1.8$, $F_4 = 5.4$, $F_5 = 6.6$, $F_6 = 1.5$, $F_7 = 1.6$, $F_8 = 9.6$) were obtained at 1% conversion. Homolytic arylation of quinoline is not of much synthetic value as reactions taken to higher conversion suffer not only from lack of selectivity, but di- and poly-substitution also take place.

Table 27 Relative Rates and Partial Rate Factors for the Arylation of Some Pyridines

Pyridine	*Radical*	*Conditions*	*Relative rate (K) py/Ph*	*Partial rate factors* F_2	F_3	F_4	F_5	F_6
Pyridine	Phenyl	Benzoyl peroxide, 80 °C	1.04	1.8	0.87	0.87	—	—
	Phenyl	Gomberg–Hey, 40 °C	1.14	1.83	1.00	1.18	—	—
	o-Tolyl	Gomberg–Hey, 40 °C	1.72	2.72	1.53	1.82	—	—
	p-Tolyl	Gomberg–Hey, 40 °C	1.44	2.51	1.13	1.36	—	—
	o-Methoxyphenyl	Gomberg–Hey, 40 °C	1.27	1.88	1.33	1.19	—	—
	p-Methoxyphenyl	Gomberg–Hey, 40 °C	1.30	2.24	1.03	1.27	—	—
	o-Bromophenyl	Gomberg–Hey, 40 °C	0.70	0.91	0.97	0.44	—	—
	p-Bromophenyl	Gomberg–Hey, 40 °C	0.87	1.39	0.87	0.69	—	—
	o-Nitrophenyl	Gomberg–Hey, 40 °C	0.47	0.60	0.71	0.21	——	
	p-Nitrophenyl	Gomberg–Hey, 40 °C	0.78	1.03	1.00	0.60	—	—
3-Me	Phenyl	Gomberg–Hey, 40 °C	1.39	3.50	—	2.37	0.57	1.74
4-Me	Phenyl	Gomberg–Hey, 40 °C	1.39	1.87	2.29	—	—	—
2-CN	Phenyl	Benzoyl peroxide	3.6	—	7.14	1.51	8.95	4.0
3-CN	Phenyl	Benzoyl peroxide	6.22	12.3	—	9.3	2.24	13.4
4-CN	Phenyl	Benzoyl peroxide	5.77	4.1	13	—	—	—

Table 28 Free Radical Acylation of Protonated Pyridines[a]

Heterocycle	*Radical source*	*Position of substitution (%)*	*% Yield*
Pyridine			
4-CN	EtCHO	2	57
Quinoline			
	MeCHO	2- and 4- (20) + 2,4- (80)	77
	EtCHO	2,4	40
4-CN	MeCHO	2	93
2-CN	MeCHO	4	90
	PhCHO	4	70
2-OMe	MeCHO	4	75
Acridine			
	EtCHO	9-acyl (50) + 9-acyl-9,10-dihydro (50)	76

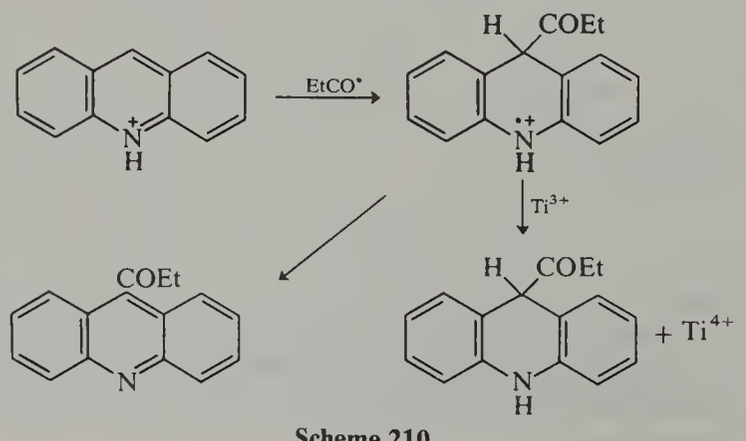
[a] ⟨74AHC(16)123, 76MI20503⟩.

20.5.6.2 Acylation

Protonated pyridines and derivatives readily undergo acylation at C-2 or C-4 (Table 28) ⟨76MI20503⟩. Acyl radicals are usually generated either by hydrogen abstraction from aldehydes (Scheme 210), or by oxidative decarboxylation of α-keto acids (Scheme 211). In the former case (Scheme 210) with acridine as the substrate, reduction can take place to give a dihydroacridine.

$$Bu^tCO_2H + Ti^{3+} \rightarrow Bu^tCO\cdot + Ti^{4+} + OH^-$$

$$Bu^tCO\cdot + EtCHO \rightarrow Bu^tCOH + EtCO\cdot$$



Scheme 210

$$S_2O_8^{2-} \rightarrow 2SO_4^{\cdot-} + RCOCO_2^- \longrightarrow RCO^{\cdot} + CO_2 + SO_4^{2-}$$

Scheme 211

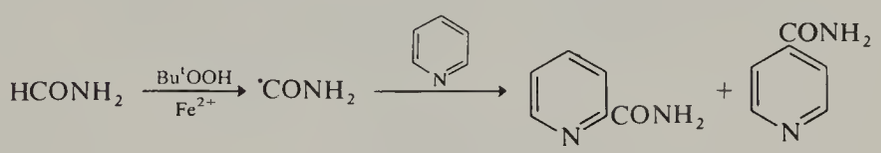
2.05.6.3 Amidation

Amidation is quite a general reaction, and substitution usually occurs at C-2 (Table 29) ⟨76MI20503⟩. The radicals are generated from the amide and hydrogen peroxide or an alkyl peroxide (Scheme 212).

Table 29 Free Radical Amidation[c]

Heterocycle	*Radical source*	*Amide*	*Position of substitution*	*% Yield*
Pyridine				
	Bu^tOOH	formamide	2+4	80
	$(Bu^tO)_2$	DMA[a]	2+4	66
4-CN	Bu^tOOH	formamide	2	97
4-CN	$Bu^tOOH + Fe^{2+}$	DMF	2	97
4-CO_2Et	Bu^tOOH	formamide	2	78
4-CO_2Et	$Bu^tOOH + Fe^{2+}$	DMF	2	36
4-COMe	Bu^tOOH	formamide	2	46
4-COMe	$Bu^tOOH + Fe^{2+}$	DMF	2	49
Quinoline	Bu^tOOH	formamide	2+4	92
	$S_2O_8^{2-}$	DMA[a]	2+4	97
	$(Bu^tO)_2$	MF[b]	2+4	48
Isoquinoline	Bu^tOOH	formamide	1	41
Acridine	Bu^tOOH	formamide	9	100

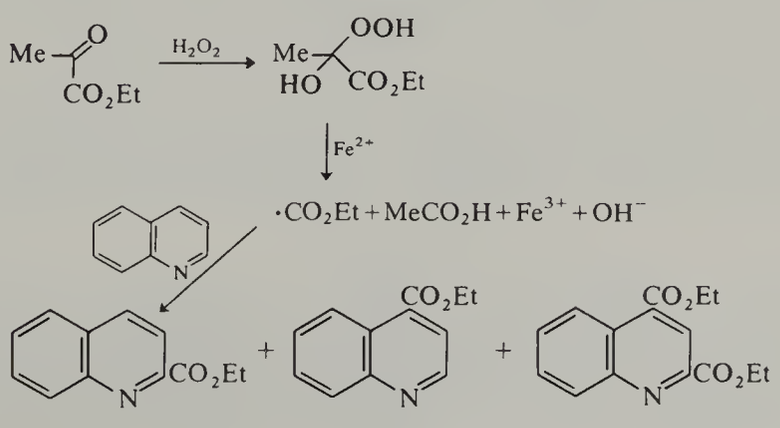
[a] DMA = *N*,*N*-dimethylacetamide.
[b] MF = methylformamide.
[c] For more examples and comprehensive reviews, see ⟨74AHC(16)123, 76MI20503⟩.



Scheme 212

2.05.6.4 Carboxylation

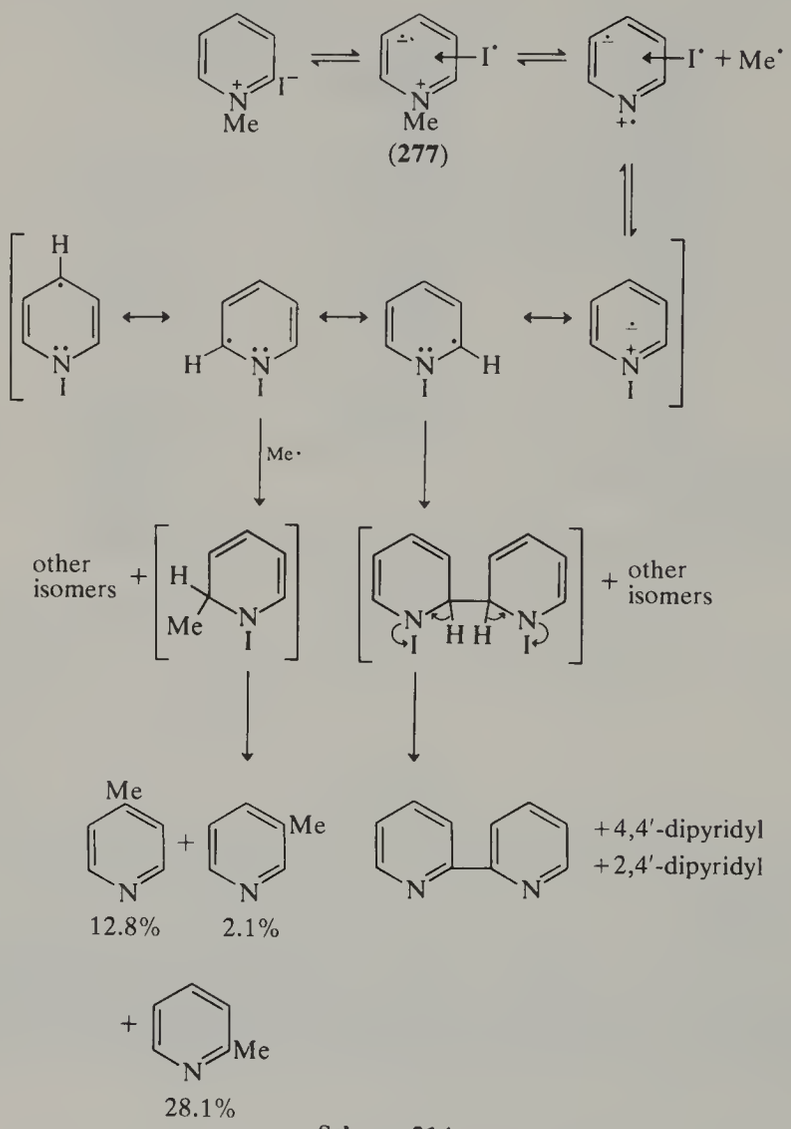
Attack by alkoxycarbonyl radicals, which are isoelectronic with but less nucleophilic than carbamoyl radicals, has been less well studied than acylation and amidation. An example is provided by the reaction of quinoline with ethyl pyruvate, hydrogen peroxide and an iron(II) salt (Scheme 213) ⟨73TL645⟩.



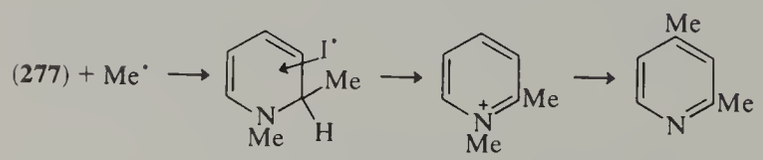
Scheme 213

2.05.6.5 Ladenburg Rearrangement

N-Alkylpyridinium salts were found, first by Ladenburg ⟨1883CB1410⟩, to undergo rearrangement to 2- and 4-alkylpyridines. Subsequently, dealkylation and polyalkylation of the pyridine ring were reported; *n*-propyl- and isopropyl-pyridinium iodides were found to give identical products ⟨61HC(14-2)155⟩. A thorough study ⟨69JCS(C)146⟩ has shown that the mechanism of this reaction involves a homolytic breaking of the *N*-alkyl bond, and in the case of iodides a charge-transfer complex (**277**) is involved (Scheme 214). Apart from the anticipated rearrangement products formed as illustrated in Scheme 214, decomposition of 1-methylpyridinium iodide yielded pyridine (38.1%) (and methane) as the main product formed by hydrogen abstraction. Some of the other products indentified were 2-ethylpyridine (2.5%), 2,3-dimethylpyridine (1.3%), 2,4-dimethylpyridine (5.6%), 2,6-dimethylpyridine (3.8%), 2,4,6-trimethylpyridine (0.9%) and 4-ethylpyridine (3.5%). Formation of these was attributed to reaction of primary radicals with the charge-transfer complex of the starting pyridinium salt (Scheme 215).

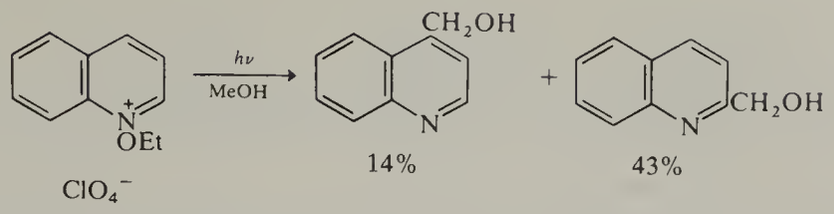


Scheme 214



Scheme 215

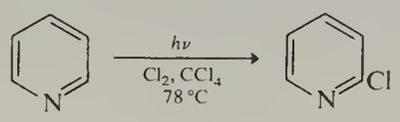
1-Alkylquinolinium iodides also undergo the Ladenburg rearrangement. 1-Methylquinolinium iodide was found to yield, on heating, at 300 °C, a mixture that contained 2-, 4-, 5- and 8-methylquinolines, and perhaps the 6- and 7-isomers as well ⟨79UP20500⟩. 1-Ethoxyquinolinium perchlorate may be hydroxymethylated by irradiation in methanol (equation 176) ⟨69CPB2633⟩.



(176)

2.05.6.6 Halogenation

The halogenation of pyridine has been discussed generally in the electrophilic substitution Section (2.05.3.4). It was pointed out that the change in orientation from β- to α- and/or γ-substitution probably reflects a change from an electrophilic to a free radical mechanism. Pyridine has been found to undergo regiospecific α-chlorination on photolysis in the presence of chlorine in carbon tetrachloride (equation 177) ⟨67JHC375⟩. Vapour phase bromination of pyridine with bromine chloride gives chiefly 2-bromopyridine whereas the use of bromine gives almost equal amounts of 2- and 3-bromopyridine (Scheme 216) ⟨67JHC377⟩.



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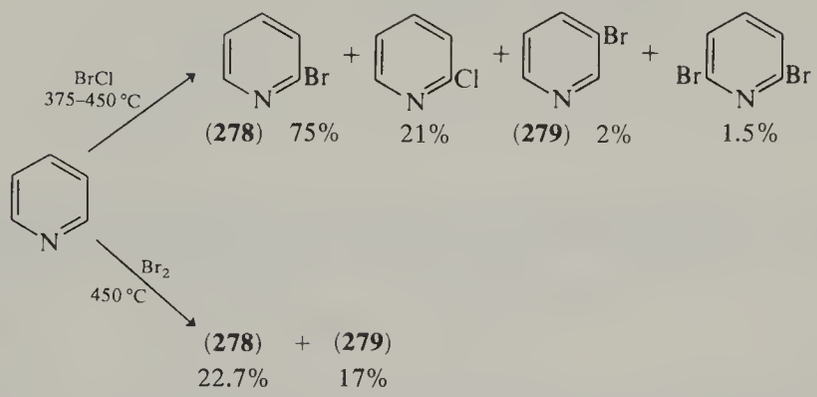
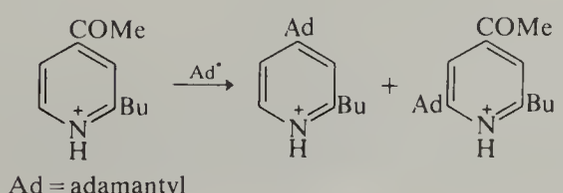


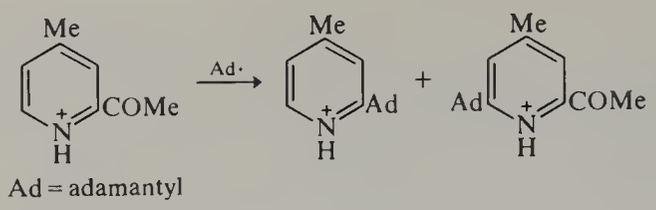
Scheme 216

2.05.6.7 *Ipso* Attack

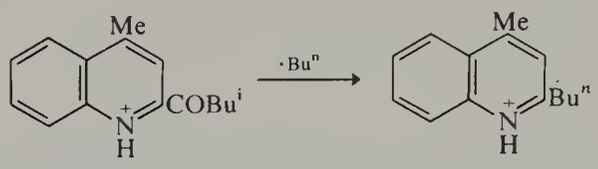
Radical ⟨80ACR51⟩ and electrophilic ⟨76ACR287⟩ *ipso* attack on aromatic substrates has been found to be more widespread than formerly realized (see Chapter 2.06). Alkyldeacetylation has been observed at positions 2 and 4 in protonated acetylpyridines (equations 178 and 179) ⟨77JCS(P2)87⟩ and position 2 in the quinoline (**280**) (equation 180) ⟨77JCS(P2)87⟩. Treatment of 2,5-diacetylpyridine with dioxanyl radicals under neutral conditions gives the products of *ipso* substitution (**281**) and (**282**) (Scheme 217). On the other hand, when the reaction is carried out under acidic conditions, substitution takes place at C-2 and C-4 (both positions are activated towards attack by nucleophilic radicals) ⟨81TL2023⟩. The orientation of attack (at C-2 and C-5) on the unprotonated pyridine is determined by the greater stability of the intermediates (**283**) and (**284**) compared with those that would result from attack at C-4 or C-6, (**285**) and (**286**), which have no *p*-acetyl substituent to stabilize the radical ⟨82T657⟩.



(178)

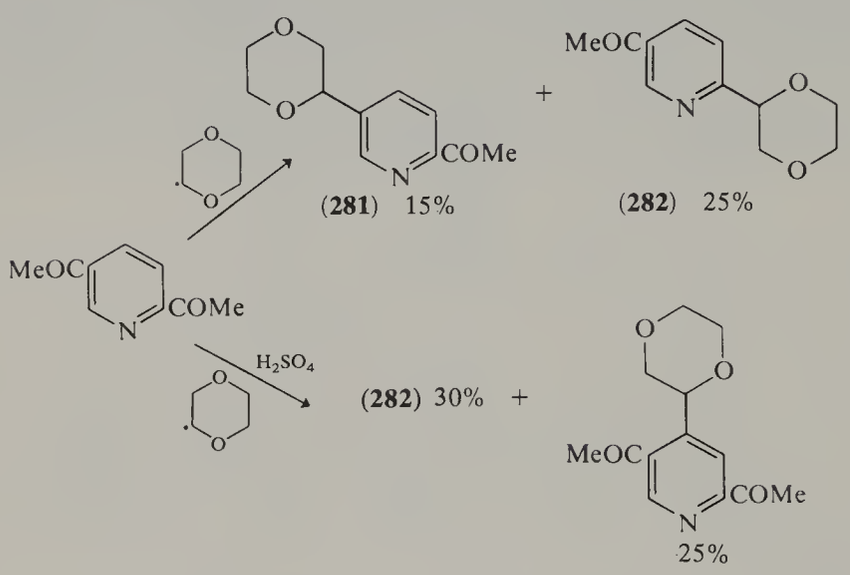


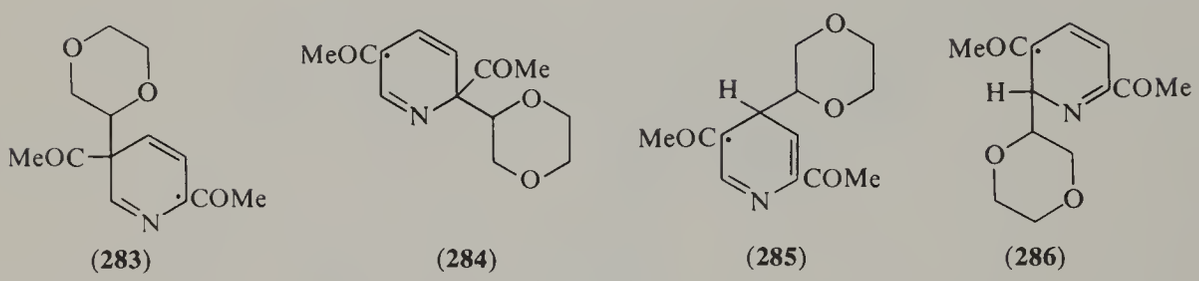
(179)



(180)

(280)



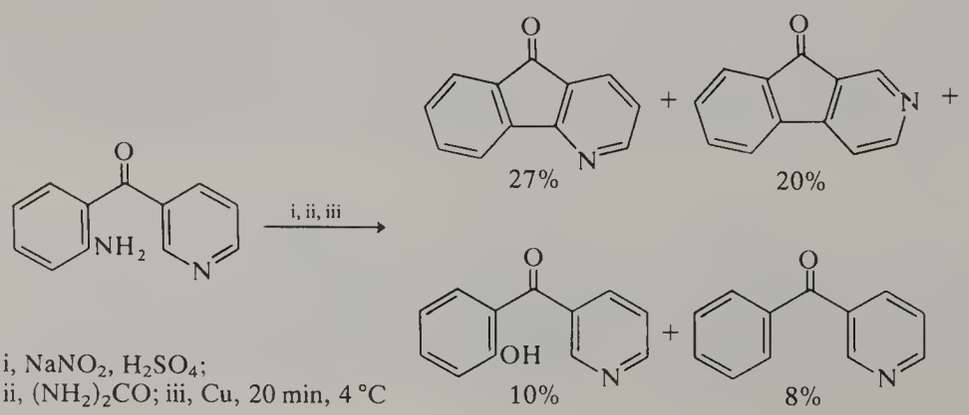


(283) (284) (285) (286)

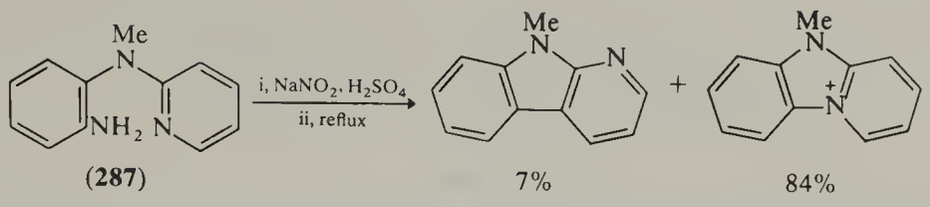
Scheme 217

2.05.6.8 Intramolecular Attack

This also may be looked upon as a substituent reaction (see Chapter 2.06) but a few examples are given here. A suitably substituted pyridine will undergo Pschorr cyclization to give 2- and 4-azafluorene and two other products (equation 181) ⟨65CJC940⟩. With a 2-substituted pyridine (**287**), cyclization on to the pyridine nitrogen is heavily favoured (equation 182) ⟨54JCS4263⟩. Decomposition of 3-(*o*-azidophenyl)pyridine results in a nitrene

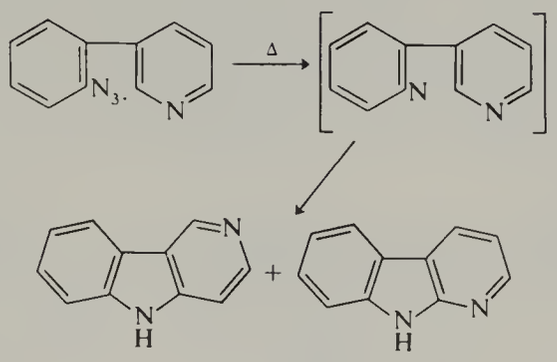


(181)

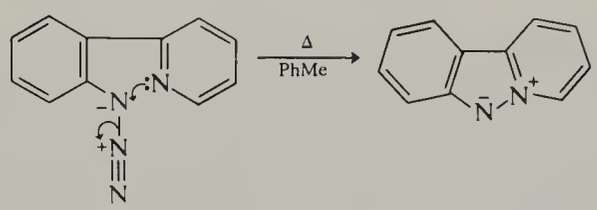


(287) 7% 84% (182)

cyclization. However, this is almost certainly not a simple triplet nitrene biradical cyclization (Scheme 218) ⟨68QR222, 69S11⟩. Cyclization of 2-(*o*-azidophenyl)pyridine probably involves an assisted loss of nitrogen (equation 183) ⟨74JHC857⟩.



Scheme 218

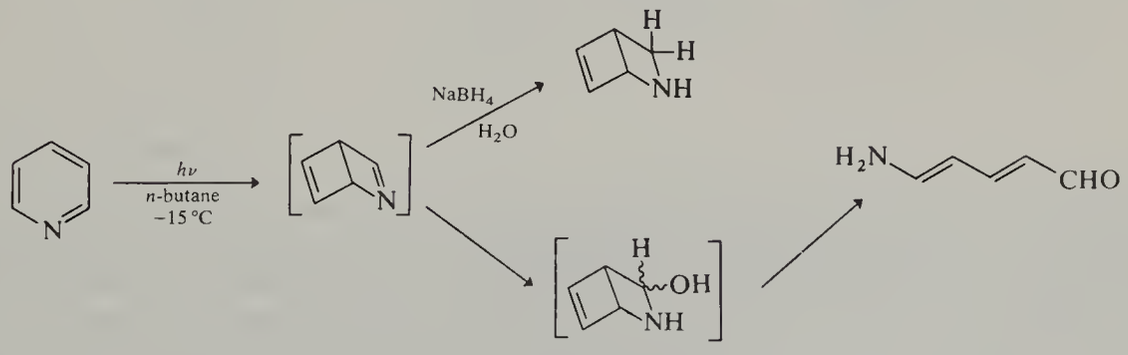


(183)

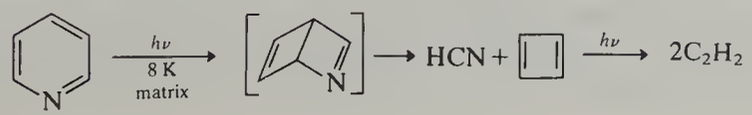
2.05.7 THERMAL AND PHOTOCHEMICAL REACTIONS AND THOSE INVOLVING CYCLIC TRANSITION STATES

2.05.7.1 Pyridines

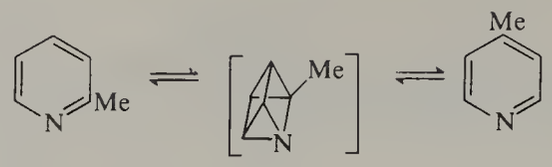
Pyridine and some of its derivatives have been photolyzed under various conditions in the quest for 'Dewar pyridines' and azaprismanes, amongst other products. This quest has proven successful ⟨76MI20503⟩. Irradiation of pyridine itself in *n*-butane at −15 °C produces Dewar pyridine that can be observed spectrophotometrically and intercepted by sodium borohydride and water (Scheme 219). When pyridine is photolyzed in a matrix, hydrogen cyanide and acetylene are formed (equation 184). The same products have been obtained from the vapour phase photolysis of pyridine. On vapour phase photolysis, alkylpyridines isomerize; for example, 2-picoline gives a mixture of 3- and 4-picolines. Azaprismanes (**288**) have been suggested as the intermediates in this process (equation 185).



Scheme 219



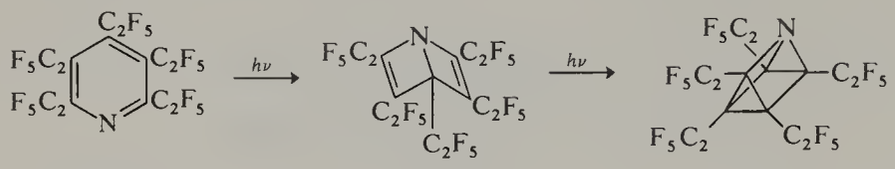
(184)



(185)

(288)

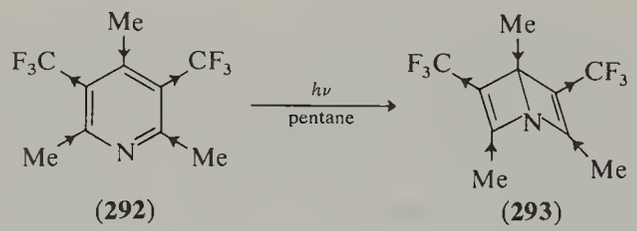
It has proved possible actually to isolate the valence bond isomers from photolysis of some perfluoropyridines. Irradiation of (**289**) gives pentakis(pentafluoroethyl)-1-azabicyclo[2.2.0]hexa-2,5-diene (**290**), a colourless liquid (b.p. 176 °C), almost quantitatively (equation 186). Further irradiation gives pentakis(pentafluoroethyl)-1-azaprismane (**291**) which is also a stable colourless liquid ⟨73JCS(P1)1542⟩. The remarkable stability of these products has been attributed in part to relief of steric strain when the planar adjacent bulky pentafluoroethyl groups take up a nonplanar position in the valence isomers.



(186)

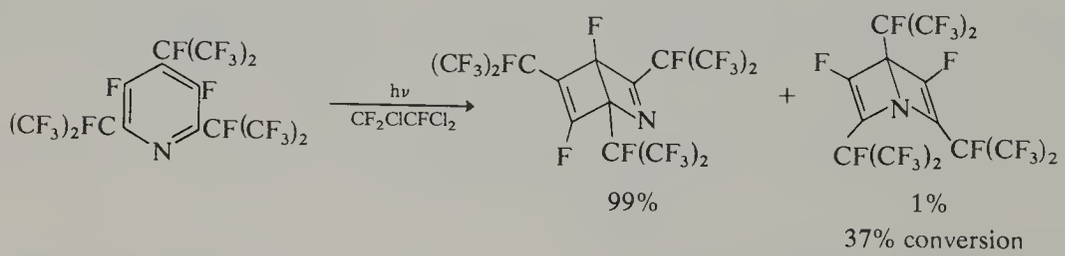
(**289**) (**290**) 95% (**291**) 91%

Not only perfluoro substituted pyridines yield Dewar pyridines. 2,4,6-Trimethyl-3,5-bis(trifluoromethyl)pyridine (**292**) gives (**293**) on photolysis in pentane, on thermolysis and by a metal-catalyzed process ⟨76CPB2219⟩. It is suggested that this product derives its stability not just from release of steric interaction on going from (**292**) to (**293**), but also from the strong electron-withdrawing effect exerted on the 2- and 6-methyl substituents by the CF_3 groups through the double bonds (equation 187). Support for this push–pull effect comes from the observation that only the 2- and 6-methyl groups undergo deuterium isotope exchange in (**293**) whereas all the methyl protons in the parent pyridine undergo exchange. A subtle manipulation of the nature and position of the perfluoro substituents in the pyridine chosen for photolysis has led to the first example of formation of a 2-azabicyclo[2.2.0]hexa-2,5-diene in preference to the 1-isomer (equation 188) ⟨77CC154⟩.



(187)

(**292**) (**293**)

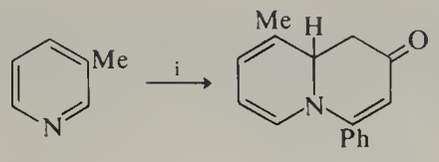


(188)

99% 1%

37% conversion

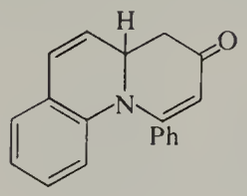
Reasons for the dramatic change in the nature of the isomer formed are worth mentioning. In the previous examples and several others like them, large perfluoroalkyl substituents were chosen to promote Dewar benzene formation but this led to the 1-aza isomer predominating over the 2-, which would of necessity be destabilized by having four large groups attached to one cyclobutene ring, whereas the 1-isomer would only have a maximum of three. It should be noted that all these valence isomers revert to the original pyridine on heating, the least stable ones doing so at room temperature. 3-Methylpyridine and quinoline form adducts (**294** and **295** respectively) with an alkynic ketone (equation 189) ⟨79JCS(P1)584⟩. Pyridine undergoes 1,3-dipolar cycloaddition with a bis(trifluoromethyl)oxazaphospholine (equation 190) ⟨75S731⟩.



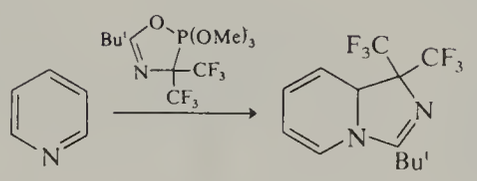
(189)

(**294**) 17%

i, PhC≡CCOMe, PhH, reflux, 7 h



(**295**) 5.6%

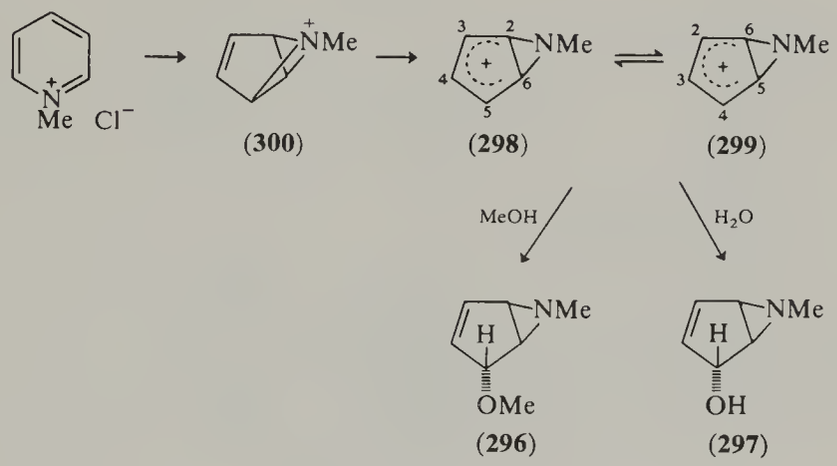


(190)

58%

2.05.7.2 Pyridinium Salts

Photolysis of methylpyridinium chloride in water or methanol affords derivatives of the rare 6-azabicyclo[3.1.0]hexenyl system (**296**, **297**); azabicyclohexenyl ions (**298**, **299**) and methylazoniabenzvalene (**300**) are implicated as intermediates (Scheme 220) ⟨72JA3283⟩. A similar mechanism might explain the isomerization of 3,5- to 2,4-lutidine-d_2 on irradiation in acidic D_2O.

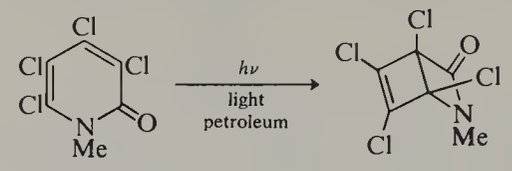


Scheme 220

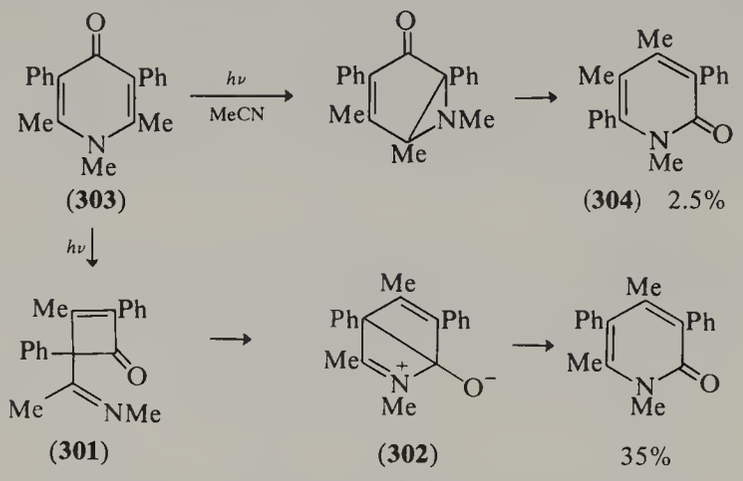
2.05.7.3 Pyridinones

N-Methylpyridin-2-one and its tetrachloro analogue form 'Dewar pyridinones' on photolysis at low temperatures in dilute solution (equation 191) ⟨73JCS(P1)1125⟩. Substituted pyridin-4-ones behave differently; they undergo rearrangement to pyridin-2-ones (Scheme 221). The involvement of a cyclobutenone (**301**) and a Dewar pyridine intermediate (**302**) has been proposed on the pathway to the major product, and a 6-azabicyclo[3.1.0]hexenone was invoked as the intermediate between (**303**) and (**304**) ⟨74JA1152⟩. Pyridin-2-ones have been known for some time to photodimerize to the *trans,anti*-1,4-dimer (equation 192) ⟨74HC(14-S1)1⟩. Recently, four isomers were characterized from the product of photolysis of *N*-substituted pyridin-2-ones in a micellar system (equation 193) ⟨81H(16)135⟩. However, photolysis of (**305**) in water gives entirely *trans* products, whereas the *cis* products are formed

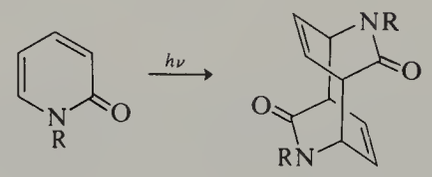
to the exclusion of the *trans* isomers on photolysis in aqueous cetyltrimethylammonium bromide solution (Scheme 222). 2-Aminopyridines also dimerize, in aqueous acidic solution, to yield similar 'butterfly' dimers (equation 194) ⟨63JA776⟩.



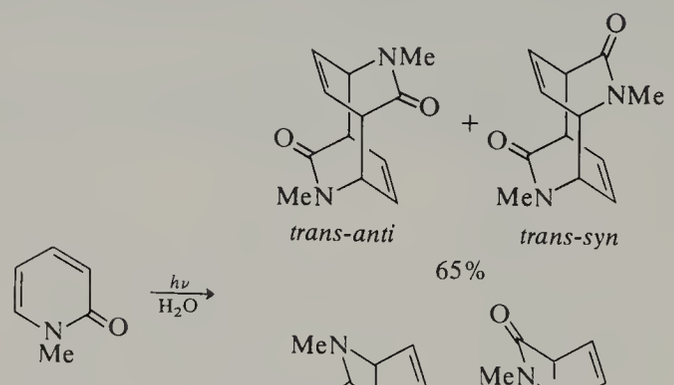
(191)



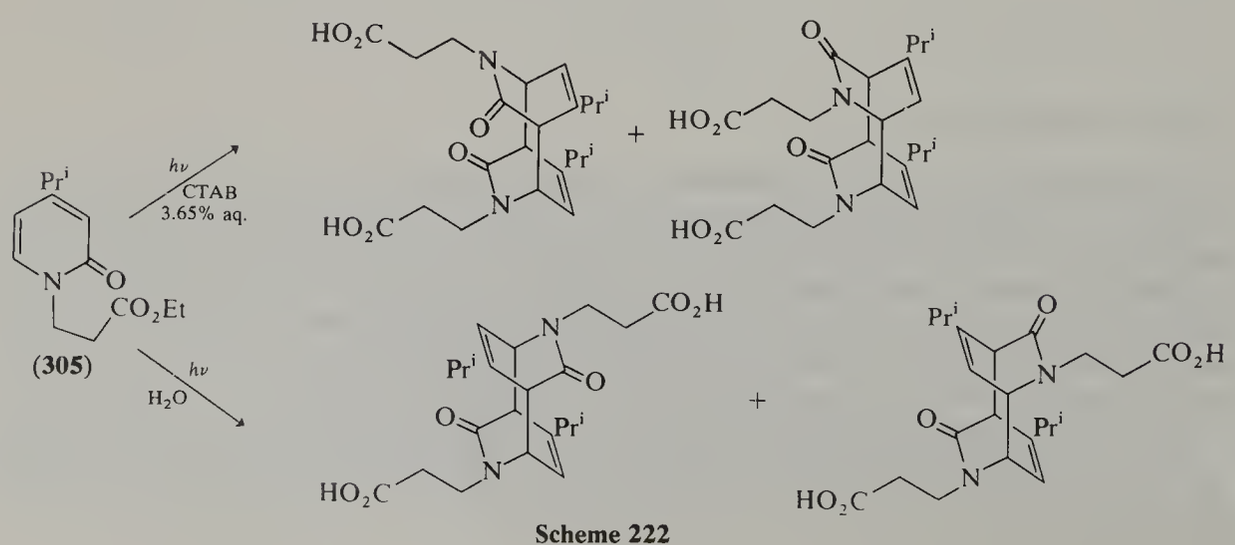
Scheme 221



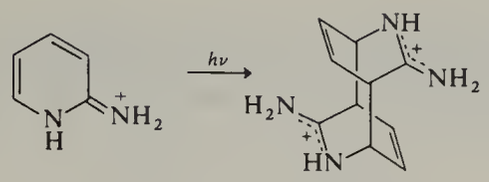
(192)



(193)

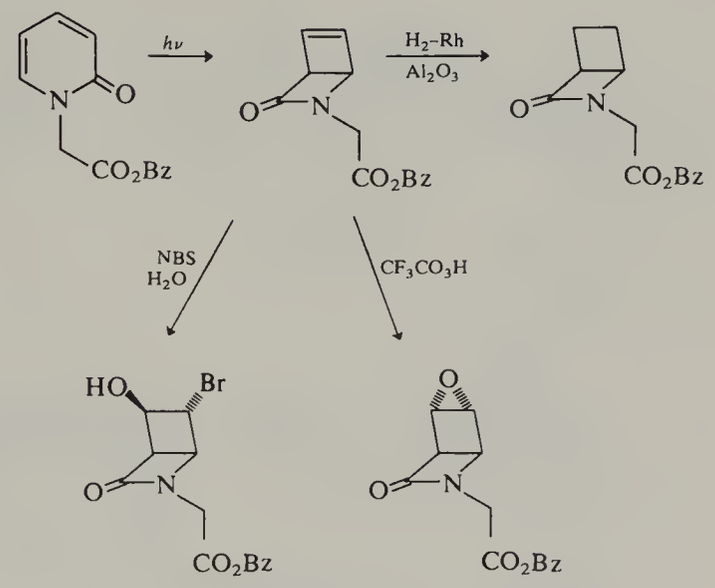


Scheme 222

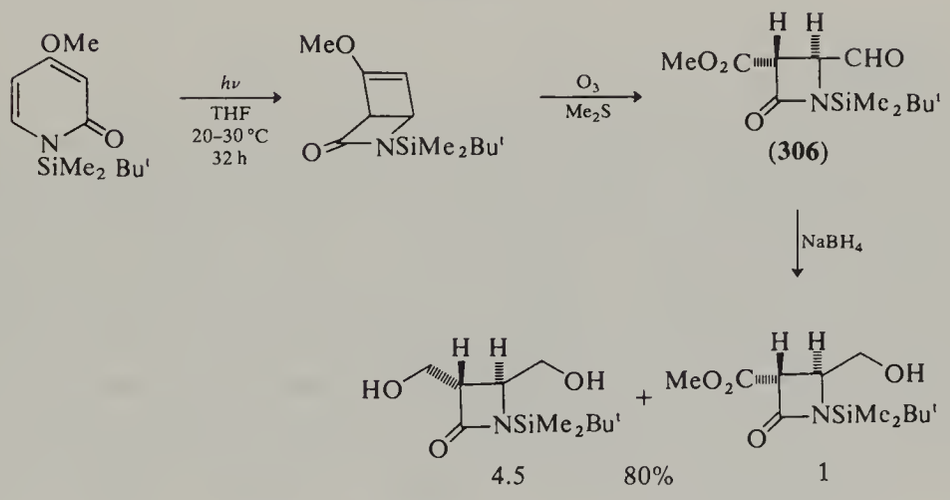


(194)

The interception of suitably substituted Dewar pyridinones (*N*-alkyl-3-oxo-2-azabicyclo[2.2.0]hex-5-enes) is increasingly being exploited as a route to novel β-lactams (Scheme 223) ⟨81JCS(P1)2620⟩. In another approach, 4-methoxypyridin-2-one has been used as a source of substituted azetidin-2-one (**306**) which is a precursor of potential carbapenam antibiotics (Scheme 224) ⟨82H(19)89⟩.

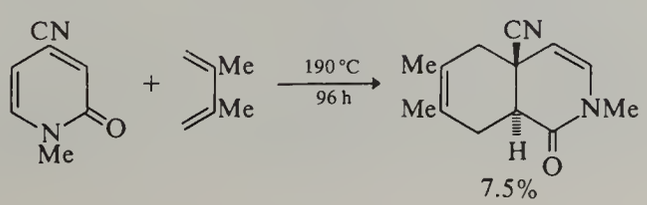


Scheme 223

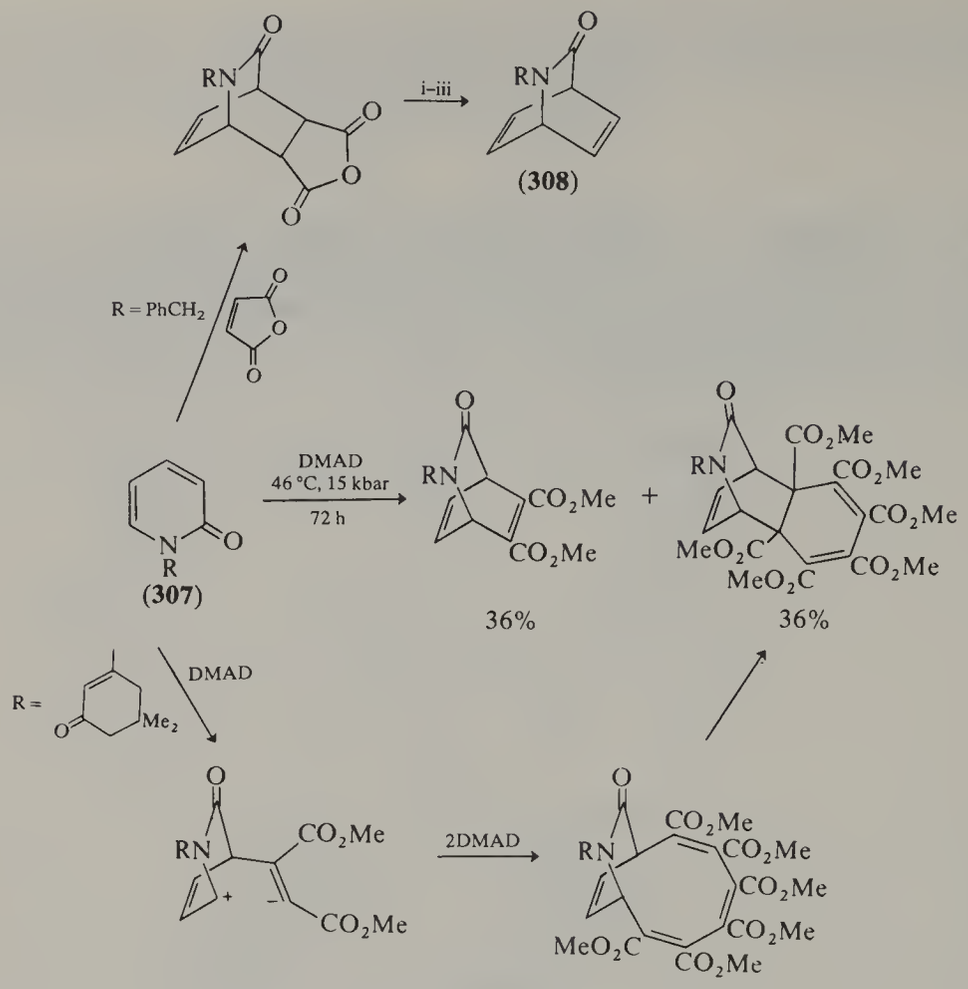


Scheme 224

Intermolecular cycloadditions involving pyridinones are well known ⟨80H(14)1793⟩. 4-Cyano-1-methylpyridin-2-one undergoes Diels–Alder reaction with a suitable diene (equation 195) ⟨79H(12)1⟩. The pyridinone (**307**) forms 1:1 and 1:3 adducts on reaction with DMAD under pressure (Scheme 225) ⟨82H(19)499⟩. 2-Azabarrelenone (**308**) may be prepared by a sequence (Scheme 225), the first step of which is the addition of maleic anhydride to 1-benzylpyridin-2-one ⟨80AG(E)463⟩.



(195)

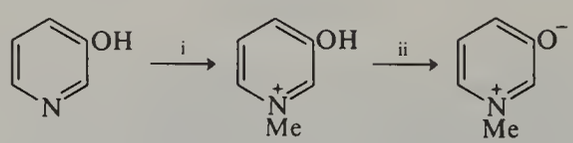


i, HO^-; ii, H_3O^+; iii, electrolysis–pyridine|H_2O|Et_3N

Scheme 225

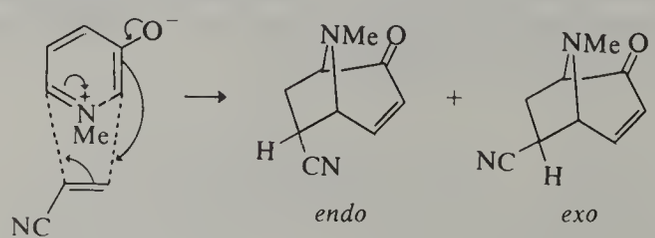
2.05.7.4 Pyridinols

1-Alkylpyridinols may be prepared and deprotonated readily to form betaines (equation 196). These betaines undergo a series of useful 1,3-dipolar cycloaddition reactions, which has been reviewed ⟨76AG(E)1⟩. 1-Methyl-3-pyridiniumolate reacts with acrylonitrile in the manner indicated to give a mixture of *endo* and *exo* isomers (Scheme 226). This reaction has been elaborated to provide a convenient entry into the tropone series (Scheme 227). An advantage of this reaction is that a mixture of isomers (**309**) may be used. Benzotropones can be obtained from a methylisoquinolinium betaine (Scheme 228). Tropones may be obtained from 1-phenylbetaines, which are easier to handle than the methyl analogues mentioned above. However, the quaternization step is more difficult than in the methyl case but use of methyl trifluoromethanesulfonate overcomes this problem. Both the 1-phenyl- and 1-methyl-betaines react with benzyne. The former yields the anticipated



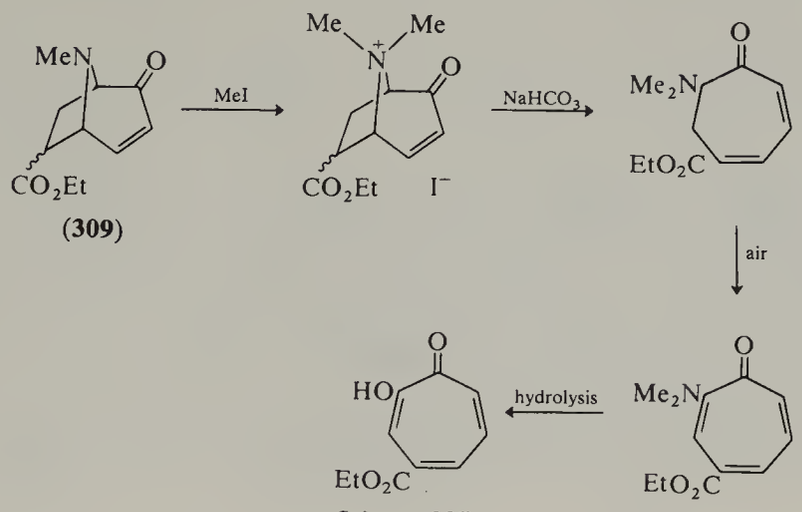
(196)

i, MeI; ii, IRA 401(OH) ion exchange resin



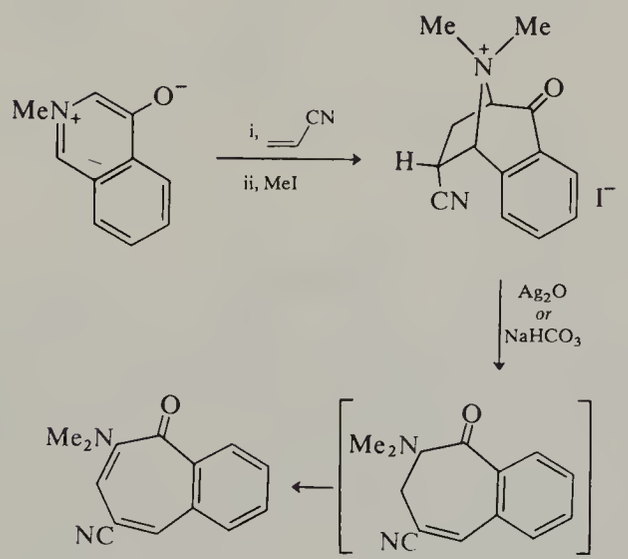
Scheme 226

adduct (**310**), whereas the latter undergoes further addition (Scheme 229) ⟨72CC707⟩. 1-(2,4-Dinitrophenyl)-3-pyridiniumolate affords a further regioisomer (**311**) on reaction with acrylonitrile (Scheme 230) but rearrangement to the *O*-aryl derivative is a side-reaction ⟨74JCS(P1)1883⟩.

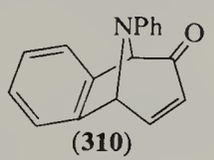


(**309**)

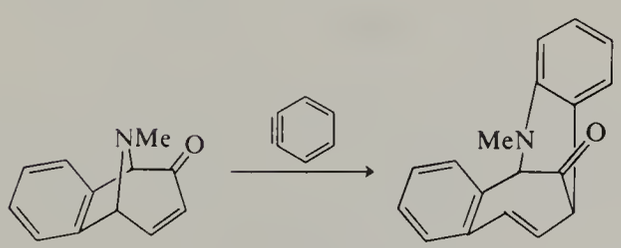
Scheme 227



Scheme 228

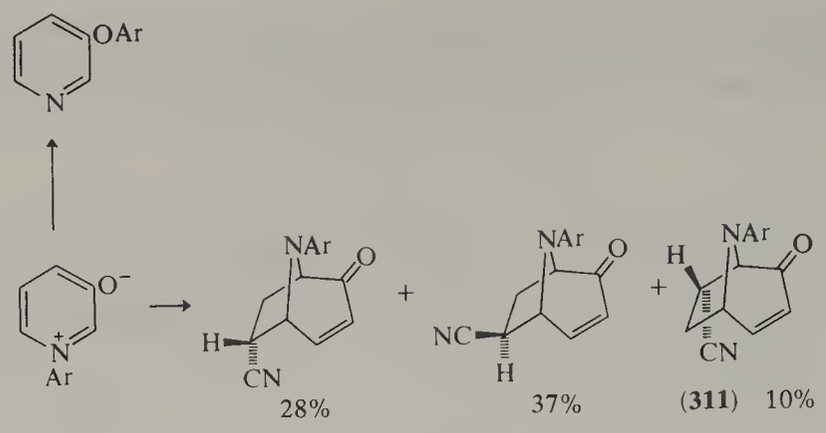


(**310**)



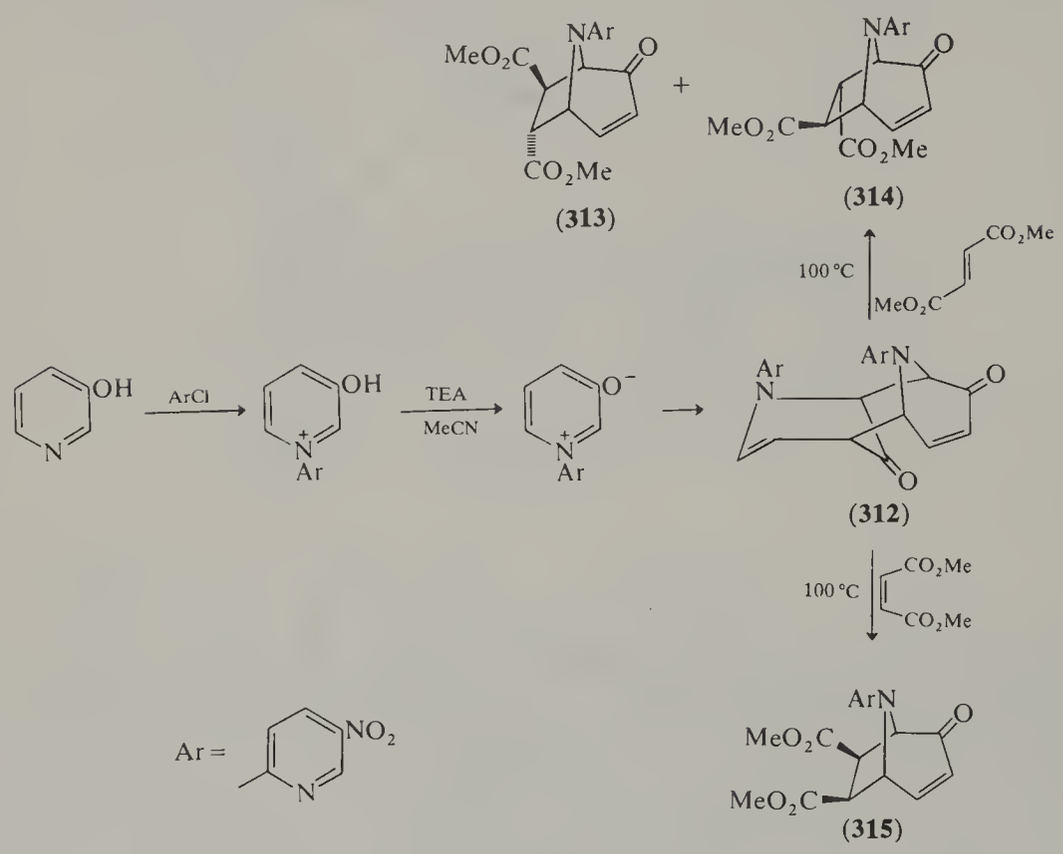
Scheme 229

1-(5-Nitro-2-pyridyl)-3-pyridiniumolate may be prepared with ease (Scheme 231) but it spontaneously dimerizes to (**312**). However, this dimer dissociates reversibly at 100 °C and the monomer can be trapped by dimethyl fumarate (to give two products **313** and **314**) or dimethyl maleate (to give **315**), which illustrates the concerted character of these cycloadditions. The betaine dimer (**312**) undergoes addition with 4π- and 6π-addends (Scheme 232). These observations are consistent with the predictions of an MO treatment ⟨76AG(E)1⟩, which considers the betaines as 4π fragments for addition 2,6- (**316**), and as 2π three-atom or 6π five-atom fragments for addition at the 2,4-positions (**317**).

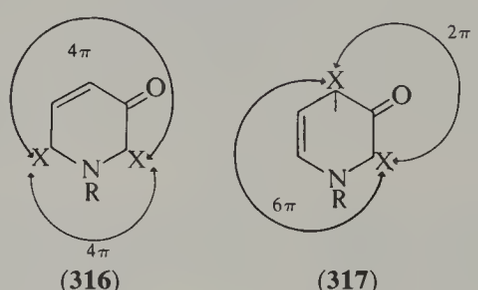


Ar = 2,4-dinitrophenyl

Scheme 230



Scheme 231



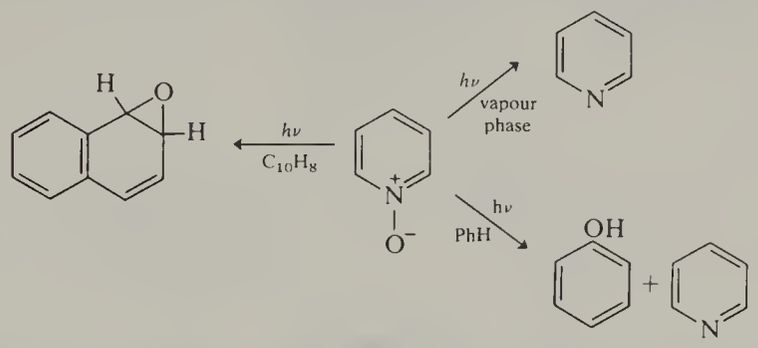
Scheme 232

2.05.7.5 *N*-Oxides

Extensive work has been carried out on the photolysis of aromatic *N*-oxides ⟨B-71MI20500, 74HC(14-S2)1⟩. The early work has been reviewed in comparison with the photochemistry of azoxy compounds and nitrones ⟨70CR231⟩, but the following discussion is based on the classification used by Streith and Bellamy in their review ⟨76H(4)1391⟩. Two competing

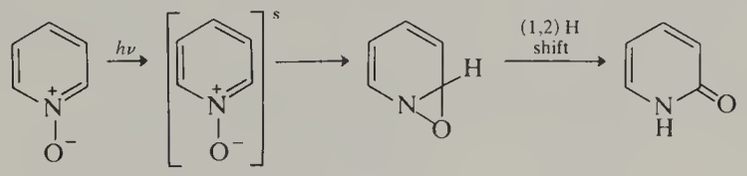
pathways have emerged: photolytic N—O bond cleavage which arises from a triplet state, and photoinduced rearrangements which proceed from a singlet state of the *N*-oxide and involve oxaziridine (1-aza-7-norcaradiene) intermediates. The nature of the products formed depends upon wavelength of irradiation and the type of solvents used. Such products may be divided into two categories, primary photoproducts which derive from one or more unstable intermediates, and secondary photoproducts which can be obtained in separate experiments from stable intermediates. Reactions leading to primary photoproducts will be considered first.

One of the first photolytic reactions of *N*-oxides to be observed was N—O bond cleavage of pyridine 1-oxide to give the parent heterocycle on irradiation in the gas phase (Scheme 233) ⟨61BCJ1440⟩. It is quite a general process for all heterocyclic *N*-oxides and has been demonstrated to occur *via* the *N*-oxide triplet state ⟨68CC1321⟩. When pyridine 1-oxide is photolyzed in solution its oxygen atom can be transferred to a suitable solvent molecule, either by CH insertion or addition to a double bond (Scheme 233). The nature of this oxygen transfer is as yet unclear, but it does not involve free oxygen atoms. Main interest in this reaction stems from the fact that it has been used as a model for the hepatic oxidase system which is responsible for the metabolic hydroxylation of aromatic substrates.

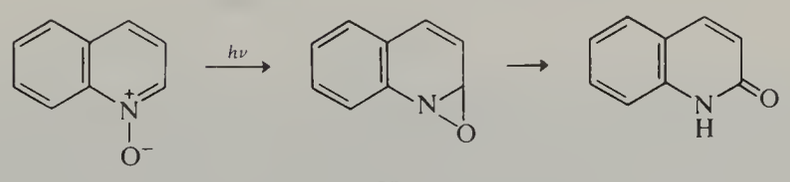


Scheme 233

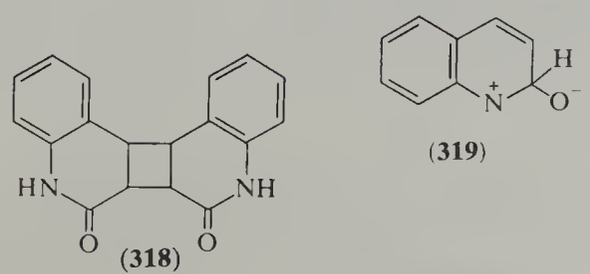
Isomerization of pyridine 1-oxide and its analogues to cyclic amides is quite facile. It is exemplified by pyridine 1-oxide photolysis in which the excited singlet state is formed initially and this converts to the oxazirine which undergoes N—O bond fission with a 1,2-hydrogen shift to give pyridin-2-one (Scheme 234). Irradiation of quinoline 1-oxides leads to carbostyrils (Scheme 235), or a dimer (**318**); again an oxazirine is considered the intermediate, although a zwitterion (**319**) might be preferred in more polar solvents ⟨76H(4)1391⟩. Yields are highest in polar solvents (91% in water) and lowest in less polar solvents (60–70% methanol, 15% diethyl ether). Photolysis of 1-methylisoquinoline 1-oxide involves a 1,2-methyl migration to yield *N*-methylisocarbostyril ⟨equation 197⟩.



Scheme 234

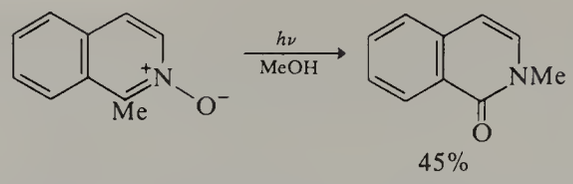


or



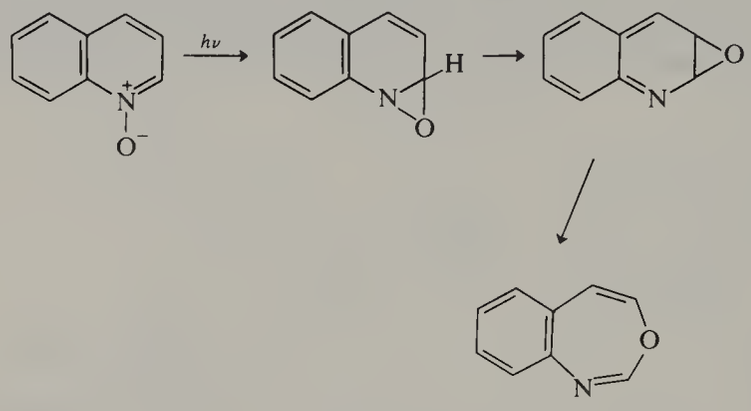
(318) **(319)**

Scheme 235



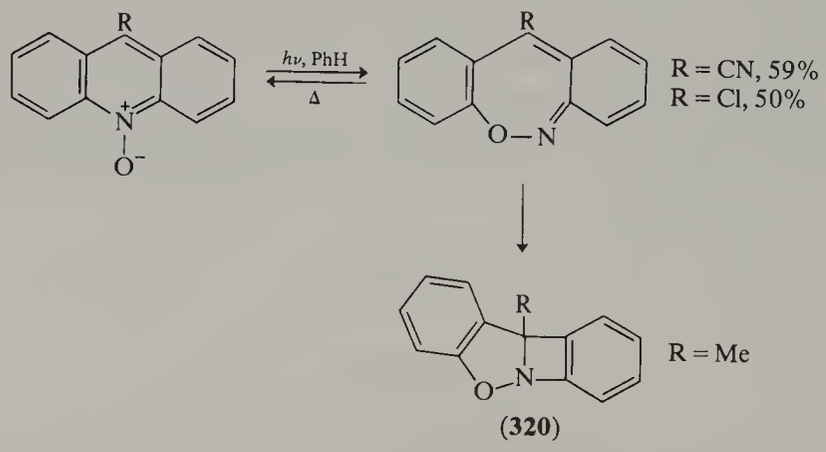
(197)

Oxaziridine formation from the excited singlet quinoline 1-oxide is postulated as the first step in the formation of 1,3-oxazepines. In this case it undergoes a 1,5-sigmatropic rearrangement rather than N—O bond cleavage to give 2,3-epoxyquinoline that ring expands (Scheme 236). Solvent polarity has little effect on ease of oxazepine formation, but oxazepines react easily with acids or bases; therefore, if they are the required product, photolysis is best carried out in nonpolar, aprotic solvents. An additional stabilizing feature is provided by the presence of an electron withdrawing substituent at the 2-position in the starting *N*-oxide. That oxazepines are truly primary photoproducts is attested by the fact that other photoproducts cannot be converted into them.



Scheme 236

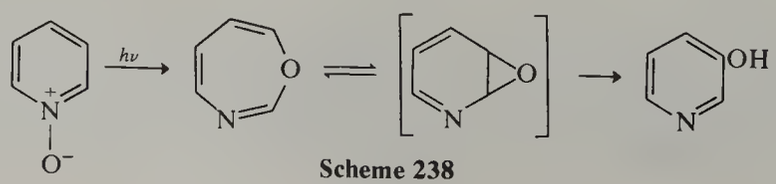
10-Cyano- and 10-chloro-acridine *N*-oxides yield 1,2-oxazepines on photolysis in benzene (Scheme 237). When the 10-substituent is methyl the unstable 1,2-oxazepine undergoes electrocyclization to a benzisoxazoline (**320**). Secondary photoproducts may be formed by direct irradiation of *N*-oxides or by rearrangement of the primary photoproduct.



(320)

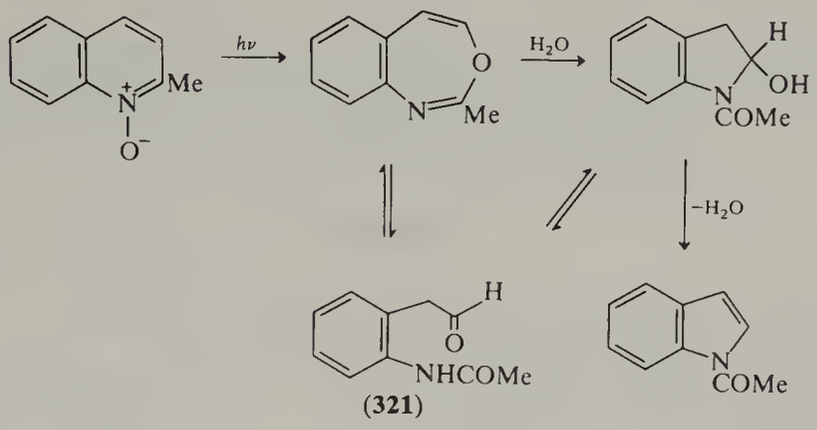
Scheme 237

3-Hydroxypyridines have been obtained by direct photolysis of several *N*-oxides, but only one example exists in the quinoline series. Reaction involves the intermediacy of 1,3-oxazepines, which rearrange to hydroxy products *via* the 2,3-epoxide (Scheme 238). 1,3-Benzoxazepine intermediates, generated on quinoline 1-oxide photolysis, are more stable than their monocyclic counterparts and therefore they undergo other reactions in preference to the above. Nonetheless, if first isolated they can be induced to isomerize in high yield to β-hydroxyquinolines.



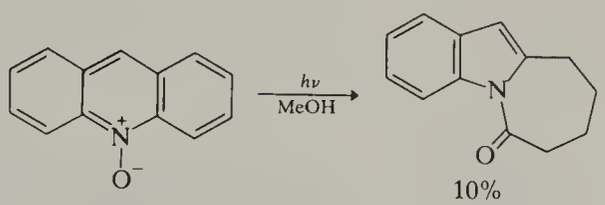
Scheme 238

1-Acyl-2-hydroxy-2,3-dihydropyrrole and analogues have been isolated from pyridine and quinoline 1-oxide photolyses (Scheme 239). They are presumed to arise by hydrolytic ring opening of 1,3-oxazepines to aminoaldehydes (**321**) followed by reversible ring closure. These products readily undergo dehydration to the corresponding pyrroles or indoles. Many other equally plausible mechanisms have been put forward to explain this transformation ⟨76H(4)1391⟩. Acridine *N*-oxide on photolysis in methanol also undergoes ring contraction but concomitant expansion of a benzene ring also takes place (equation 198).



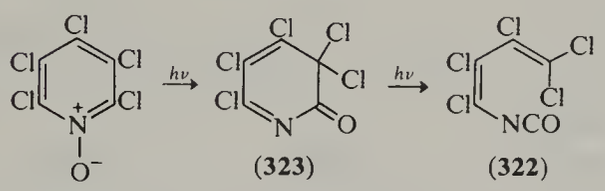
(**321**)

Scheme 239



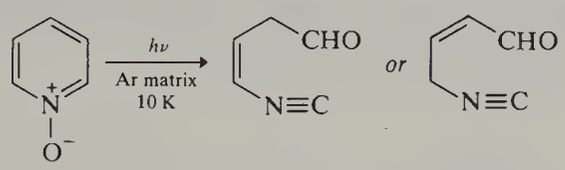
10% (198)

Photolysis of pentachloropyridine 1-oxide gives an aliphatic isocyanate (**322**), probably by way of the pyridinone (**323**; Scheme 240) ⟨72CC505⟩. More recently, opening of pyridine 1-oxide itself has been found on photolysis in an argon matrix at 10 K (equation 199) ⟨77H(6)583⟩.



(**323**) (**322**)

Scheme 240

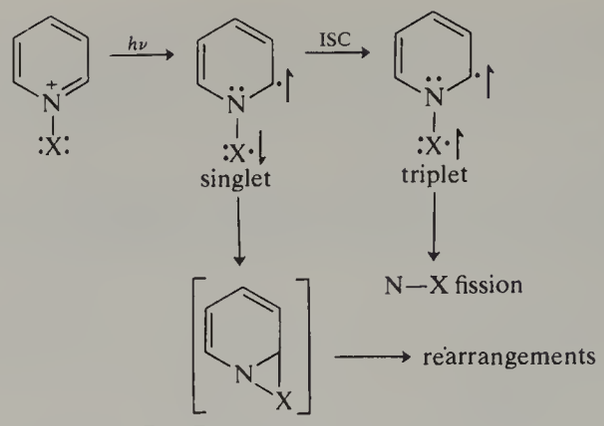


(199)

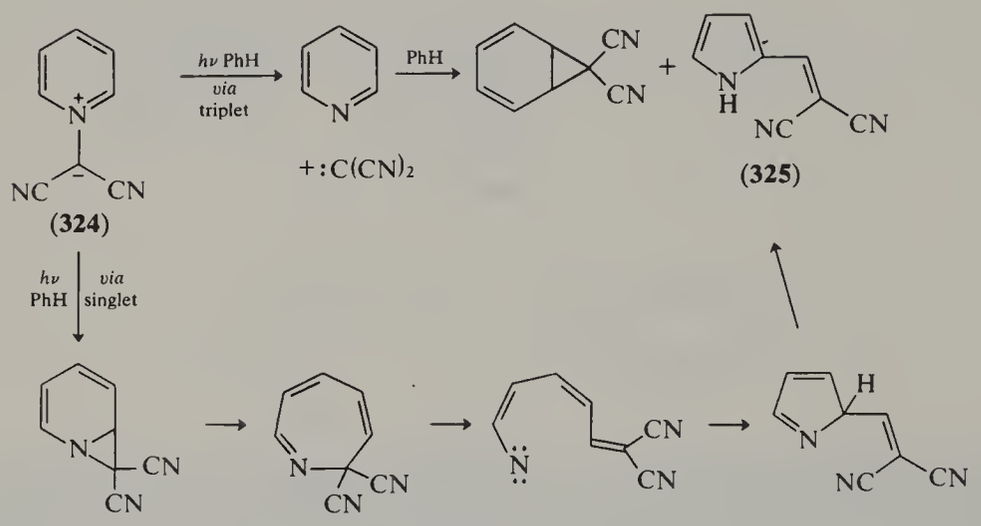
2.05.7.6 *N*-Imines and *N*-Ylides

The photochemical behavior of these compounds closely parallels that of the corresponding *N*-oxides ⟨77PAC305⟩. Pople–Pariser–Parr calculations and experimental work ⟨71HCA1645⟩ suggest involvement of a $\pi \rightarrow \pi^*$ transition on photolysis of 1-ethoxycarbonyliminopyridinium ylide, which leads to negative charge being transferred into the ring from the exocyclic ylide atom. If one assumes this mechanism to be general, the initial steps in the photolysis of *N*-oxides, *N*-imines and *N*-ylides may be represented as in Scheme 241.

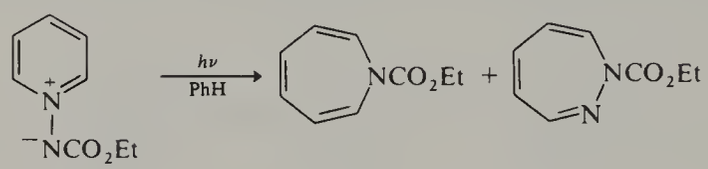
Irradiation of the pyridinium dicyanomethylide (**324**) in benzene gives the substituted pyrrole (**325**), by the postulated route shown (Scheme 242) which originates from the singlet excited ylide. 7,7-Dicyanoazanorcaradiene presumably arises by N—C bond fission in the triplet which produces a dicyanocarbene (of dubious multiplicity) which is trapped by the solvent benzene ⟨67CR(C)(264)1307⟩. Photolysis of the imino-ylide (**326**) in benzene (equation 200) follows the same pathways initially but the two products result from ring expansions,



Scheme 241

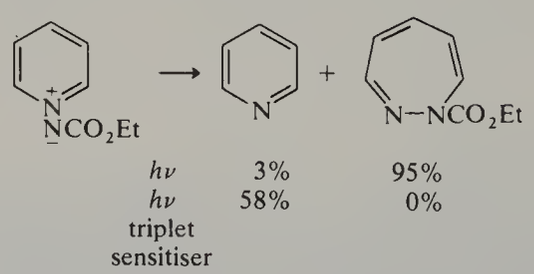


Scheme 242



(200)

one (**327**) from attack of ethoxycarbonylnitrene on benzene and the other (**328**) by ring expansion of intermediate diaziridine. Formation of 1,2-diazepines is the most favored reaction of *N*-iminopyridinium ylides on photolysis, but it can be totally suppressed by use of a triplet sensitizer (Scheme 243) ⟨68AG(E)129⟩.



Scheme 243

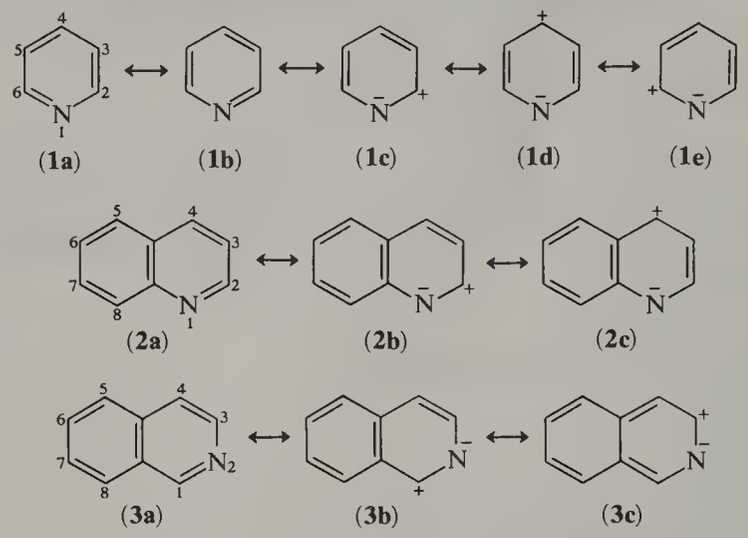
2.06

Pyridines and their Benzo Derivatives: (iii) Reactivity of Substituents

B. C. UFF
Loughborough University of Technology

2.06.1 INTRODUCTION: THE EFFECT OF THE PYRIDINE RING ON REACTIONS OF SUBSTITUENTS

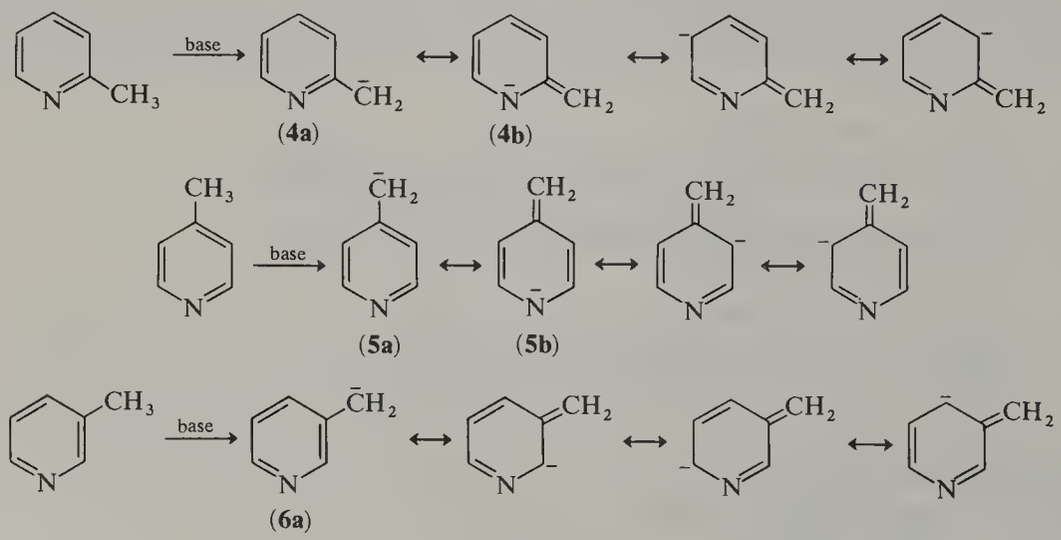
The electronegative ring nitrogen in pyridine (**1**) and its benzo analogues (*e.g.* **2** and **3**) has an uneven effect on the ring atoms and hence on substituent groups. Calculations of the π-electron densities in pyridine show that the atoms at positions 2, 4 and 6 are the most affected by the electron withdrawal, and dipole moment evidence also indicates the relevance of contributions from the ionic canonical forms (**1c**, **1d** and **1e**) to the structure. In an analogous way, π-electron density calculations for quinoline (**2**) and isoquinoline (**3**) show significant electron withdrawal from positions 2 and 4, and 1 and 3 respectively. The Kekulé canonical forms (**1a**, **1b**, **2a** and **3a**) are of principal importance and π-bond order calculations show high orders for the 5,6- and 7,8-bonds of (**2a**) and (**3a**) (see Chapter 2.04).



Scheme 1

It is a predictable consequence, therefore, that substituents at positions α and γ to the ring nitrogen have an enhanced reactivity, whereas substituents β to ring nitrogen or in a fused benzo ring behave more as would be the case if they were attached to the equivalent benzenoid carbocyclic system.

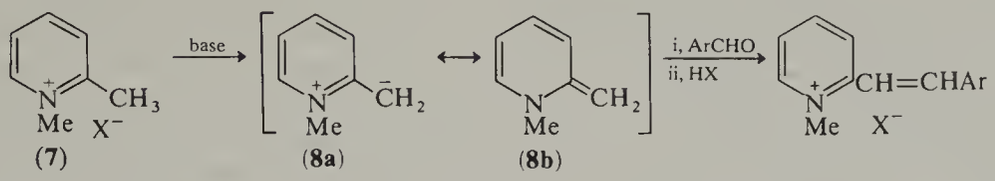
The effect of the ring heteroatom can be seen in the reactivity of alkylpyridines. Deprotonation from the α-carbon of a substituent at position 4 or 2 is much easier than from a similar substituent at position 3. For example, mesomeric stabilization of the negative charge in (**4a**) and (**5a**) will involve contributions from canonical forms (**4b**) and (**5b**) in which the charge is carried on ring nitrogen, but a similar contributor cannot be drawn for (**6a**; Scheme 2).



Scheme 2

The effects of electron withdrawal by ring nitrogen are increased in pyridinium and related cations. Hence *N*-protonation, *N*-alkylation or *N*-oxide formation results in greater substituent reactivity at the α- and γ-positions. In quaternary pyridinium salts, *e.g.* (**7**),

deprotonation of the α- and γ-alkyl groups occurs much more readily than with the uncharged system. The intermediate (**8a**) can be stabilized by a contribution from the uncharged anhydro base form (**8b**; Scheme 3), and in some cases anhydro bases can actually be isolated.



Scheme 3

There are further consequences in fused systems. For example, electrophilic substitution through the intermediacy of the quinolinium ion results in substitution at positions 5 and 8, whereas when substitution takes place on the free base the products are the 3-, 6- and 8-substituted derivatives.

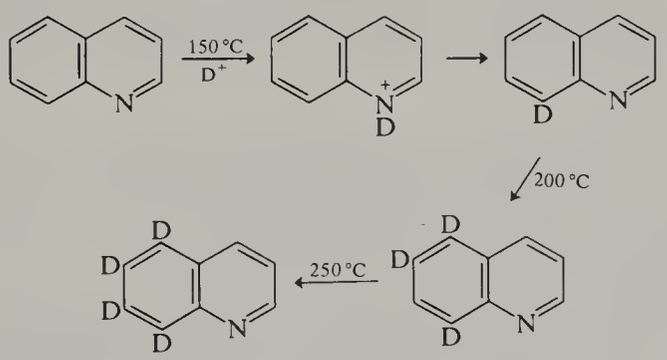
The remainder of the chapter exemplifies these effects and others on substituent reactivity in the π-deficient aromatic heterocycles under discussion. Available reviews of specific topics are indicated in the text and many excellent general reviews are also available ⟨81HC(38-1)1, B-79MI20600, B-79MI20601, B-79MI20602, B-79MI20603, 79AHC(25)303, B-78MI20600, 77HC(32-1)1, B-76MI20600, B-76MI20601, B-76MI20602, B-76MI20603, 76AHC(S1)1, 75HC(14-4)1, 74HC(14-1)1, 74HC(14-2)1, 74HC(14-3)1, 73HC(9)1, B-72MI20600, B-71MI20600, B-67MI20600, B-67MI20601, B-67MI20602, B-66MI20600⟩.

2.06.2 FUSED BENZENE RINGS

2.06.2.1 Substitution Reactions in Fused Benzene Rings

2.06.2.1.1 Deuteration

Replacement of the proton by deuterium represents the simplest electrophilic substitution; the process is effected by concentrated deuteriosulfuric acid. Deuteration studied over the ranges 45–96% acid and 150–250 °C showed that for both quinoline and quinoline *N*-oxide reaction occurs in the positions 8 > 5,6 > 7 > 3 and rates increased both with increasing acid concentration and with temperature. The mechanism proceeds *via* the conjugate acid (Scheme 4) ⟨75TL1395, 72IZV2092, 71JCS(B)4, 67CPB826⟩.



Scheme 4

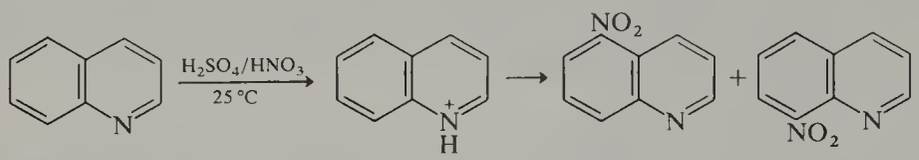
In isoquinoline at 180 °C, using 90% deuteriosulfuric acid, hydrogen exchange of the 5-proton occurs first, followed by that of the 8-proton, and exchange at these sites also occurs with isoquinoline *N*-oxide. The mechanism in each case goes *via* the conjugate acid species. At 245 °C and lower acidities exchange occurs at the 1- and 4-positions by a different mechanism (see Chapter 2.05) ⟨71JCS(B)4⟩.

2.06.2.1.2 Nitration

In general, the likely orientation of electrophilic substitution will be indicated by several factors including the extent of bond fixation, the extent of prior electrophilic attack at

nitrogen and calculations of the electron localization energies of various positions (although these calculations are not always in agreement with observed orientations) ⟨59JCS3451, 57JCS2521⟩.

Nitration of the benzopyridines in strongly acidic media occurs relatively easily, and preferentially in the carbocyclic rings. Quinoline with nitric and sulfuric acids at 0 °C gives 5-nitroquinoline and 8-nitroquinoline in the proportions 52.3 to 47.7% respectively ⟨57JCS2521⟩ and kinetic studies have shown the quinolinium ion to be the reacting species. The rate of nitration in 80–98% sulfuric acid is of the same order as that of *N*-methylquinolinium perchlorate ⟨63JCS4204, 63CI(L)1283⟩. A study of the nitration of the quinolinium ion in 80.05% sulfuric acid at 25 °C showed the products to be 5- (50.1%), 8- (42.3%), 6- (1.61%), 7- (0.014%) and 3-nitroquinoline (0.0013%) (Scheme 5) ⟨71JCS(B)1254⟩.



Scheme 5

It has been estimated that the pyridinium ion is at least 10^5 times less reactive than the quinolinium ion ⟨63JCS4204⟩. Also, the overall reaction rates of benzene and the quinolinium ion differ by a factor of 4×10^7, which leads to partial rate factors of 7.5×10^{-8} at the 5- and the 8-position of the quinolinium ion ⟨63JCS4204⟩.

Under more vigorous nitration conditions the products from quinoline are 5,7- and 6,8-dinitroquinoline. Nitration of 6-nitroquinoline with potassium nitrate and sulfuric acid in a sealed tube at 140 °C gives 5,6- and 6,8-dinitroquinoline; under the same conditions 7-nitroquinoline gives 5,7- and 7,8-dinitroquinoline.

As would be expected, less forcing conditions are required to nitrate alkylquinolines. 5-Methylquinoline in sulfuric acid below 5 °C nitrates at positions 6 and 8; 7-methylquinoline gives 7-methyl-8-nitroquinoline ⟨77T1765⟩.

The situation is totally different for nitrations with acetic anhydride as solvent. The main product from quinoline is 3-nitroquinoline in only 6.2% yield (HNO_3–Ac_2O at 100 °C) together with traces of 6- and 8-nitroquinoline. 5-Nitroquinoline is absent. The mechanism is thought to involve a dihydroquinoline intermediate. Addition of the electrophile to the N-atom gives the *N*-nitroquinolinium ion to which the nucleophile can add at the 2-position. The resulting aminostyrene structure should then react with electrophiles at the 3,4-double bond and at the 6- and 8-positions ⟨63PMH(1)124⟩. (See Chapter 2.05 for further discussion of hetero ring substitution.)

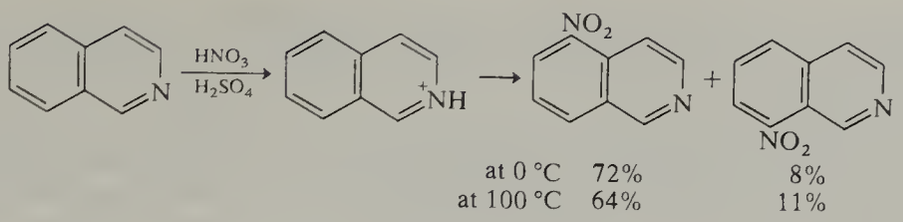
The use of transition metal nitrato compounds can be of value. For example, tetranitratozirconium(IV), $Zr(NO_3)_4$, on shaking with quinoline at room temperature, gives a 90% yield of almost pure 7-nitroquinoline ⟨74JCS(P1)1751⟩.

Pernitrous acid (aq. $NaNO_2$–H_2O_2–H_2SO_4) with quinoline at 0 °C gives low yields of 5-, 6-, 7- and 8-nitroquinolines ⟨57JCS944⟩.

Nitration of quinoline *N*-oxide can give substitution in either ring depending on the conditions. To obtain reaction in the benzo ring, nitration with mixed nitric and sulfuric acids at 0–20 °C is used. This gives 8-nitroquinoline *N*-oxide as major product, together with the 5-isomer ⟨B-71MI20600⟩. It is known that the reaction occurs *via* the 1-hydroxyquinolinium cation, whereas conditions which achieve nitration at the 4-position do not ⟨68JCS(B)316⟩. Nitration of quinoline *N*-oxide at high temperature (>*ca.* 120 °C) is accompanied by deoxygenation and 5- and 8-nitroquinolines result.

Nitration of isoquinoline with nitric and sulfuric acids occurs preferentially at positions 5 and 8, the former predominating, in the approximate ratio of 9 : 1 at 0 °C. The amount of 8-nitro isomer is slightly increased at higher temperatures. Electrophilic localization energies predict the reactivity order 5 > 8 > others. Over the range 71–85% sulfuric acid it has been shown that the reaction proceeds *via* the isoquinolinium cations (Scheme 6) ⟨63CI(L)1283, 60T(8)23, 57JCS2521⟩.

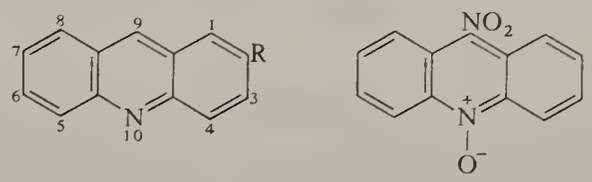
The nitration of isoquinoline *N*-oxide gives 5-nitroisoquinoline *N*-oxide and kinetic studies suggest that the reaction proceeds through the conjugate acid ⟨66JCS(B)870⟩. In



Scheme 6

contrast to the quinolinium case, therefore, it is of no value for altering the position of nitration.

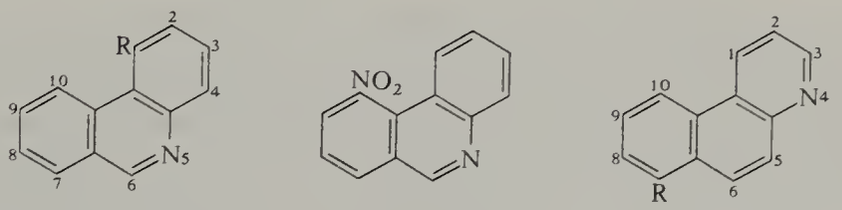
The nitration of acridine (**9**; R = H) in sulfuric acid is an unsatisfactory reaction in that the mixed isomers produced are difficult to separate. The main product is 2-nitroacridine (**9**; R = NO_2) the order of reactivity being 2 > 4 > 1 > 3 and product ratio 130:25:5:1 respectively ⟨B-66MI20600⟩. Acridine *N*-oxide, however, undergoes nitration at 0 °C to produce 9-nitroacridine *N*-oxide (**10**) ⟨60JCS3367⟩.



(**9**) (**10**)

Phenanthridine (**11**; R = H) undergoes nitration in the benzo rings principally to give the 1-nitro- (**11**; R = NO_2) and 10-nitro- (**12**) isomers in 26% and 21% yields respectively. The other products are the 8- (11%), 3- (6%), 2- (3%) and 4-isomers (1%) ⟨B-78MI20600⟩.

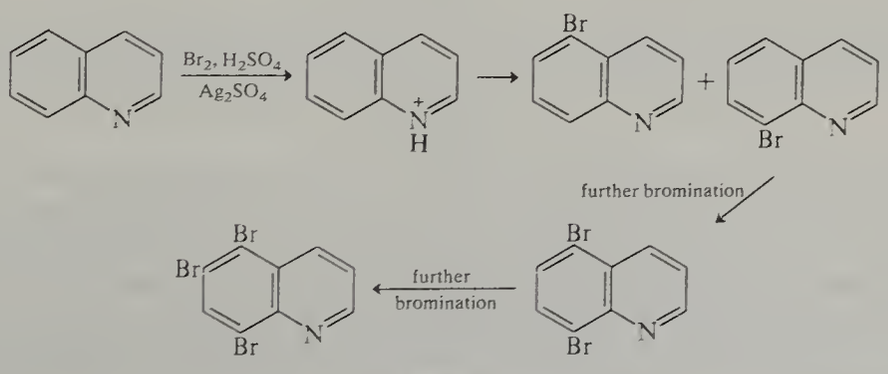
Benzo[*f*]quinoline (**13**; R=H) on nitration at −15 °C gives 7-nitrobenzo[*f*]quinoline (40%) (**13**; R = NO_2) together with smaller amounts of the 10- (13%) and 9-nitro derivatives (9%). At 0 °C the 7,9-dinitro derivative is obtained. Nitration of benzo[*f*]quinoline *N*-oxide gives 7-nitrobenzo[*f*]quinoline *N*-oxide.



(**11**) (**12**) (**13**)

2.06.2.1.3 Halogenation

Bromination of quinoline in sulfuric acid containing silver sulfate gives in good yield almost equal amounts of 5- and 8-bromoquinoline. With an excess of bromine and silver sulfate 5,8-dibromoquinoline becomes the major product. The dibromo compound is similarly formed from 5- and 8-bromoquinoline. Further bromination gives 5,6,8-tribromoquinoline (Scheme 7). With 3-bromoquinoline as starting material, formed, for example, from bromine in carbon tetrachloride (see Chapter 2.05), the silver sulfate/sulfuric acid method converts it into 3,5-dibromo- and 3,5,8-tribromo-quinoline. Bromination with

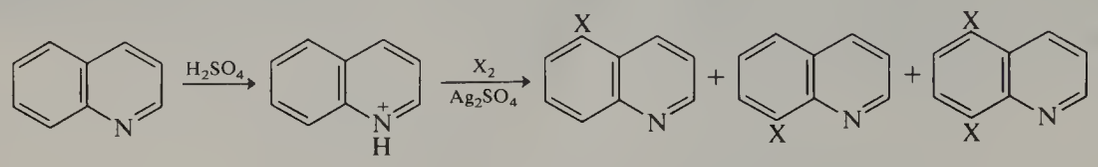


Scheme 7

silver sulfate/sulfuric acid is considered to be electrophilic in character, the positively charged brominating species (possibly $BrH_2SO_4^+$ or $BrSO_3^+$) attacking the protonated base ⟨75JHC1015, 60JCS561⟩.

The aluminum chloride complex of quinoline is also brominated in a similar manner, except that less 8-bromoquinoline is formed, presumably reflecting steric hindrance by the aluminum chloride complexed at nitrogen. The 5,6- and 5,8-dibromoquinolines and 5,6,8-tribromo derivative can also be obtained by this procedure. Reaction of the complex with chlorine gives the 5,8-dichloro and 5,6,7,8-tetrachloro derivatives ⟨67JHC410, 64JOC329⟩.

Chlorination of quinoline in the presence of silver sulfate in sulfuric acid gives 5-chloro, 8-chloro- and 5,8-dichloro-quinoline ⟨63CI(L)1840, 66MI20601⟩. Similarly, addition of iodine to quinoline and silver sulfate in sulfuric acid at 150–200 °C gives 5-iodo-, 8-iodo- and 5,8-diiodo-quinoline (Scheme 8). It is thought that I^+ is the electrophile ⟨64CI(L)1753, 66MI20602⟩.



Scheme 8

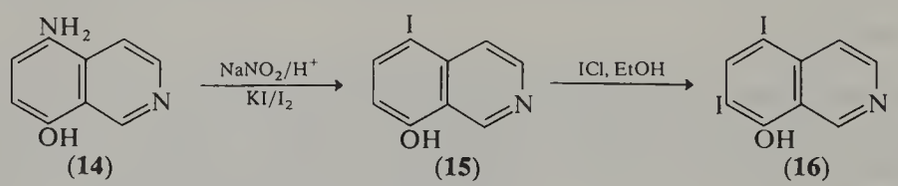
Reactions involving chlorination of quinoline in both rings result from a variety of conditions. Chlorine in carbon tetrachloride gives 3,4,6,8-tetrachloroquinoline whereas gaseous chlorine and thionyl chloride produce 4,5,7,8-tetrachloroquinoline. The major product with sulfuryl chloride at 55–60 °C is 3,4,5,6,7,8-hexachloroquinoline (57%) together with 3,4,6,8-tetrachloroquinoline (37%) ⟨74MIP20600, 74S356, 73YZ73⟩.

The 5-, 6-, 7- and 8-halo compounds are frequently prepared from the corresponding amino compounds by the Sandmeyer reaction.

Quinoline *N*-oxide is brominated in the 3- and 6-positions on treatment with bromine in acetic anhydride, the mechanism probably involving an addition process in the hetero ring ⟨65YZ62⟩.

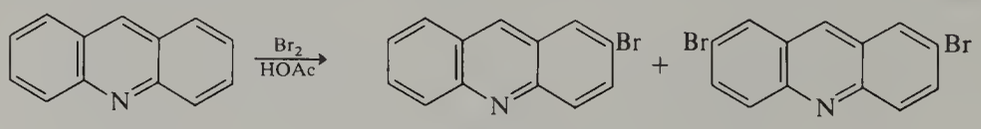
Bromination of isoquinoline in strong acid gives 5-bromoisoquinoline. Bromination of isoquinoline complexed with aluminum chloride gives substitution in the following sequence: 5-bromo-, 5,8-dibromo- and 5,7,8-tribromo-isoquinoline. Chlorination of the isoquinoline–aluminum chloride complex gives similar results, although the chlorinating agent is less selective and gives some 5,6,7,8-tetrachloroisoquinoline on exhaustive treatment ⟨64JOC329⟩.

Again the Sandmeyer reaction is frequently used to convert amino- to halo-isoquinolines. The diazonium salt of 5-amino-8-isoquinolinol (**14**) on treatment with potassium iodide and iodine gives the 5-iodophenol (**15**). Iodination of the hydrochloride of (**15**) with iodine monochloride in ethanol gives (**16**; Scheme 9) ⟨66JMC46⟩.



Scheme 9

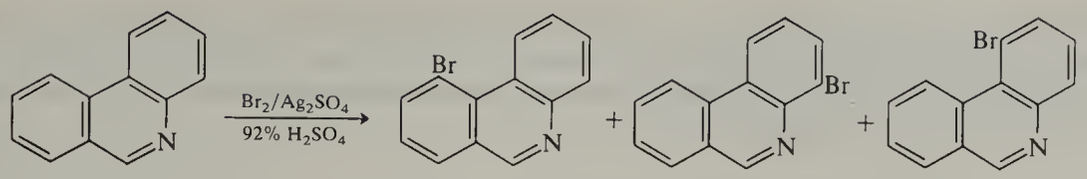
Bromination of acridine in acetic acid gives mainly 2-bromoacridine together with some 2,7-dibromoacridine (Scheme 10).



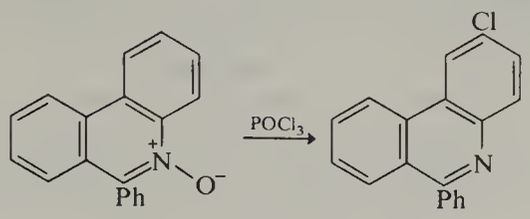
Scheme 10

Whereas treatment of phenanthridine with *N*-bromosuccinimide gives only 2-bromophenanthridine, use of bromine and silver sulfate in 92% sulfuric acid gives, in low yields, 10-, 4- and 1-bromo-phenanthridines in the ratio 9.5 : 6.4 : 1 together with some dibromo products (Scheme 11) ⟨69AJC1105⟩. This order of reactivity contrasts with that observed for nitration of phenanthridine (Section 2.06.2.1.2).

Treatment of 6-phenylphenanthridine *N*-oxide with phosphorus oxychloride results in reductive chlorination, the chlorine entering at position 2 (Scheme 12).



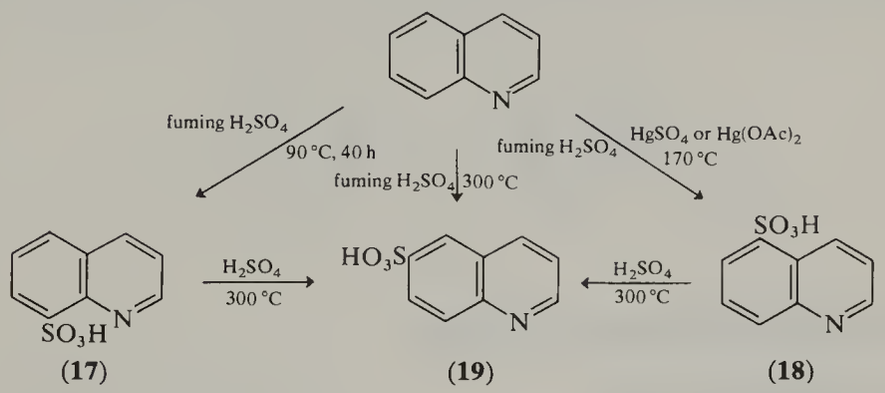
Scheme 11



Scheme 12

2.06.2.1.4 Sulfonation

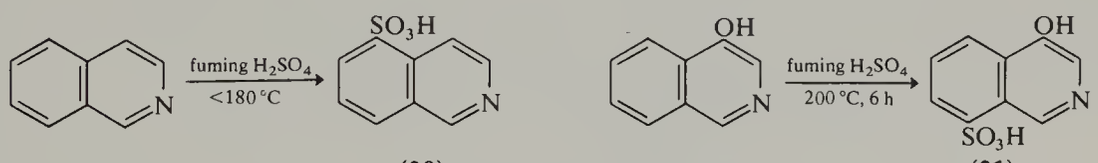
Treatment of quinoline with fuming sulfuric acid (30% SO_3) at 90 °C gives quinoline-8-sulfonic acid (**17**) in 54% yield with the 5- and 7-isomers as minor products. The quantity of 5-sulfonic acid (**18**) increases with reaction temperature and use of mercury or one of its salts as a catalyst in fuming sulfuric acid at 170 °C gives (**18**) as exclusive product. However, the thermodynamically favoured quinoline-6-sulfonic acid (**19**) is obtained when heating at 300 °C either the 8- or 5-sulfonic acid or quinoline itself with fuming sulfuric acid (Scheme 13).



(**17**) (**19**) (**18**)

Scheme 13

Sulfonation of isoquinoline with 40% oleum or higher SO_3 content, at temperatures up to 180 °C, gives isoquinoline-5-sulfonic acid (**20**) as main product. At higher temperatures the 8-sulfonic acid is also formed. Sulfonation of 4-hydroxyisoquinoline with 20% oleum for six hours at 200 °C gives the 8-sulfonic acid (**21**; Scheme 14) ⟨72IZV457⟩.



(**20**) (**21**)

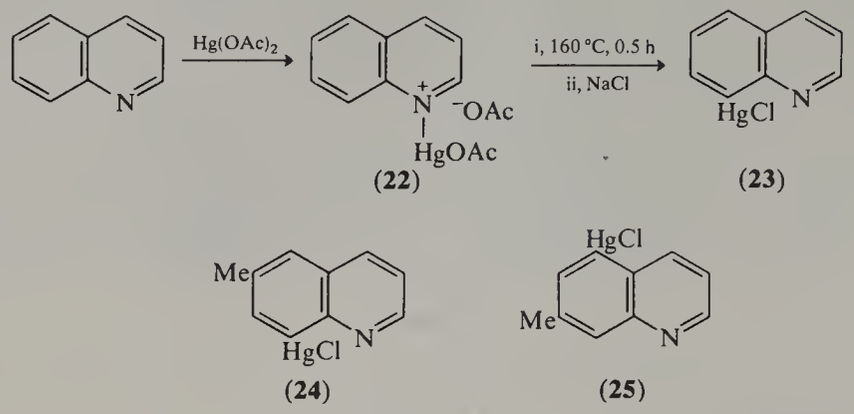
Scheme 14

Although sulfuric acid at 100 °C does not sulfonate acridine, at 180 °C fuming sulfuric acid causes self-condensation, giving 9,9′-biacridine-tri- and -tetra-sulfonic acids. The sulfonation of 9-aminoacridine is thought to give 2,7-substitution ⟨B-66MI20600⟩.

2.06.2.1.5 Mercuration

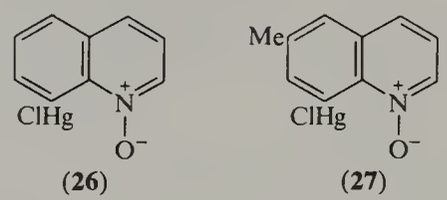
Quinoline on treatment with mercury(II) acetate gives the quaternary 1-mercurioacetate salt (**22**). On heating the salt to 160 °C and adding sodium chloride solution, quinoline-8-mercuriochloride (**23**) is formed. Similar treatment of 6- and 7-methylquinoline gives 6-methylquinoline-8-mercuriochloride (**24**) and 7-methylquinoline-5-mercuriochloride

(**25**) as products respectively (Scheme 15). Each is converted to the corresponding bromo derivative on displacement of the chloromercury substituent with bromine. Isoquinoline under the same conditions is reported not to give a benzo ring-substituted product, but rather isoquinoline-4-mercuriochloride.



Scheme 15

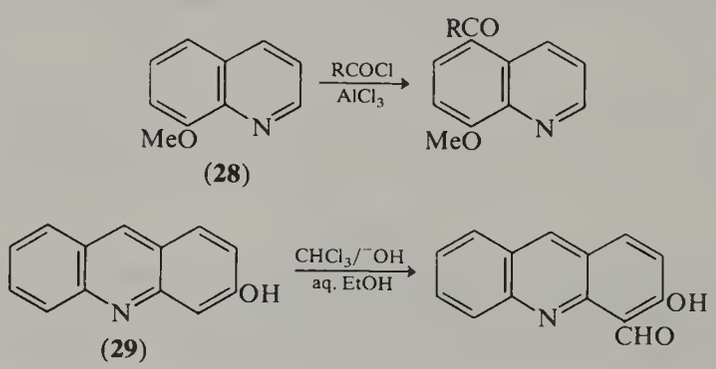
Mercuration of quinoline *N*-oxide in acetic acid or perchloric acid gives the 8-mercuriochloride (**26**) as the main product and small amounts of the 3-, 5-, 6- and 7-isomers. In the absence of solvent mercury(II) sulfate gives all the possible isomers although the total yield is poor. 6-Methylquinoline *N*-oxide gives the 8-substituted derivative (**27**). The preferential 8-orientation is accounted for in terms of preliminary coordination of the mercury atom at the oxygen of the *N*-oxide. When the 8-position is blocked, as in 8-bromoquinoline *N*-oxide, mercuration is reported to occur at the 4-position ⟨55YZ490, 69CPB906⟩.



2.06.2.1.6 Acylation, alkylation and arylation

2.06.2.1.6(i) Electrophilic processes

Friedel–Crafts acylation fails with quinoline, isoquinoline, acridine and many derivatives. However, when sufficient activation is present substitution can result. For example, 8-methoxyquinoline (**28**) in the presence of aluminum chloride and acetyl or benzoyl chloride gives the 5-acetyl and 5-benzoyl derivatives in 25% and 35% yields respectively.



Scheme 16

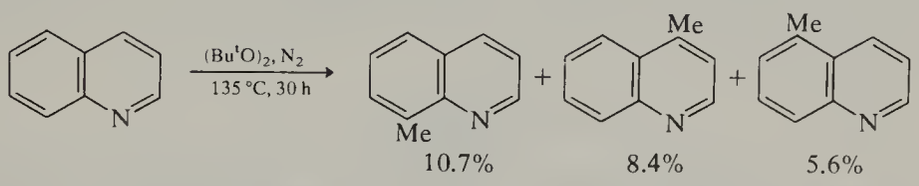
3-Hydroxyacridine (**29**) is formylated in the 4-position in a Reimer–Tiemann reaction (Scheme 16) ⟨61JCS182⟩.

2.06.2.1.6(ii) Homolytic processes

Homolytic substitution processes have the drawback that they frequently give mixtures of products and proceed in rather low yield. The topic has been reviewed ⟨72MI20601,

74AHC(16)123, 77HC(32-1)53⟩. Phenylation of quinoline, using benzoyl peroxide, gives all seven phenylquinolines. In neutral medium the monophenylquinoline fraction contains up to 32% 8-phenyl- and 22% 5-phenyl-quinoline. In acid medium figures fall to 13% and 8% of the fraction respectively, the predominant products then being the 2- and 4-phenylquinolines ⟨58AJC200, 71BSF2612⟩.

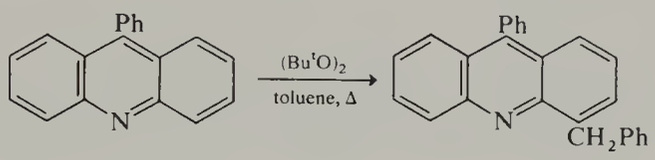
Homolytic methylation of quinoline in non-acidic media shows the order of positional reactivity as $8 > 4 > 5 > 2$, which is not in agreement with that predicted from atom localization energies of quinoline. Using *t*-butyl peroxide as radical source gives a total yield of methylquinolines of 34.7% of which the 8-isomer constitutes 30.8%, the 4-isomer 24.2%, the 5-isomer 16.1%, the 2-isomer 10.2% and the other isomers 18.7% (Scheme 17) ⟨70JCS(C)2169⟩. Radical methylation of quinoline in acid media gives 2- and 4-methylquinolines as principal products, and most other studies have concentrated on conditions giving radical substitution in the hetero ring rather than in the benzo ring (see Chapter 2.05).



Scheme 17

Radical attack on isoquinoline, as either free base or isoquinolinium cation, always occurs at position 1 and the method is not suitable for the preparation of benzo ring-substituted products. The same can be said of radical attack on the *N*-oxides of quinoline and isoquinoline.

Treatment of 9-phenylacridine with benzyl radicals gives 4-benzyl-9-phenylacridine (10%) as the main product (Scheme 18) ⟨57JCS253⟩.



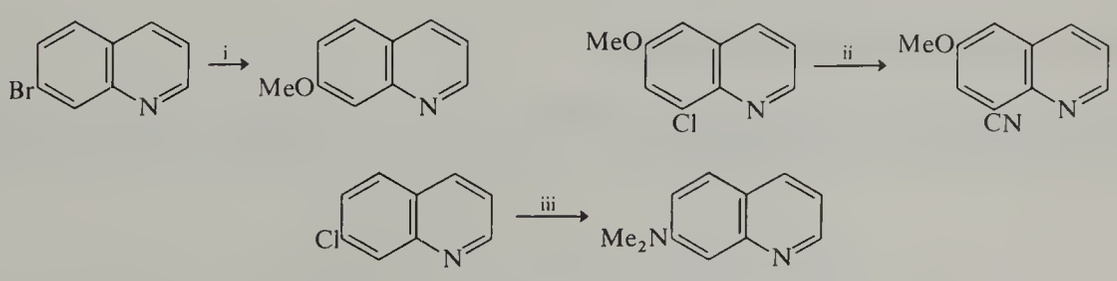
Scheme 18

2.06.2.1.7 Nucleophilic Substitution

In general, nucleophilic substitution occurs not in the fused benzene rings but in the hetero ring. However, benzo ring substitution can be achieved by activation by groups already in the benzo ring or by displacement of existing groups, particularly nitro and halogen.

Quinoline is normally substituted by nucleophiles at position 2 and to a lesser extent at position 4 (see Chapter 2.05), and replacement of a halogen in the benzo ring occurs less readily than replacement of one at positions 2 or 4. The latter process requires, in general, temperatures of 50–100 °C whereas the former requires temperatures of 150–200 °C or more (Scheme 19). There are many examples of replacement of halogens that are activated by electron-withdrawing groups. The topic has been reviewed ⟨77HC(32-1)526⟩.

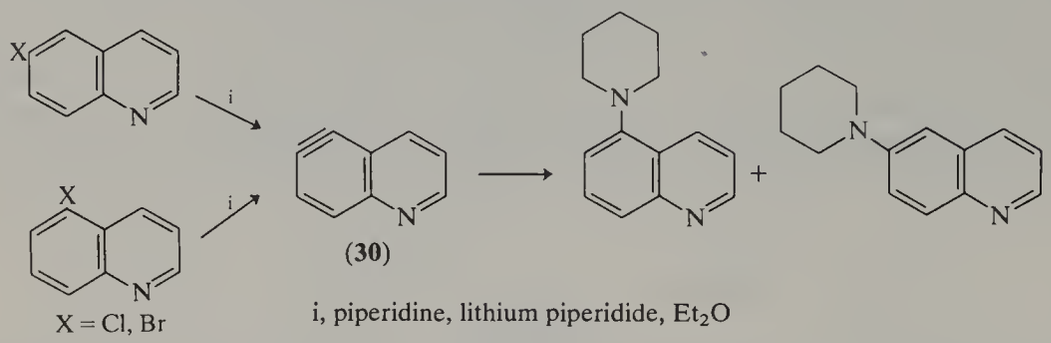
Displacement reactions in the benzo ring can also occur *via* aryne intermediates. Treatment of 6-choroquinoline with a fourfold excess of potassium amide in ether at −33 °C



i, NaOMe/MeOH, 250 °C under pressure, 7 h; ii, fuse with CuCN; iii, aq. Me_2NH, 250–290 °C, sealed tube, 8 h.

Scheme 19

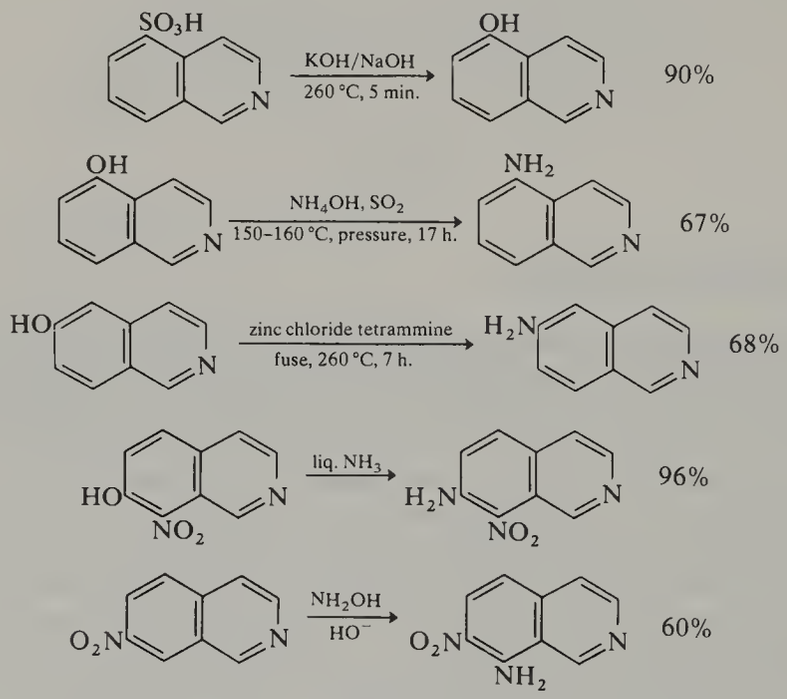
gives 5- and 6-aminoquinoline in the ratio 34:66 and in an overall yield of 77%. 6-Bromoquinoline gives the same isomers in a similar ratio (31:69 respectively) ⟨74MI20601⟩. Treatment of 6-bromoquinoline with lithium piperidide and piperidine in boiling dry ether gives 5- and 6-piperidinoquinoline in the ratio 30:70. 5-Bromoquinoline under the same conditions gives the same products in the ratio 28:72. Similar results are obtained with the 5- and 6-chloroquinolines. The data are consistent with an elimination–addition mechanism (*EA*) *via* a 5,6-dehydroquinoline (5,6-quinolyne) (**30**; Scheme 20).



Scheme 20

7-Haloquinolines on similar treatment give 7,8-dehydroquinoline which gives 7- and 8-piperidinoquinolines in approximately equal amounts. 8-Haloquinolines undergo a normal addition–elimination process (AE_n) giving 8-piperidinoquinoline as sole product ⟨64LA(680)31⟩.

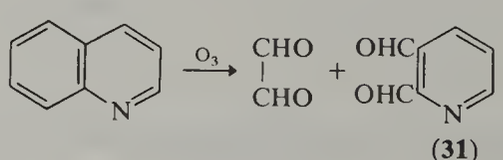
As may be expected, isoquinoline readily undergoes attack by nucleophiles in the hetero ring (at position 1) (see Chapter 2.05). As with quinoline, substitution in the benzo ring is usually achieved by displacement of an existing substituent, or substitution of hydrogen at a suitably activated position. Some examples are given in Scheme 21 ⟨62JOC4571, 69AJC2489, 75AP413⟩.



Scheme 21

2.06.2.2 Oxidation of Fused Benzene Rings

Opening of the benzo ring of quinoline can be achieved with a large variety of oxidizing agents. Ozonolysis at −25 °C proceeds by a primary attack at the 5,6- and 7,8-bonds,

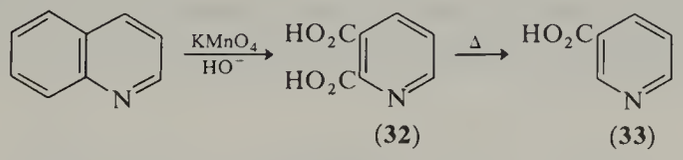


(**31**)

Scheme 22

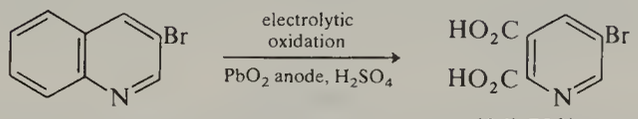
leading, after reduction of the ozonides, to glyoxal and 2,3-diformylpyridine (**31**; Scheme 22). 6,7-Dimethylquinoline gives biacetyl and (**31**) ⟨55RTC241⟩. The data are consistent with a high bond order for the 5,6- and 7,8-bonds.

Alkaline permanganate converts quinoline to pyridine-2,3-dicarboxylic acid (quinolinic acid) (**32**), as do chromic acid, manganese dioxide in oleum, and cobalt(III) acetate ⟨74USP3829432⟩. Heating quinolinic acid (**32**) yields nicotinic acid (**33**) and the latter is frequently reported as a product in quinoline oxidations; such reactions have been the subject of many patents (Scheme 23). Reagents used include nitric acid ⟨64GEP1161563⟩, nitric acid mixed with sulfuric acid ⟨67MI20603⟩ and sulfuric acid in mixtures containing selenium ⟨64MI20600⟩. Oxidation of quinoline in the vapour phase to nicotinic acid occurs over vanadium oxide ⟨73MI20600⟩.



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

Scheme 23

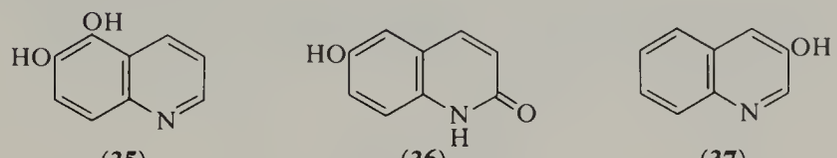


(**34**) 73%

Scheme 24

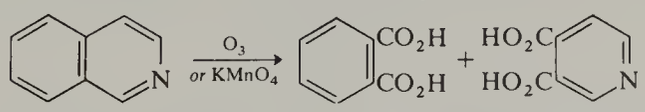
Quinolinic acids can be obtained from quinolines and substituted quinolines in good yields by electrolytic oxidation in sulfuric acid with anodes of lead dioxide or platinum. For example, 3-bromoquinoline gives 5-bromoquinolinic acid (**34**; Scheme 24) ⟨61JOC808⟩.

Oxidation of quinoline not involving ring cleavage is unusual, other than for the formation of the *N*-oxide with peracids (see Chapter 2.05). Use of hydrogen peroxide in the presence of sulfuric acid followed by addition of formic acid is reported to convert quinoline in low yield (3%) to 5-hydroxyquinoline ⟨64CPB345⟩. Hydroxylation can also be achieved biologically. For example, by feeding quinoline to rabbits, 5,6-dihydroxyquinoline (**35**), 6-hydroxycarbostyril (**36**) and 3-hydroxyquinoline (**37**) can be detected in the urine hydrolysates ⟨61MI20600⟩.



(**35**) (**36**) (**37**)

Whereas with quinoline the benzo ring is the more susceptible to oxidative ring opening, with isoquinoline the matter is more finely balanced. Use of ozone or alkaline permanganate results in attack on both the rings, the products being phthalic acid and pyridine-3,4-dicarboxylic acid (cinchomeronic acid) (**38**; Scheme 25).

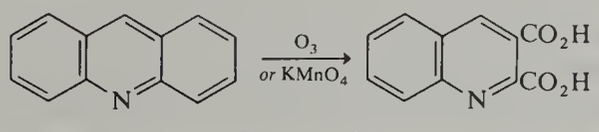


(**38**)

Scheme 25

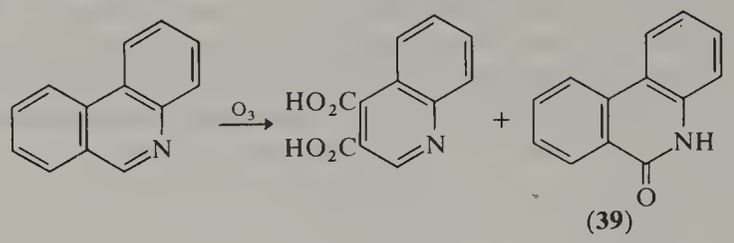
Permanganate oxidation of isoquinoline carrying benzo methoxy groups, or a 5-iodo- or 5-carboxy group, gives hetero ring fission whereas when a 5-amino group is present the pyridine-3,4-dicarboxylic acid is formed.

Benzo ring cleavage of acridine results from oxidation with permanganate, the product being quinoline-2,3-dicarboxylic acid (acridinic acid), which is also the main product of ozonolysis in methanol (Scheme 26) ⟨64JA38⟩.



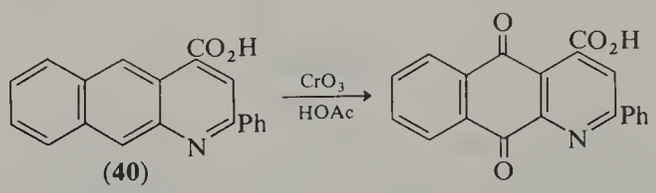
Scheme 26

Ozonolysis of phenanthridine in methylene chloride followed by alkaline peroxide oxidation gives quinoline-3,4-dicarboxylic acid (2%) and phenanthridone (**39**; 23%) as the main product (Scheme 27) ⟨64JA38⟩.



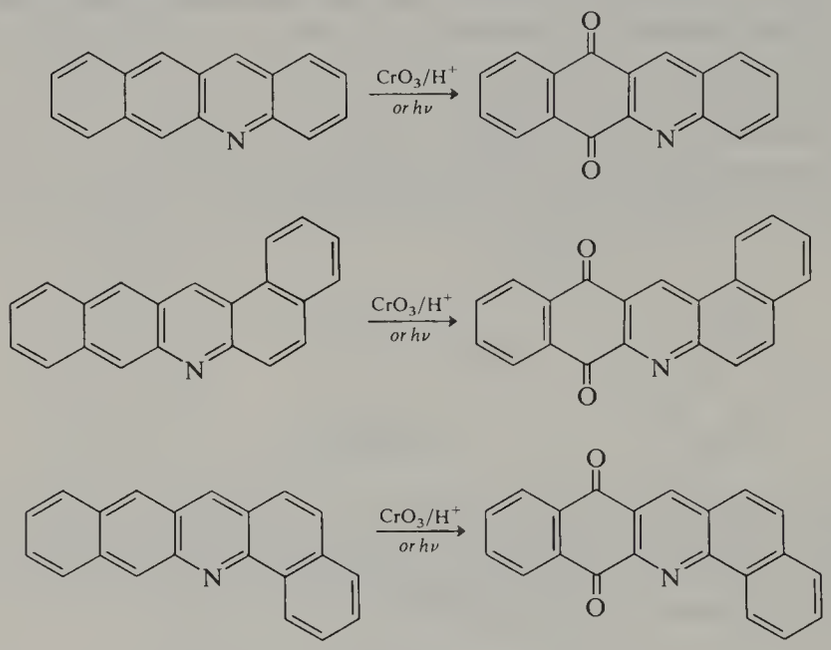
Scheme 27

Benzo[*g*]quinolines, *e.g.* (**40**), and benzo[*g*]isoquinolines are oxidized to the corresponding azaanthraquinones using, for example, chromium trioxide in acetic acid (Scheme 28) ⟨79KGS517⟩.



Scheme 28

Benzo analogues of the above systems can also be oxidized to quinones; some examples are shown in Scheme 29. The oxidation in each case can be carried out either with chromic acid, or photochemically *via* the endoperoxide ⟨60CB850, 54BSF748⟩.

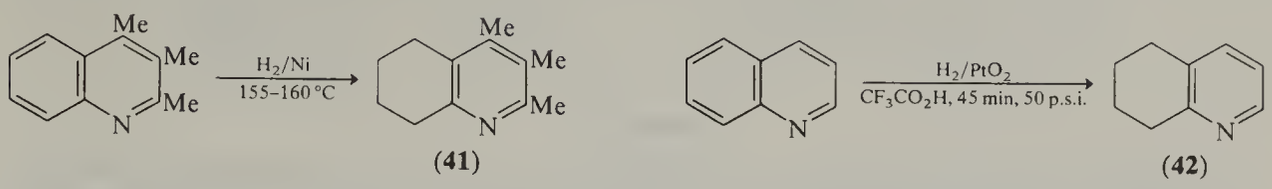


Scheme 29

2.06.2.3 Reduction of Fused Benzene Rings

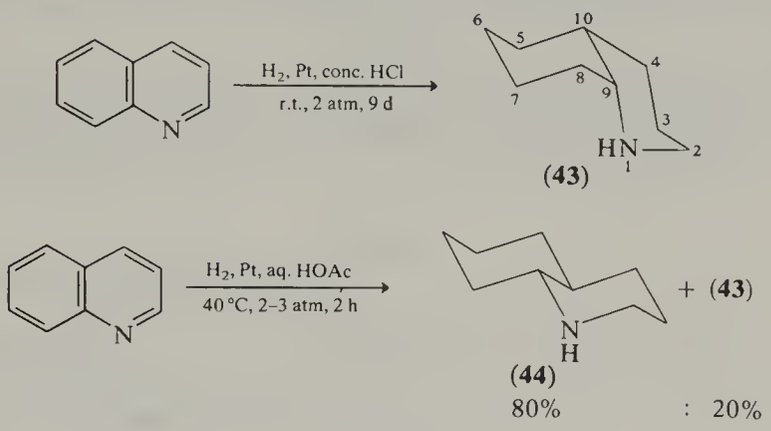
Reduction of the carbocyclic ring of quinoline is less frequently encountered than reduction of the hetero ring. Although hydrogenation of quinoline with a nickel catalyst at 210–215 °C gives the 1,2,3,4-tetrahydroquinoline, the presence of methyl groups in the hetero ring leads to reduction also in the benzo ring. 2,3-Dimethylquinoline at 150 °C gives 56% of the corresponding 1,2,3,4-tetrahydroquinoline and 44% of the 5,6,7,8-tetrahydroquinoline, and hydrogenation of 2,3,4-trimethylquinoline with nickel at 155–160 °C gives entirely 5,6,7,8-tetrahydro-2,3,4-trimethylquinoline (**41**; Scheme 30). Quinoline can be reduced to 5,6,7,8-tetrahydroquinoline (**42**; Scheme 30) in 76% yield by hydrogenation over platinum in trifluoroacetic acid at 50 psi. Also formed are decahydroquinoline (mostly *cis*) and some $\Delta^{1,9}$-octahydroquinoline; which may arise from the salt of $\Delta^{9,10}$-octahydroquinoline. Analogous reductions have also been effected with 2-, 3-, 6- and 8-

methylquinolines to give the corresponding 5,6,7,8-tetrahydromethylquinolines ⟨80JCS(P1)1933, 75JOC2729⟩.



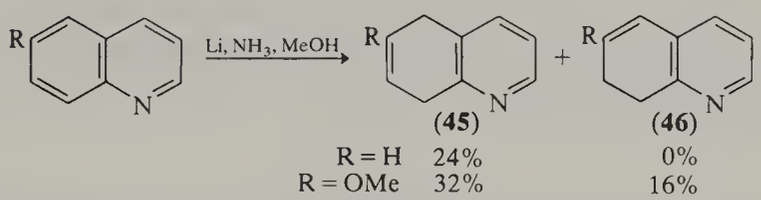
Scheme 30

Practically pure *cis*-decahydroquinoline (**43**) (containing ⩽3% *trans* isomer) can be obtained by prolonged hydrogenation of quinoline in concentrated hydrochloric acid over platinum black ⟨72JCS(P2)615⟩. Hydrogenation over platinum in aqueous acetic acid gives a preponderance (80%) of the *trans*-decahydroquinoline (**44**; Scheme 31).



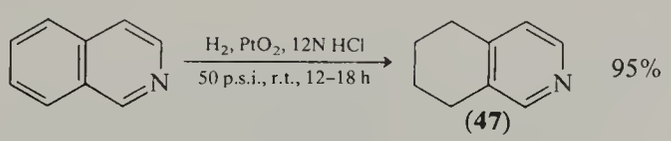
Scheme 31

Reduction of quinoline with lithium in liquid ammonia in the absence of a proton source gives mainly 1,2,3,4-tetrahydroquinoline. However, if methanol is present throughout the reaction the main product is 5,8-dihydroquinoline (**45**; R = H). 6-Methoxyquinoline gives (**45**; R = OMe) together with some 6-methoxy-7,8-dihydroquinoline (**46**; R = OMe) as main products (Scheme 32) ⟨71JOC279⟩.



Scheme 32

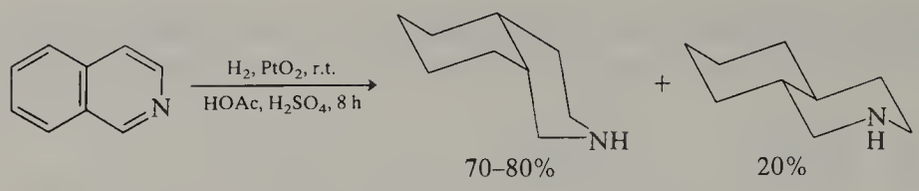
Isoquinoline can be hydrogenated in high yield to 5,6,7,8-tetrahydroisoquinoline (**47**) by use of platinum oxide and concentrated hydrochloric acid at 50 psi (Scheme 33). The method employs a relatively large amount of catalyst (1 g of PtO_2 for 8.6 g of isoquinoline) ⟨75JOC2729⟩.



Scheme 33

A similar method using more dilute conditions, 4N HCl–MeOH, at atmospheric pressure is also reported to give high yields of (**47**) ⟨75JOC1191⟩ but has proved difficult to repeat ⟨78TH20600⟩. 4-Aminoisoquinoline in acid gives 4-amino-5,6,7,8-tetrahydroisoquinoline on catalytic reduction using platinum oxide or Raney nickel. 4-Acetamido- or 4-benzamido-isoquinoline under the same conditions gives reduction of the hetero ring, but use of acetic acid/sulfuric acid with platinum oxide yields 4-acetamido- and 4-benzamido-5,6,7,8-tetrahydroisoquinoline respectively ⟨67YZ547⟩.

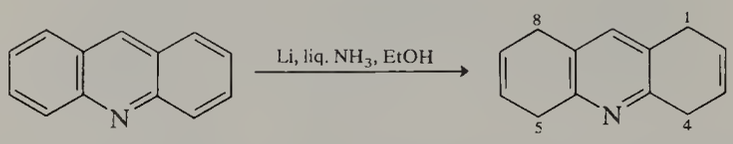
Hydrogenation of isoquinoline in acetic acid with a trace of concentrated sulfuric acid gives a high yield of *cis*- and *trans*-decahydroisoquinoline in the approximate ratio 4:1 (Scheme 34) ⟨48JA2617⟩.



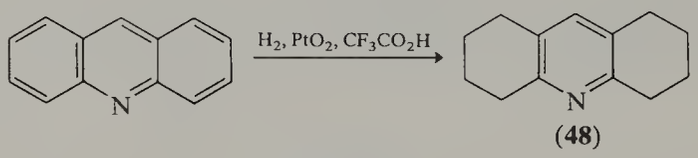
Scheme 34

2-Methyl-5-nitroisoquinolinium *p*-toluenesulfonate in acetic acid and concentrated sulfuric acid hydrogenated over platinum oxide at 50 psi for 120 h gives 5-amino-2-methyldecahydroisoquinoline (95%). The stereoisomers of the product have been studied ⟨68JOC2510⟩.

Benzo ring reduction in acridine can be achieved in a variety of ways. 1,4,5,8-Tetrahydroacridine is given by lithium in liquid ammonia and ethanol (Scheme 35) ⟨69AJC1105⟩. The symmetrical octahydroacridine (**48**) can be obtained by hydrogenation of acridine over platinum oxide in trifluoroacetic acid. The product is obtained in quantitative yield (Scheme 36) ⟨75JOC2729⟩.



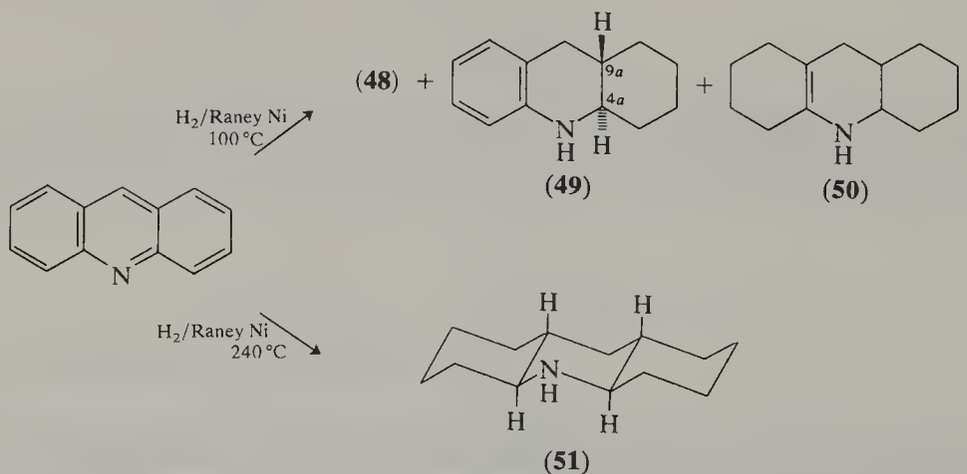
Scheme 35



(**48**)

Scheme 36

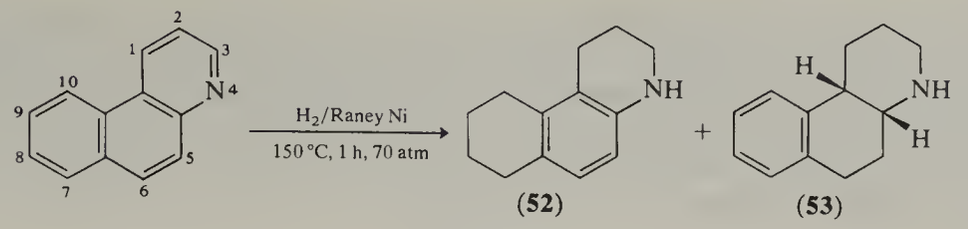
1,2,3,4,5,6,7,8-Octahydroacridine (**48**) also accompanies the unsymmetrical isomer 1,2,3,4,4a,9,9a,10-octahydroacridine, mainly in the *trans* form (**49**), when acridine is hydrogenated with Raney nickel at 100 °C. Some dodecahydro product (**50**) is also formed (Scheme 37). The *trans* isomer (**49**) also results from reduction of acridine with phosphorus and hydriodic acid; when tin and hydrochloric acid are used both the *cis*- and *trans*-1,2,3,4,4a,9,9a,10-octahydroacridines are given. The stereochemistry of the products has been demonstrated by NMR ⟨63T91⟩. Hydrogenation of acridine with Raney nickel at 240 °C gives complete reduction to the α-perhydroacridine (**51**). This has the *trans,syn,trans* configuration (Scheme 37) ⟨68BCJ2458⟩.



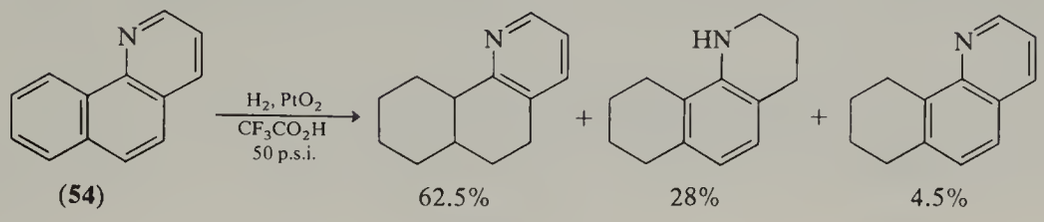
Scheme 37

The hydrogenation of phenanthridine at 250 °C under pressure in the presence of a sodium–rubidium catalyst in benzene is reported to give octahydrophenanthridines. Acridine similarly forms a variety of reduction products ⟨71JOC694⟩.

Hydrogenation of benzo[*f*]quinoline over Raney nickel at 150 °C and 70 atm gives 1,2,3,4,7,8,9,10-octahydrobenzo[*f*]quinoline (**52**) as the main product, together with some *cis*-1,2,3,4,4a,5,6,10b-octahydro isomer (**53**; Scheme 38). Use of sodium in pentyl alcohol gives the *trans* isomer of (**53**) together with (**52**) ⟨64JOC1419⟩.



Scheme 38



Scheme 39

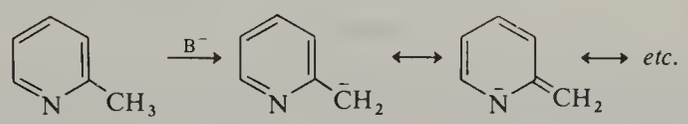
Benzo ring reduction is the main pathway in the platinum-catalyzed hydrogenation of benzo[*h*]quinoline (**54**) in the presence of trifluoroacetic acid; the products are shown in Scheme 39 ⟨75JOC2729⟩.

2.06.3 *C*-LINKED SUBSTITUENTS

2.06.3.1 Alkyl Groups

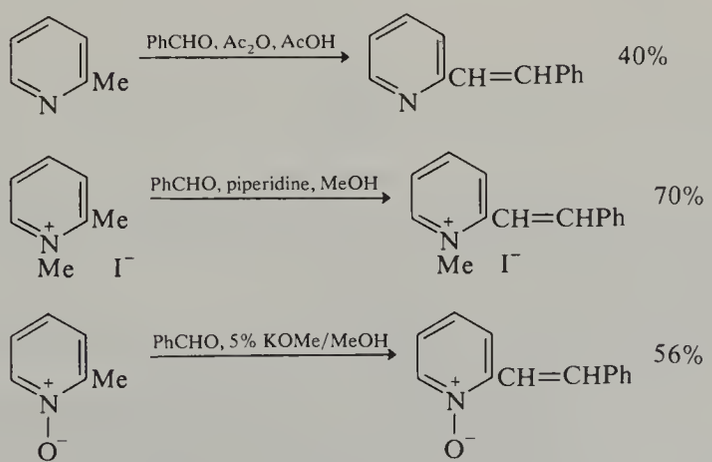
2.06.3.1.1 Alkyl substituents attached to carbon

Alkyl groups α and γ to the ring nitrogen of pyridine are significantly more reactive than alkyl groups attached to a benzene ring, particularly in base-catalyzed processes involving deprotonation of the alkyl substituent. This is because the carbanion produced is stabilized by charge delocalization involving the ring, one of the canonical forms carrying the negative charge on the nitrogen atom (Scheme 40).



Scheme 40

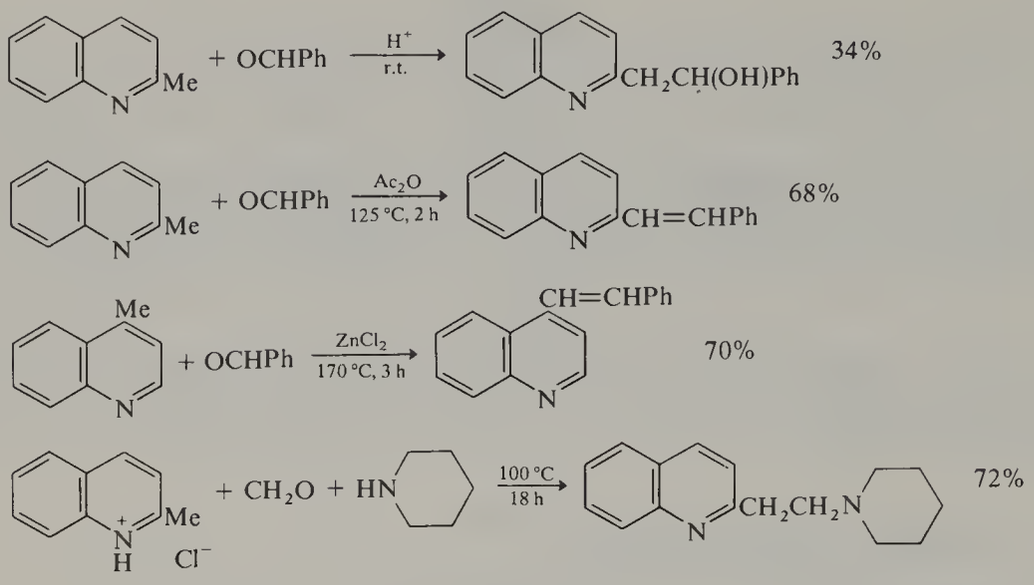
Proton removal from an α- or γ-alkyl group is made even easier when the ring nitrogen bears a positive charge, as in quaternary salts and *N*-oxides ⟨58LA(613)171⟩, and mild basic catalysts are effective with these substrates (Scheme 41).



Scheme 41

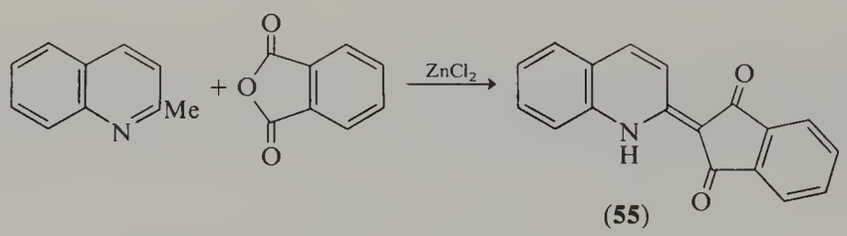
In the quinoline series, the 2- and 4-methyl derivatives (quinaldine and lepidine respectively) will also undergo condensations at the methyl groups. Use of an aldehyde gives the secondary alcohol, which may then be dehydrated to provide the styryl compound

⟨59JCS1641⟩. The ease of deprotonation is in the order 4>2>3, but, possibly for steric reasons, the 2-methyl substituent is found to be the more reactive, as condensation of 2,4-dimethylquinoline with 2,4-dinitrobenzaldehyde rapidly gives the 2-styryl derivative; the 2,4-distyryl compound is formed only on prolonged reflux. Quinaldine will take part in the Mannich reaction to give β-aminoethylquinoline derivatives. Examples of the above reactions are shown in Scheme 42.



Scheme 42

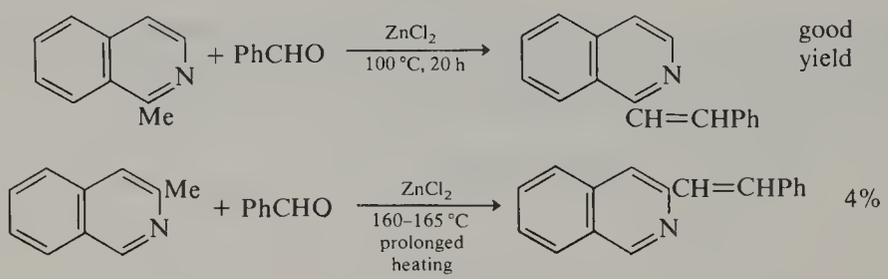
Condensation of quinaldine with phthalic anhydride in the presence of zinc chloride gives the dye Quinoline Yellow (**55**), used mainly in oils and varnishes (Scheme 43).



(**55**)

Scheme 43

A methyl group at position 1 in isoquinoline is sufficiently reactive to condense with an aromatic aldehyde to give a 1-styrylisoquinoline. The C-3 methyl group is far less reactive and more forcing conditions are required (Scheme 44).

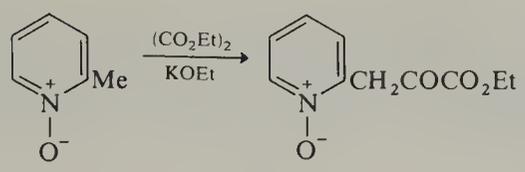


Scheme 44

The reactivity of 9-methylacridine is, as might be expected, similar to that of 4-methylpyridine and lepidine, aromatic aldehydes giving either α-aryl-β(9-acridyl)ethanols or styrene derivatives depending on the conditions.

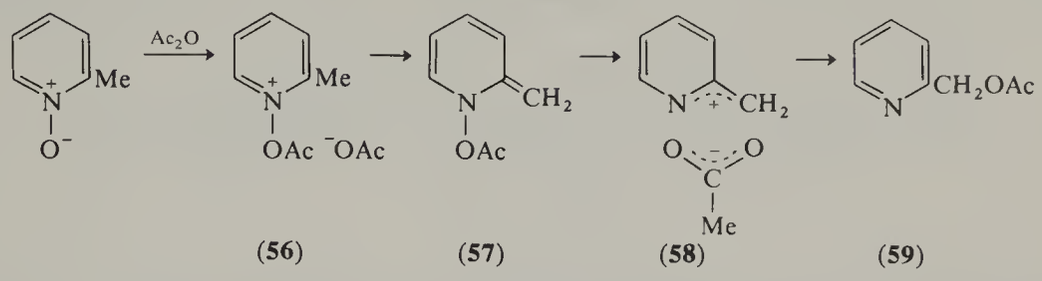
For less reactive methyl groups, condensation with the aldehyde anils, rather than the aldehydes themselves, can be more effective ⟨78AHC(23)171⟩.

As seen in many of the above examples, acetic anhydride and zinc chloride each make effective condensation catalysts for the free bases, presumably by efficient coordination with the ring nitrogen. The quaternary salts condense readily in the presence of piperidine. Potassium hydroxide, methoxide or piperidinium acetate are suitable for condensations with 2- and 4-methylpyridine *N*-oxides. For example, the Claisen condensation is effective with these *N*-oxides using ethoxide catalyst (Scheme 45) but the reaction fails with the parent picolines unless activated by nitro substitution ⟨69JHC775⟩.



Scheme 45

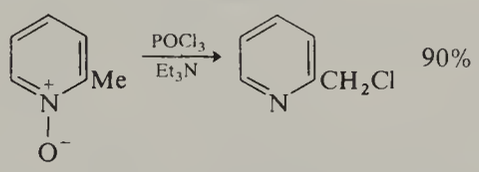
Treatment of 2-methylpyridine *N*-oxide with acetic anhydride gives 2-pyridylmethyl acetate (**59**) as main product, together with some 3- and 5-acetoxy-2-methylpyridine. The reaction proceeds similarly for other 2- and 4-alkylpyridine *N*-oxides. The mechanism of the process has been the subject of considerable study. Data suggest that the first formed *N*-acetoxypyridinium acetate (**56**) undergoes deprotonation to the anhydro base (**57**) which then rearranges *via* an ion pair (**58**) rather than a radical pair intermediate (Scheme 46), although radicals have been detected in the reaction ⟨72JA932, 70JOC2792, 68JCS(B)831, 62JA3359⟩.



(**56**) (**57**) (**58**) (**59**)

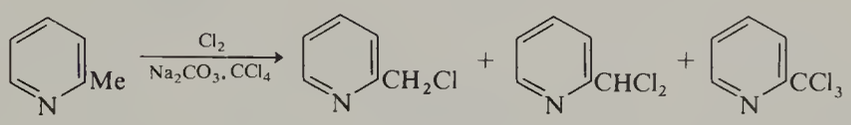
Scheme 46

Reaction of 2-methylpyridine *N*-oxide with *p*-toluenesulfonyl chloride or phosphorus oxychloride gives 2-pyridylmethyl chloride (Scheme 47), and related reactions with reactive halides have also been studied ⟨62JOC3856, 81JHC939⟩.



Scheme 47

Halogenoalkylpyridines also result from direct halogenation of alkylpyridines. For example, the chlorination of 2-methylpyridine gives 2-chloromethylpyridine with small amounts of the di- and tri-chloromethyl compounds (Scheme 48) ⟨63AG(E)144⟩.

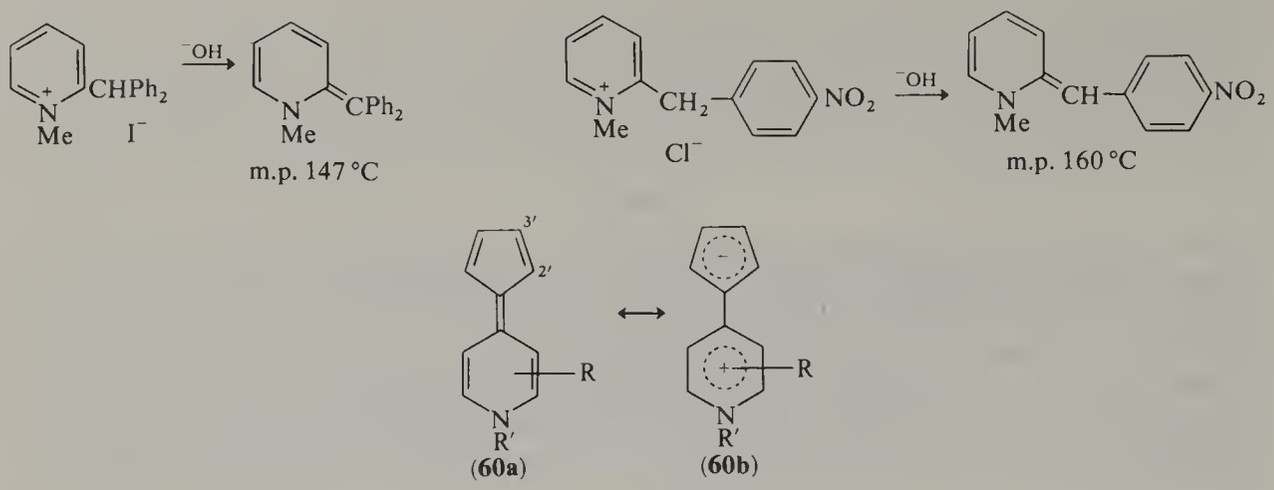


Scheme 48

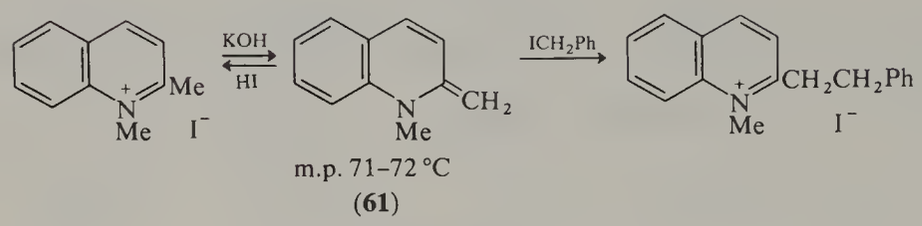
The intermediacy of an anhydro base (**57**) was referred to in Scheme 46. Analogous anhydro bases (pyridone methides) can be formed by deprotonation of quaternary salts of 2- and 4-benzylpyridines and the like. The pyridone methides are usually highly reactive and not readily isolable; some stable examples are shown in Scheme 49. Pyridine methides are intermediates in the base-catalyzed alkylation and acylation reactions of pyridinium salts at the exocyclic carbon. Compounds of type (**60**) have been estimated to have 25–30% dipolar character. Protonation of (**60**) occurs at the 2′- and 3′-positions in the ratio 4:1 respectively ⟨70JCS(C)800⟩.

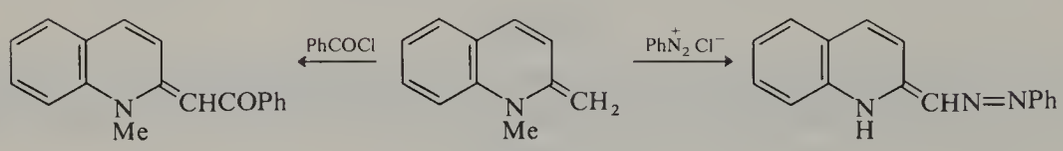
The anhydro bases, *e.g.* (**61**), formed by deprotonation of 2- and 4-alkylquinolinium salts, are more stable than the pyridone methides and are usually isolable. They are reactive enamines and some typical chemistry is shown in Scheme 50.

Closely related are the cyanine dyes, for example cyanine (**62**) itself, which is formed from the ethiodide salts of lepidine and 4-iodoquinoline in the presence of base (Scheme 51). Analogous monomethine cyanines can have the quinoline nuclei linked 2,2′ (pseudocyanines) and 2,4′ (isocyanines). Quinaldine ethiodide on condensation with ethyl orthoformate gives the 2,2′-linked trimethine cyanine (carbocyanine) (**63**), known as pinacyanol (Scheme 51).

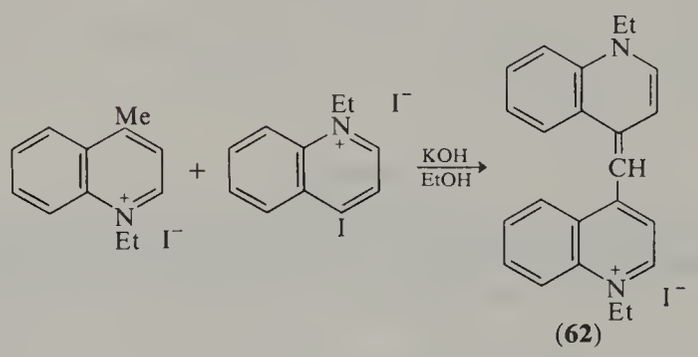


Scheme 49





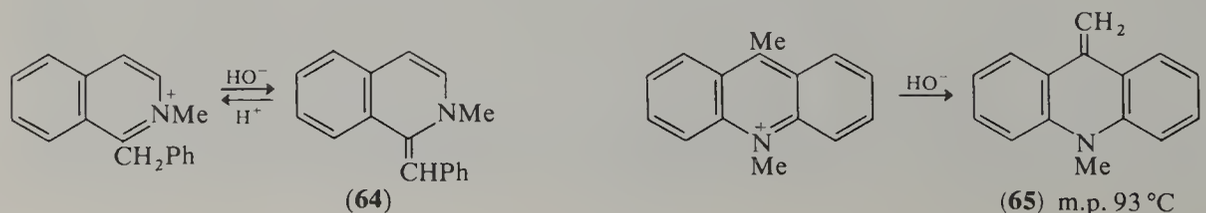
Scheme 50



Scheme 51

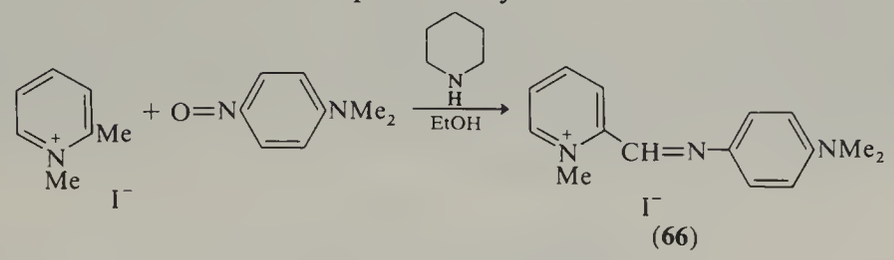
Such dyes found early application as sensitizers in photography and many thousands of related structures have been made. Suitable dyes when added to the photographic emulsion extend the sensitivity of the silver halide from the blue and UV region towards the green, red and near IR. The sensitivity of the dyes can be balanced throughout the visible spectrum to give panchromatic emulsions.

Stable anhydro bases, *e.g.* (**64**), can be formed from 1-alkyl- or 1-benzyl-isoquinolinium salts on treatment with alkali; the reaction is reversed in acid. 9-Methylacridinium salts similarly form stable anhydro bases, *e.g.* (**65**; Scheme 52).



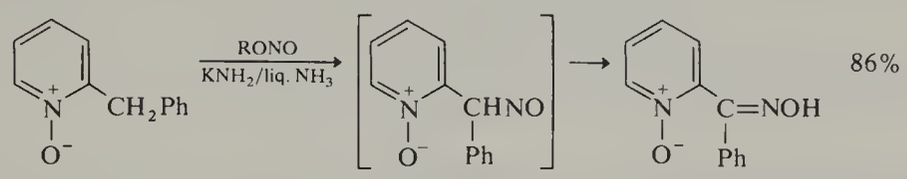
Scheme 52

2-Methylpyridine methiodide condenses with *N*,*N*-dimethyl-4-nitrosoaniline in the presence of piperidine to give the Schiff base (**66**; Scheme 53). The reaction fails with 2-methylpyridine itself but *N*-oxide analogues condense similarly ⟨63JCS4600⟩. 9-Methylacridine condenses with *C*-nitroso compounds to yield anils or nitrones.



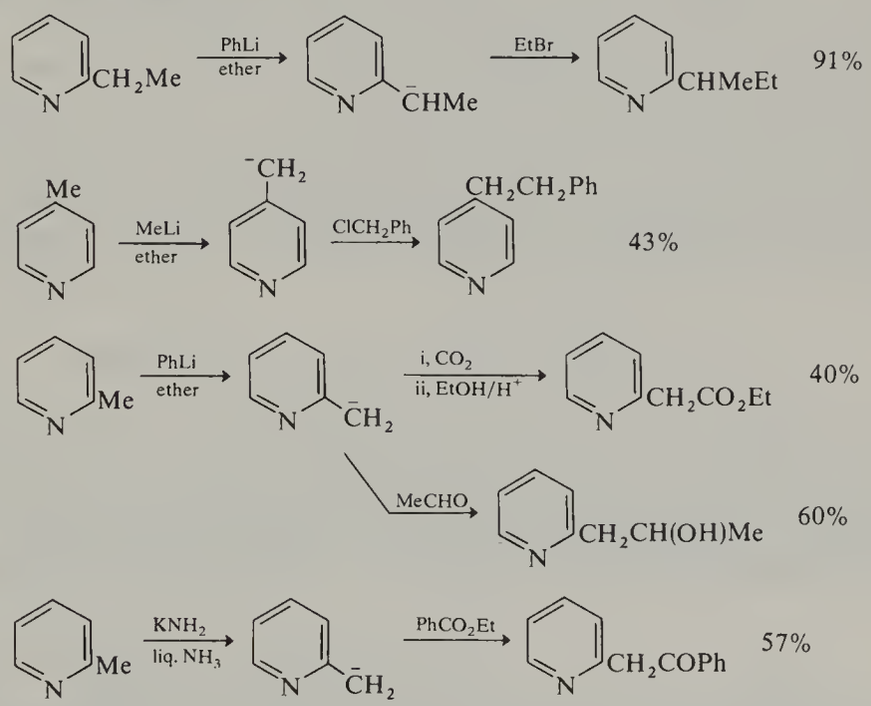
Scheme 53

Nitrosation of 2- and 4-alkylpyridines, their quaternary salts and *N*-oxides, can be effected with an alkyl nitrite and sodamide in liquid ammonia; the product is an oxime (Scheme 54) ⟨69AP494, 65YZ451⟩.



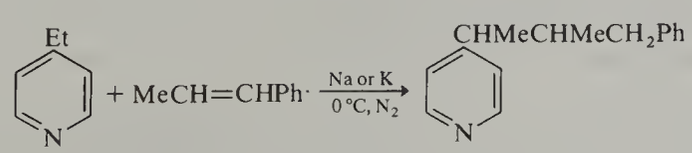
Scheme 54

The use of strong bases such as sodamide in liquid ammonia, lithium diisopropylamide and the alkyl- and aryl-lithiums gives essentially quantitative deprotonation at a side-chain alkyl group. The carbanions produced can undergo reactions with a wide range of electrophiles, as exemplified in Scheme 55.



Scheme 55

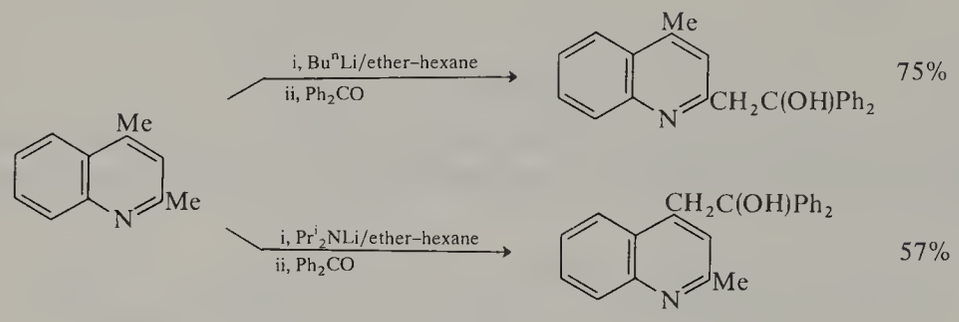
2- and 4-Alkylpyridines also undergo alkali metal-catalyzed side-chain alkylation, aralkylation and alkenylation. An example is shown in Scheme 56. In some cases di- and tri-adducts are also formed ⟨72JOC2799, 69JOC2113⟩.



Scheme 56

With 2,4-dimethyl-pyridine and -quinoline it is possible to achieve selective alkylation or acylation at either position. Although it might be expected that the greater acidity of

the 4-methyl group would lead to its exclusive ionization with a single molar equivalent of base, it is found that under these conditions lithiohydrocarbons promote only ionization of the 2-methyl groups. This is ascribed to strong prior complexation of the lithium cation with the ring nitrogen, so facilitating and favouring carbanion formation at the adjacent 2-methyl group. When, however, the reagent base is an amine anion, as with the lithium diisopropylamide, the lithium remains preferentially complexed to the amine anion rather than to the pyridine ring nitrogen, and the reagent is 'free' to ionize the more acidic 4-methyl group. Electrophiles added selectively include alkyl halides, esters, nitriles and ketones (Scheme 57) ⟨74JOC3835, 73JOC71, 73BSF3381⟩.

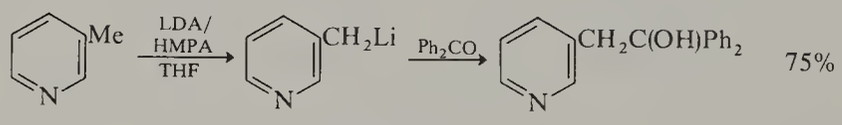


Scheme 57

The above discussion has related to the enhanced reactivity of alkyl groups substituted α or γ to the ring nitrogen. Alkyl groups at the β-position are considerably less reactive and only slightly more reactive than alkyl groups attached to a benzene ring, as a consequence of the overall electron deficiency of the pyridine ring system. 3-Methylpyridine will not undergo condensation with aldehydes under the conditions of Scheme 41 and use of lithiohydrocarbons results only in ring substitution (at positions 2 and 6) ⟨69JCS(B)901⟩. In the presence of sodamide, however, alkylation of 3-methylpyridine is possible; the compound also adds to alkenes in the presence of alkali metals ⟨71JOC2304⟩.

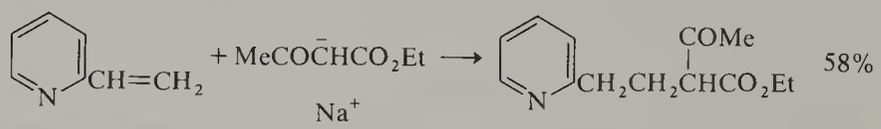
Treatment of 2,6- or 2,7-dimethylquinoline under either of the sets of conditions in Scheme 57 gives only condensation at position 2 ⟨73JOC71⟩. An anion formed on the 7-methyl substituent could be delocalized on to the nitrogen but the loss of the aromaticity of the benzo ring presumably makes this energetically a less favourable pathway.

Lithium diisopropylamide complexed with HMPA will give the lithium derivative of 3-picoline and of 3-methylquinoline, and the products have been condensed with a variety of electrophiles (*e.g.* Scheme 58) ⟨76JOC716, 75S705⟩.



Scheme 58

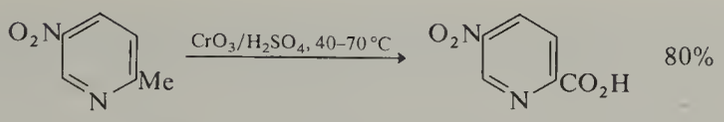
The chemistry of alkenylpyridines is much as would be expected. The 2- and 4-vinylpyridines are readily attacked by nucleophiles at the β-carbon of the substituent (*e.g.* Scheme 59).



Scheme 59

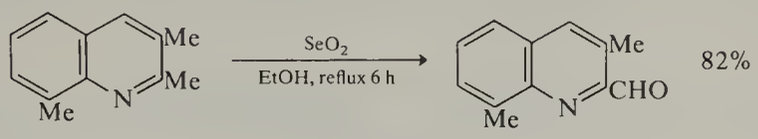
Ozonolysis of alkenylpyridines gives pyridinecarbaldehydes ⟨61JOC4912⟩ and the latter also result from oxidation of 2- and 4-methylpyridines with iodine and dimethyl sulfoxide ⟨70JOC841⟩ or with selenium dioxide, although this last method also gives pyridinecarboxylic acids ⟨69MI20600, 69MI20602⟩.

Pyridinecarboxylic acids also result from the oxidation of alkylpyridines with potassium permanganate ⟨55OS(3)740⟩, nitric acid, and chromium trioxide in sulfuric acid (Scheme 60) ⟨71S31⟩. Alkylquinolines can be oxidized at the side chain with potassium dichromate and sulfuric acid.



Scheme 60

Methyl groups at positions 2 and 4 in quinoline are selectively oxidized by selenium dioxide ⟨76BSF789⟩. For example, 2,3,8-trimethylquinoline gives 3,8-dimethylquinoline-2-carbaldehyde (Scheme 61).

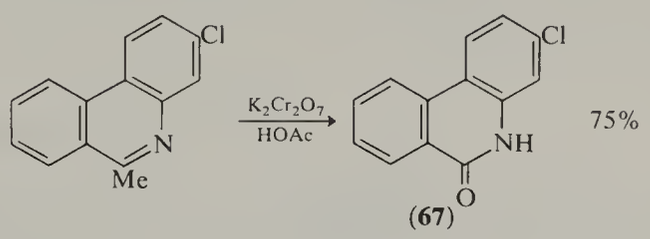


Scheme 61

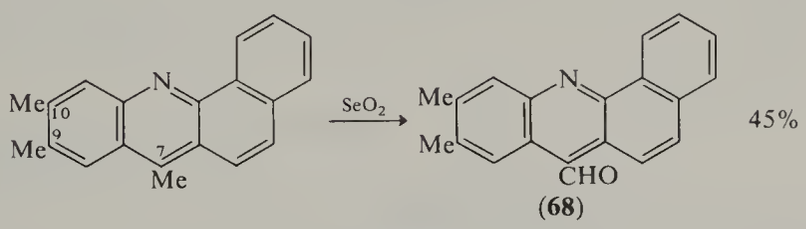
With methyl-3-nitropyridine *N*-oxides, use of selenium dioxide results in complete oxidative demethylation ⟨80TL2433⟩. In isoquinoline methyl groups at positions 1 and 3 are efficiently oxidized to the corresponding aldehyde with selenium dioxide.

Oxidation of 6-methylphenanthridines with potassium dichromate in acetic acid results in oxidative loss of the methyl group, the product being the phenanthridone (*e.g.* **67**; Scheme 62) ⟨61JCS3771⟩. If a second methyl group is present it remains unchanged. Selenium dioxide oxidizes the 6-methyl group to the aldehyde.

The general principle of methyl group reactivity is also seen in the oxidation of 7,9,10-trimethylbenz[*c*]acridine to give the 7-formyl compound (**68**), the 9- and 10-methyl groups being unaffected (Scheme 62) ⟨64JCS5622⟩.



(**67**)



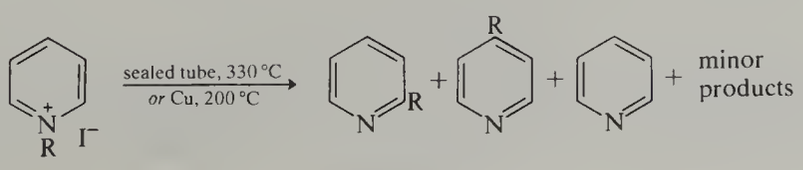
(**68**)

Scheme 62

Electrophilic substitution of benzylpyridines occurs in the benzyl ring. Nitration of 4-benzylpyridine in *ca.* 85% sulfuric acid gives products in the ratio *ortho* 14%, *meta* 6% and *para* 80% ⟨71JCS(B)712⟩. Nitration of 1- and 4-benzylisoquinolines gives *p*-nitrobenzyl derivatives.

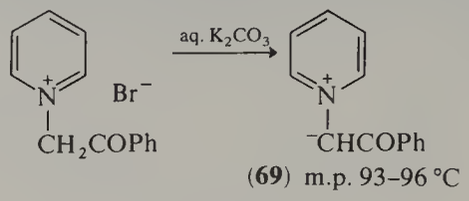
2.06.3.1.2 Alkyl substituents attached to nitrogen

Thermal rearrangement of *N*-alkyl groups as in Scheme 63 (the Ladenburg rearrangement) can be induced by heating, either in the presence or absence of copper powder. The mechanism is thought to be radical and intermolecular in character, the substituent in *N*-alkylpyridinium salts principally migrating to the 2- or 4-position, although a considerable number of minor products can also be formed ⟨71BSF111, 69JCS(C)146, 69CCC2787, 69BSF4425⟩. 1-Methylquinolinium iodide gives 2-, 4-, 5- and 8-methylquinolines and other products ⟨B-79MI20601⟩.



Scheme 63

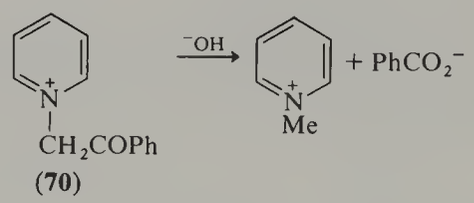
In *N*-alkylpyridinium salts the positively charged ring nitrogen facilitates the removal of a proton from the adjacent *N*-alkyl carbon. If other electron withdrawing groups are attached to the same carbon then its reactivity will be further increased. As a result, carbanions can be generated and condensation reactions effected. For example, treatment of phenacylpyridinium bromide with aqueous potassium carbonate gives the *N*-pyridinium phenacylide (**69**; Scheme 64). The solid begins to decompose after a few hours.



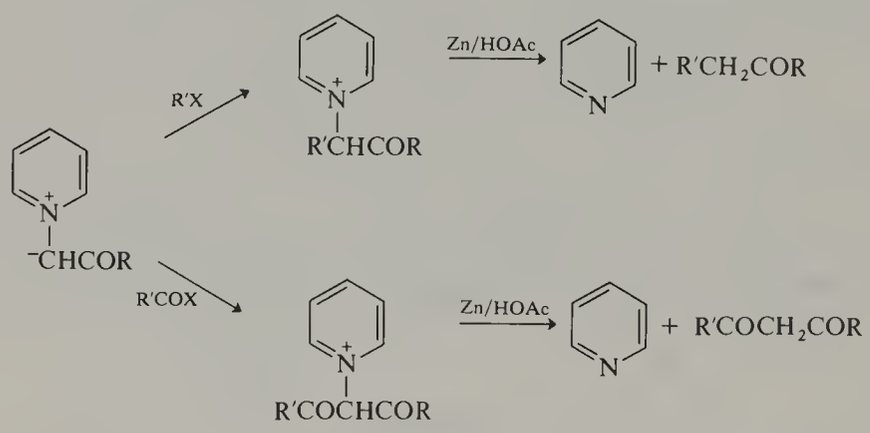
(**69**) m.p. 93–96 °C

Scheme 64

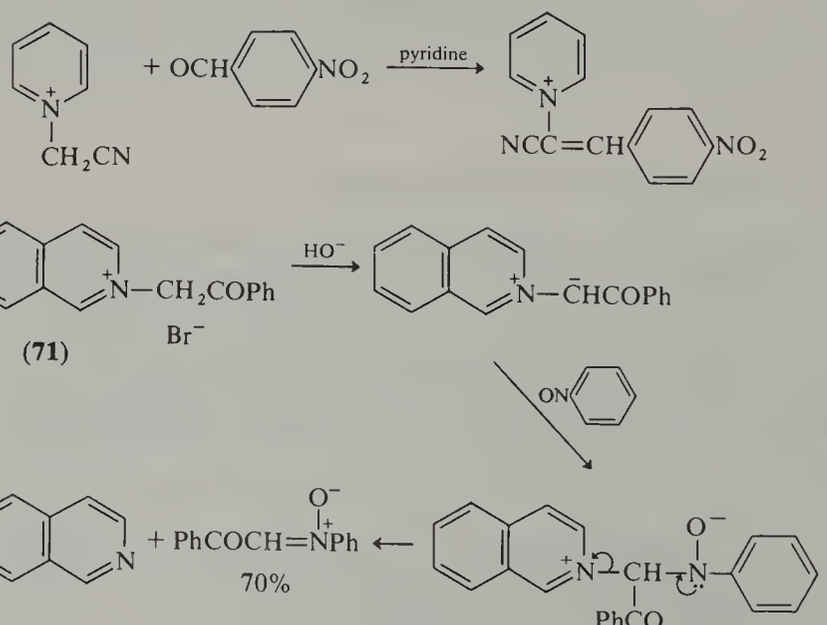
Ylides generated in this way have found considerable use in synthesis and the topic has been reviewed ⟨B-66MI20603, 63AG(E)225, 63AG(E)380, 62AG(E)626⟩. The *N*-methylene group in (**70**) is comparable in reactivity with the methylene group in β-keto esters. For example, strong alkali will cause fission (Scheme 65). Ylide alkylation or acylation can be effected and reduction of the product cleaves the bond to the pyridine nitrogen, liberating a ketone or a β-diketone respectively (Scheme 65) ⟨67AJC2441, 67AJC2445, 67AJC2479⟩.



(**70**)



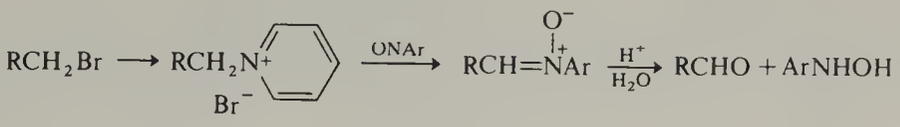
Scheme 65



Scheme 66

Aldehydes will condense with pyridinium ylides in a manner similar to the Knoevenagel condensation (Scheme 66) ⟨53AG617⟩. However, the corresponding condensation of aromatic nitroso compounds results in the elimination of the parent heterocycle, the product being a nitrone. The reaction is illustrated with phenacylisoquinolinium bromide (**71**; Scheme 66).

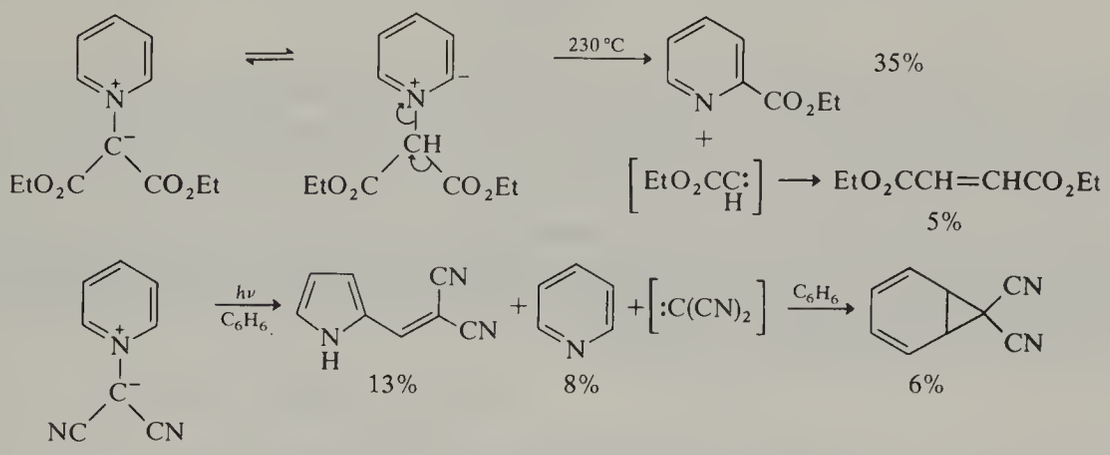
Acid hydrolysis of the nitrone provides the aldehyde corresponding to the original alkyl halide (the Kröhnke oxidation) (Scheme 67) ⟨53AG605⟩.



Scheme 67

Pyridinium ylides will undergo dipolar cycloaddition reactions; the topic has been reviewed ⟨B-76MI20601⟩.

Both ylide thermolysis and photolysis can give products formally derived from the intermediacy of carbenes. Examples are shown in Scheme 68 ⟨71M404, 69BSF948⟩.



Scheme 68

Betaine intermediates result from the addition of pyridines to such systems as α,β-unsaturated esters, quinones and epoxides. The use of acetylenic esters in such reactions has been reviewed ⟨63AHC(1)143⟩.

2.06.3.2 Aryl Groups

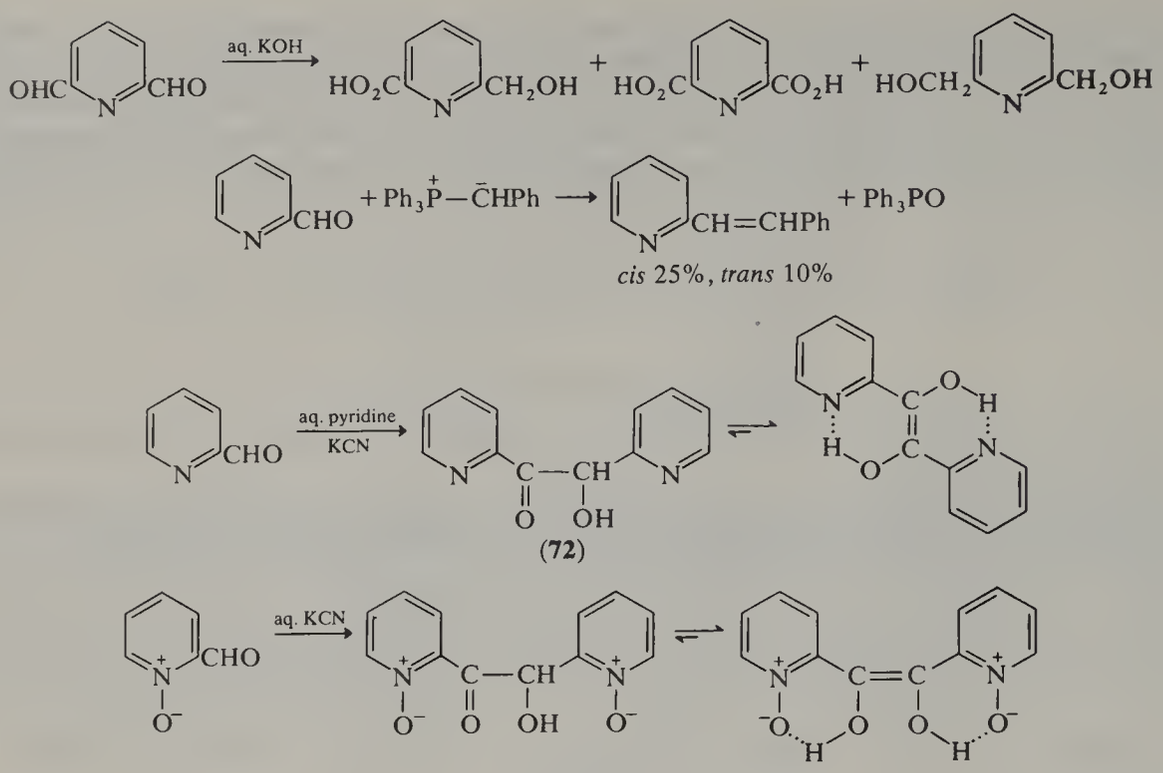
The chemistry of aryl groups attached to the π-deficient heterocycles is unexceptional and much as might be expected. Thus, electrophilic substitution of phenylpyridines occurs exclusively in the phenyl ring. 4-Phenylpyridine gives mononitration products in the ratio *o* : *m* : *p*, 20 : 33 : 47 ⟨68JCS(B)862, 71JCS(B)712⟩. The oxidation of phenylpyridines can lead to either a pyridinecarboxylic acid or benzoic acid.

Nitration of 1-methyl-2-phenylquinolinium sulfate with nitric acid gives 1-methyl-2-(*m*-nitrophenyl)quinolinium sulfate (97%), indicative of the marked electron-withdrawing power of the charged quinolinium system.

2.06.3.3 Acyl Groups

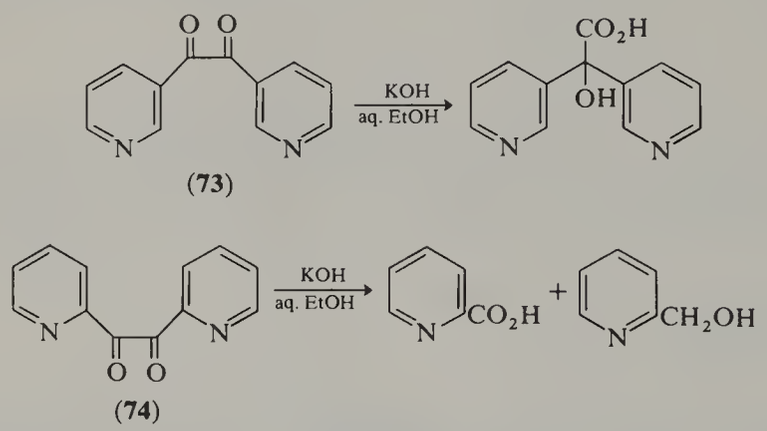
In general, the chemistry of acylpyridines and their benzo derivatives resembles that of phenyl ketones and aldehydes. For example, pyridinecarbaldehydes will undergo the Cannizzaro reaction ⟨53CB584⟩, reactions of the Wittig type ⟨59CB2499, 61JOC5243, 63JOC387⟩ and the benzoin condensation. Examples are shown in Scheme 69. 2,2′-Pyridoin (**72**) can also be obtained by treating pyridine-2-carbaldehyde with acetic acid ⟨53AG491, 58LA(618)152⟩. Pyridinecarbaldehydes are hydrated in aqueous solution.

Oxidation of the pyridoins, *e.g.* with iodine, gives the corresponding α-diketones. The significant electron withdrawal exerted by the π-deficient heterocyclic system on carbonyl groups at the α- and γ-positions can be demonstrated in the behaviour of the diketones under benzilic acid rearrangement conditions. Whereas 3,3′-pyridil (**73**) gives a normal



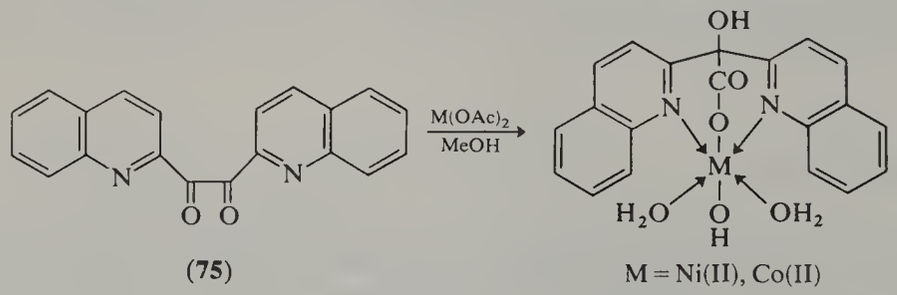
Scheme 69

rearrangement, the 4,4′- and 2,2′-pyridils (*e.g.* **74**) under the same conditions are cleaved to the pyridinecarboxylic acid and aldehyde; the latter then undergoes a Cannizzaro reaction *in situ* (Scheme 70) ⟨62NKK478, 62NKK480⟩.



Scheme 70

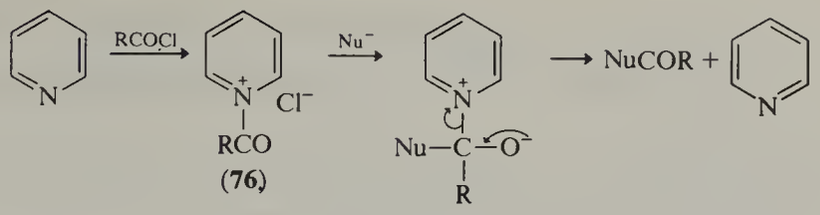
A benzilic acid rearrangement can be achieved with 2,2′-pyridil and with the quinoline analogues (**75**) under mild conditions by using methanolic nickel(II) or cobalt(II) acetates. The product acid is isolated as a metal complex (Scheme 71) ⟨69AJC1439⟩.



Scheme 71

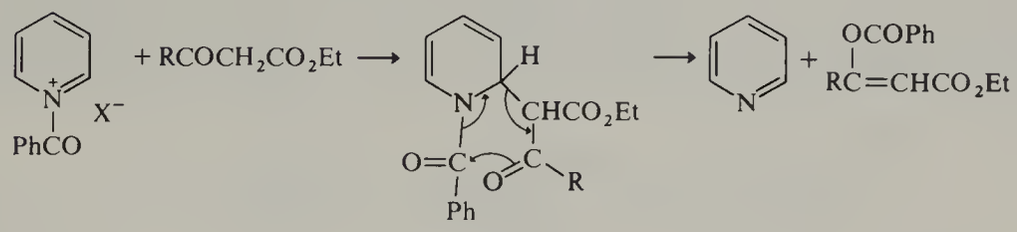
Ketones of the π-deficient heterocycles form the usual derivatives, phenylhydrazones, semicarbazones, *etc.* The oximes undergo the Beckmann rearrangement ⟨70JCS(B)1687⟩.

Treatment of pyridines with acyl halides or anhydrides gives *N*-acylpyridinium salts (**76**). They are isolable, though highly reactive, and are postulated as intermediates in acylations in pyridine solution (Scheme 72). They are rapidly hydrolyzed by moisture. The benzo analogues of pyridine behave similarly.



Scheme 72

In the case of the *O*-acylation of β-keto esters with *N*-acylpyridinium salts a mechanism as shown in Scheme 73 has been suggested ⟨61JOC1684⟩.



Scheme 73

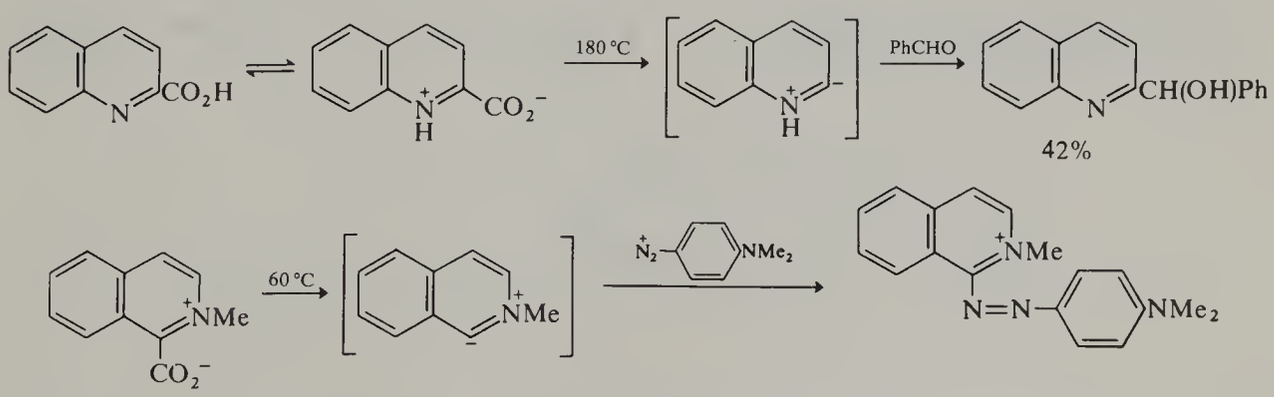
More stable *N*-acylpyridinium salts can be formed by using 4-(*N*,*N*-dialkylamino)pyridines. The salts are less readily hydrolyzed and are effective in the acylation of sterically hindered alcohols ⟨72S619⟩ and in the formation of *N*-*t*-butoxycarbonyl derivatives of α-amino acids in aqueous alkali, for use in peptide synthesis ⟨71CC267⟩.

It will be appreciated that *N*-acylpyridinium salts are potentially ambident; nucleophilic attack can occur at either the acyl carbonyl or by addition to a ring atom. Examples of the latter behaviour are discussed in the previous chapter.

2.06.3.4 Carboxylic Acids and Derivatives

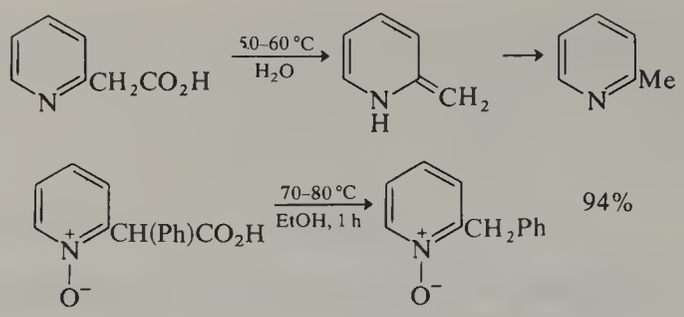
Pyridinecarboxylic acids exist largely in the zwitterion form in water ⟨57JA2050⟩. They can be converted into esters with alcohols and mineral acid catalysis, and by use of diazoalkanes. Use of alkyl halides in alkali gives *N*-alkylbetaines. Esters can also be formed from acid chlorides but the latter are liable to self-quaternization.

Pyridinecarboxylic acids undergo decarboxylation on heating, the general order of reactivity being $\alpha > \gamma > \beta$. This is seen in the stepwise decarboxylation of pyridine-2,3,4-tricarboxylic acid. A temperature of 180 °C removes the 2-carboxy group and at 240 °C the product is mainly pyridine-3-carboxylic acid. Ylide intermediates have been detected in the decarboxylation of pyridine-2-carboxylic acid and *N*-alkylpyridinium-2-carboxylate by trapping with electrophiles such as benzaldehyde (the Hammick reaction) and diazonium salts. Analogous behaviour is observed in the isoquinoline and quinoline series (Scheme 74). The use of aldehydes and ketones for trapping provides a useful route to the secondary and tertiary alcohols thus produced ⟨70LA(732)43, 69JA6115⟩.



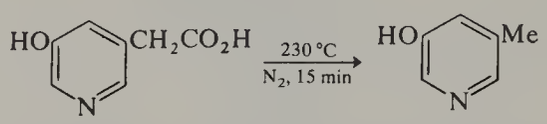
Scheme 74

Side-chain carboxylic acids containing a carboxymethyl group α or γ to the ring nitrogen are susceptible to facile decarboxylation (Scheme 75). The process is analogous to that with β-keto acids and it is often very difficult to isolate the compounds ⟨64CPB588⟩. In consequence, it is usual to isolate them as esters or other suitable derivatives (see example in Scheme 55) ⟨55OSC(3)413⟩.



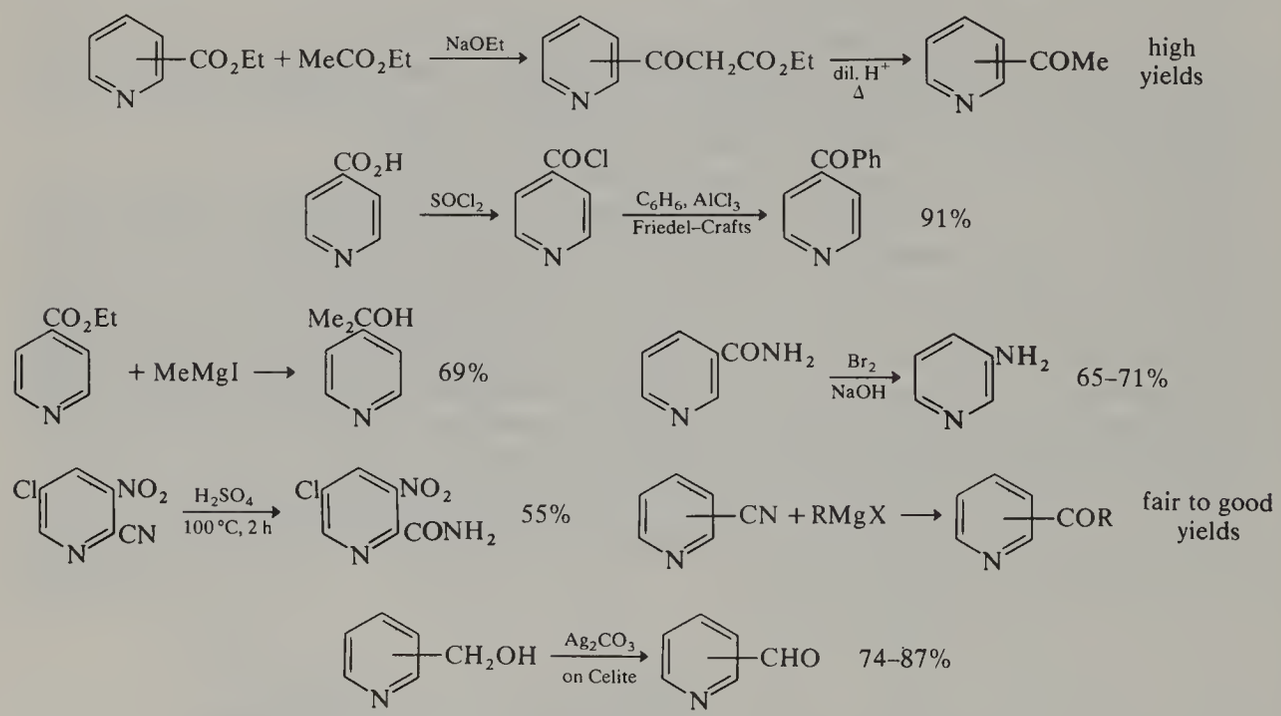
Scheme 75

In contrast, when the carboxymethyl group is placed β to the ring nitrogen the acids are much more stable and higher temperatures are needed to effect decarboxylation (Scheme 76) ⟨59JA740⟩.



Scheme 76

Carboxylic acid derivatives of pyridine and its benzo analogues in general show normal reactivity at the functional group and their chemistry is consequently largely predictable. The topic has been reviewed ⟨62HC(14-3)212⟩. Some typical reactions are exemplified in Scheme 77. Cyanopyridines can be reduced to the corresponding aminomethyl compounds catalytically or with lithium aluminum hydride. With the latter reagent reduction of the ring is sometimes a competing process. Reductive decyanation of pyridinecarbonitriles can be achieved with titanium trichloride in acetic acid ⟨80TL1675⟩. Oxidation of hydroxymethylpyridines to the aldehydes can be achieved with manganese dioxide or silver carbonate on Celite ⟨76HCA211, 76JHC525⟩.



Scheme 77

2.06.4 *N*-LINKED SUBSTITUENTS

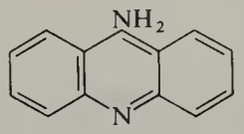
The chemistry of the *N*-linked substituents of the π-deficient heterocycles principally concerns the reactivity of amino and nitro functions. The many other nitrogen functions are usually derived from either or both the amino or nitro parents and so are discussed within the two main Sections (2.06.4.1 and 2.06.4.2) below, as appropriate.

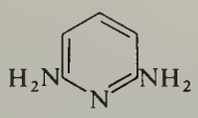
2.06.4.1 Amino Groups and Related Functions

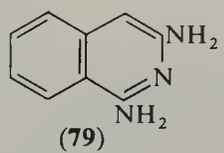
2.06.4.1.1 Amino groups attached to carbon

It is well established that for most aminopyridines and their benzo derivatives the amino form greatly predominates over the pyridone-imine tautomer ⟨76AHC(S1)152, 63AHC(1)404⟩.

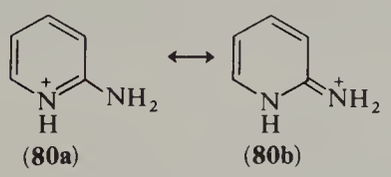
The amino structure for 9-aminoacridine (**77**) has been confirmed by IR studies ⟨65JCS5230⟩, and NMR spectral data in DMSO are consistent with the diamino structures (**78**) and (**79**) ⟨64JCS1423⟩. Amino groups on fused benzene rings and β to nitrogen in hetero rings exist in the amino form, and the reactions of these compounds are similar to those of aniline and the naphthylamines. Aminopyridine *N*-oxides exist very predominantly in the amino form ⟨57JCS4375⟩.

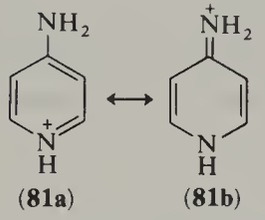

(77)

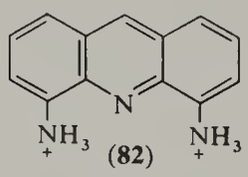

(78)


(79)

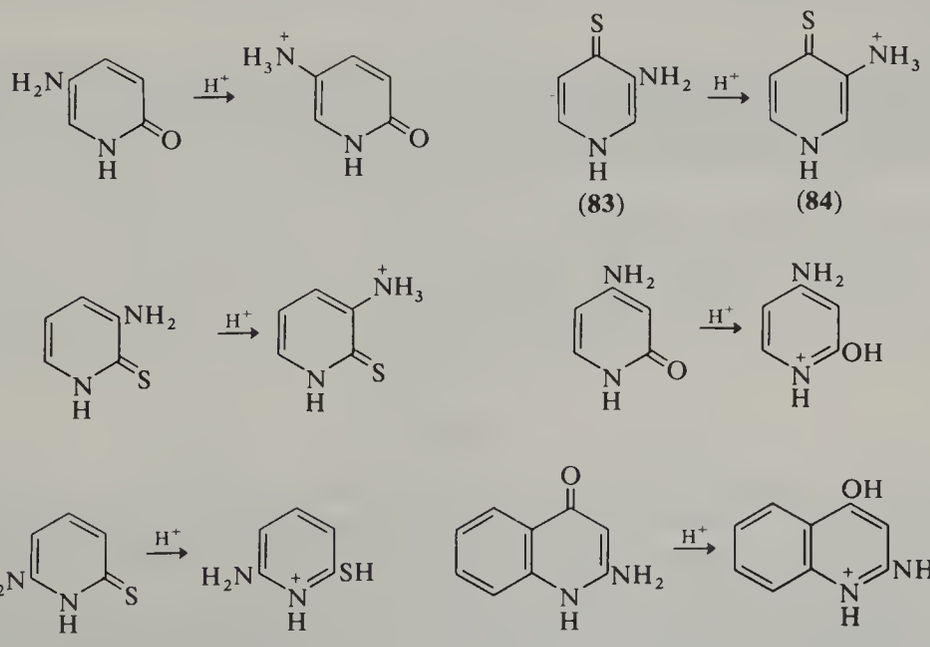
Protonation of 2-, 3- and 4-aminopyridines to form monocations occurs on the ring nitrogen. Vibrational spectra of the 2- and 4-aminopyridinium cations (**80**) and (**81**), suggest that the amidinium forms (**80b**) and (**81b**) are the principal contributors to the charge-delocalized structures ⟨62JCS3119, 65JCS3825⟩. The dication is formed only with considerable difficulty, particularly with 2- and 4-aminopyridine. Ring *N*-protonation has also been demonstrated for most of the monoaminoacridines, for 6-, 7- and 2-aminoquinoline and 4-amino-2-methylquinoline. In contrast, 4-amino-5-methylacridine is monoprotonated principally at the amino group in ethanol but at the ring nitrogen in aqueous solution, and 4,5-diaminoacridine undergoes successive protonations to give (**82**) in preference to ring nitrogen protonation, probably because of steric effects ⟨65JCS4653⟩.


(80a) (80b)


(81a) (81b)

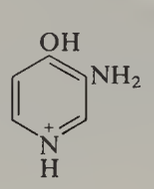

(82)

Protonation of amino-substituted 2- and 4-pyridones and the thione analogues has been studied largely by use of UV spectroscopy. In most cases, when the amino group is on a carbon α or γ to the oxo or thioxo group then protonation occurs predominantly on the exocyclic amino nitrogen. For β-related amino groups protonation occurs predominantly on the oxygen or sulfur. Some examples are shown in Scheme 78 ⟨73JCS(P1)1314, 72JCS(P2)1459, 71JCS(B)1425⟩.

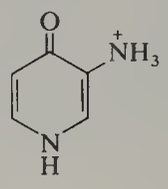


Scheme 78

There are exceptions to the above generalization. For example, when pyrid-4-one carries a 3-amino group protonation is thought to occur at the oxygen atom (**85**) as with the 2-amino isomer, although the UV spectrum suggests the possibility of a small contribution from (**86**). This is thought to be connected with the higher basic strength of pyrid-4-one (pK_a 3.27) relative to its 2-isomer (pK_a 0.75) ⟨71JCS(B)1425⟩. In contrast, the protonation of 3-aminopyridine-4-thione (**83**) occurs at the amino group (**84**), the mercapto compounds being weaker bases by *ca.* 2 pK units ⟨72JCS(P2)1459⟩.

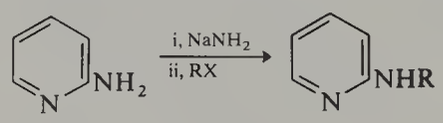


(**85**)



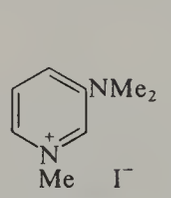
(**86**)

Alkylation of aminopyridines normally occurs at the ring nitrogen in the absence of added base, that being the more nucleophilic site. (The lone pair on the side-chain amino nitrogen participates in conjugation with the ring.) However, in the presence of strong base, *e.g.* sodamide, deprotonation of the side-chain amino group occurs, leading to alkylation at the exocyclic nitrogen (Scheme 79). 2-Alkylaminopyridines behave similarly.

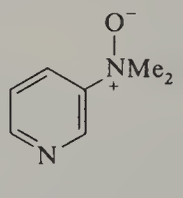


Scheme 79

Interestingly, 2-dimethylaminopyridine undergoes methylation and *N*-oxide formation on the exocyclic nitrogen whereas 4-dimethylaminopyridine suffers both reactions at the ring nitrogen. 3-Dimethylaminopyridine is methylated on the ring, giving (**87**), but its *N*-oxide results from attack at the side-chain giving (**88**) ⟨71LA(749)12⟩. 8-Aminoquinoline with methyl iodide gives the hydriodide of 8-methylaminoquinoline; it is thought that steric effects hinder ring nitrogen alkylation in this case ⟨76JHC125⟩.



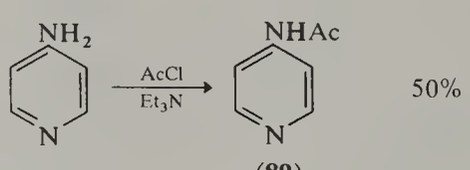
(**87**)



(**88**)

9-Aminoacridine with methyl iodide gives 9-amino-10-methylacridinium iodide whereas the other isomers give mixtures of methylated products which are difficult to separate ⟨B-66MI20600⟩.

Monoacylation of aminopyridines, although probably initially occurring at the ring nitrogen, leads to the exocyclic acylamino derivative ⟨81FES862, 59JCS1317⟩. The products exist predominantly in the acylamino form (*e.g.* **89**; Scheme 80). Further acylation generally occurs at the same position to give (diacylamino)pyridines.

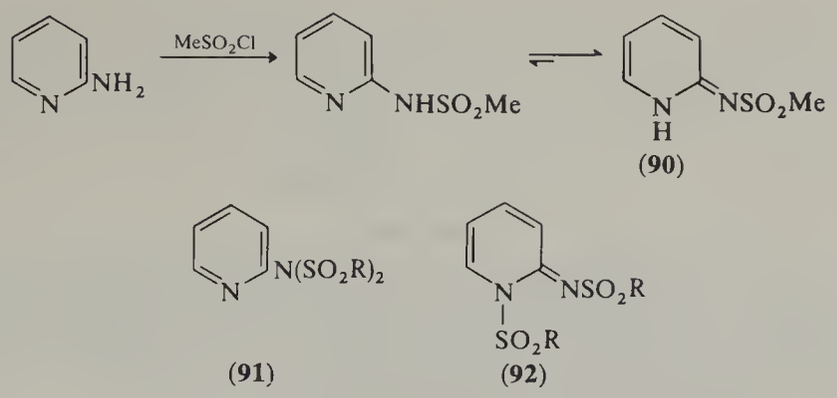


(**89**)

Scheme 80

Methanesulfonyl halide also reacts at the side-chain nitrogen, the 2- and 4-product isomers existing largely in the imino form, *e.g.* (**90**), and the 3-isomer in the sulfonamido form ⟨61JCS378⟩. Further treatment gives disulfonyl derivatives and both types (**91**) and (**92**) have been isolated (Scheme 81) ⟨64CB695, 64RTC189⟩.

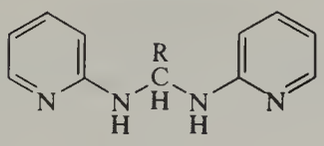
Similarly, aminoquinolines are readily acylated and tosylated; 9-aminoacridine gives the 9-(*N*,*N*-diacetylamino) derivative.



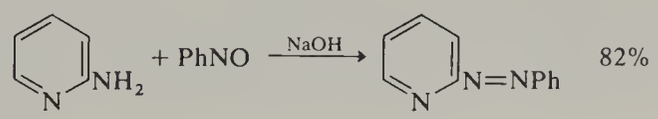
(90) **(91)** **(92)**

Scheme 81

Schiff base formation occurs normally with 3-aminopyridine ⟨69CR(C)(269)1319⟩ and aldehydes, but imines of 2-aminopyridine, though isolable, are less stable and bis(pyridylamino) compounds (*e.g.* **93**) are readily formed. 9-Aminoacridine fails to react with benzaldehyde. Nitrosobenzenes condense with aminopyridines in alkali (but not in acetic acid) to give azopyridines (Scheme 82).

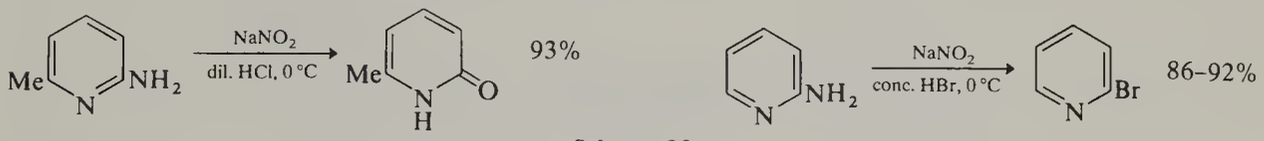


(93)



Scheme 82

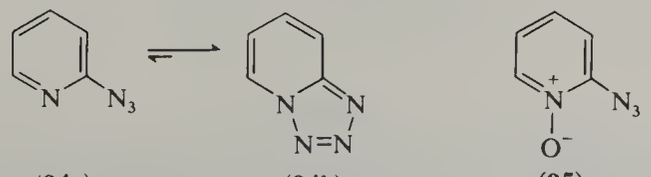
β-Aminopyridines and their benzo analogues give normal diazonium salts with nitrous acid, which can, for example, be converted into the β-halogeno compounds by the Sandmeyer reaction. The α- and γ-aminopyridines, however, give diazonium salts of exceptional reactivity. Attempts to prepare these diazonium salts in dilute acid lead directly to the corresponding pyridones (Scheme 83). The 2- and 4-halogenopyridines can be obtained by effecting the diazotization in concentrated hydrohalic acids (Scheme 83) ⟨55OSC(3)136⟩. Aminopyridine *N*-oxides give diazonium salts which do not show this unusual reactivity but behave normally ⟨66USP3249597⟩.



Scheme 83

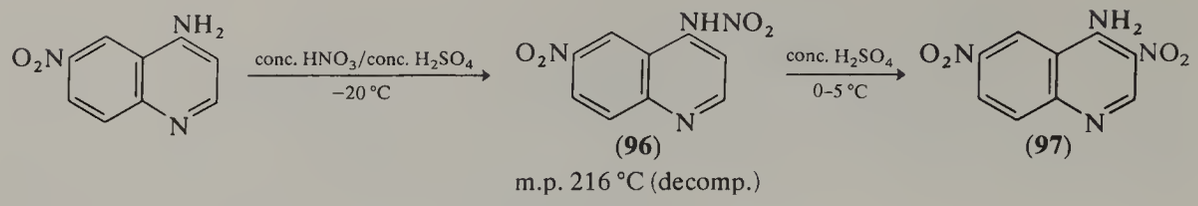
Oxidation of aminopyridines with Caro's acid gives nitropyridines; the use of peroxytrifluoroacetic acid leads to nitropyridine *N*-oxides ⟨60JOC1716⟩. Oxidation with alkaline hypochlorite converts aminopyridines into symmetrical azopyridines, and azoxypyridines are formed by oxidation with persulfate ⟨59YZ549⟩.

Reduction of pyridinediazonium salts and those of the benzo analogues gives the corresponding hydrazino compounds, which are also obtained by reduction of nitraminopyridines. Hydrazinopyridines are converted to azidopyridines on reaction with nitrous acid. 2-Azidopyridine (**94**) exists principally in the tetrazolo[1,5-*a*]pyridine form (**94b**) ⟨73S123⟩; the corresponding *N*-oxide exists as such (**95**) ⟨76JA1478⟩.



(94a) **(94b)** **(95)**

Nitraminopyridines, mentioned above, are intermediates formed during the nitration of aminopyridines. An example (**96**) from the quinoline series is shown in Scheme 84. The nitramines undergo acid-catalyzed rearrangement to ring nitro compounds (**97**).

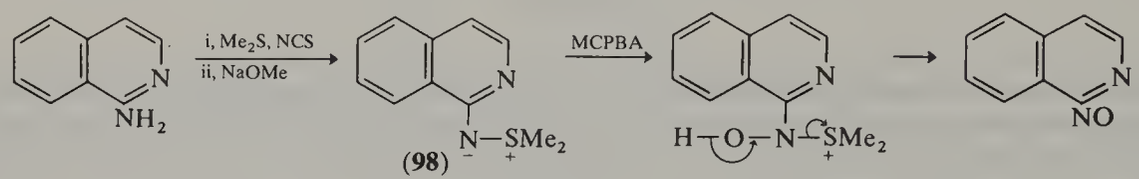


(96) m.p. 216 °C (decomp.)

(97)

Scheme 84

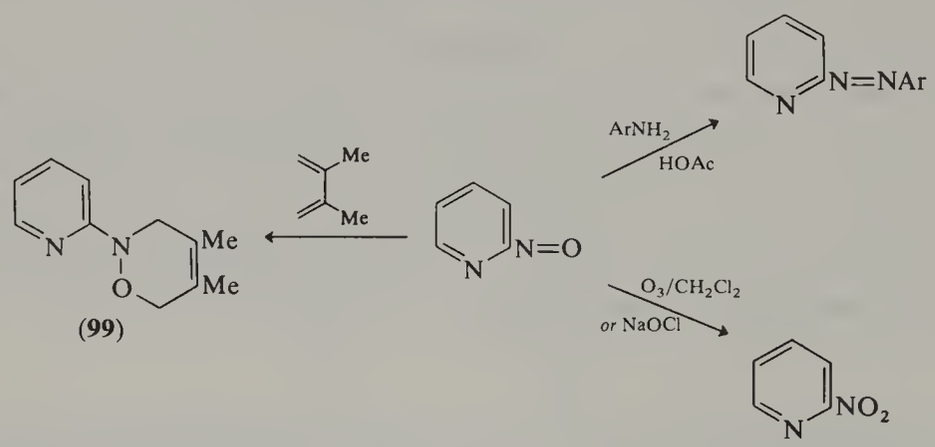
Treatment of various 2-aminopyridines and of 1-aminoisoquinoline with dimethyl sulfide and *N*-chlorosuccinimide gives the corresponding salt which on deprotonation with base provides a sulfilimine (*e.g.* **98**) ⟨76JCS(P1)2166⟩. Oxidation of the latter with *m*-chloroperbenzoic acid gives the corresponding nitroso heterocycle (Scheme 85).



(98)

Scheme 85

This route to the α-nitroso derivatives of the π-deficient heterocycles has permitted an exploration of their chemistry. They are extremely reactive and condense readily with 1,3-dienes to give 3,6-dihydro-1,2-oxazines (*e.g.* **99**), and with aromatic amines in the presence of acid to give azo compounds (Scheme 86). This latter reaction is particularly useful in view of the instability of the corresponding 2-pyridinediazonium salts referred to above, which limits conventional access. The α-nitroso heterocycles are oxidized by ozone or sodium hypochlorite to the α-nitro compounds (Scheme 86) ⟨82JOC553⟩.

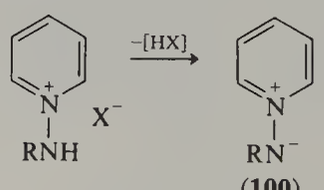


(99)

Scheme 86

2.06.4.1.2 Amino groups attached to nitrogen

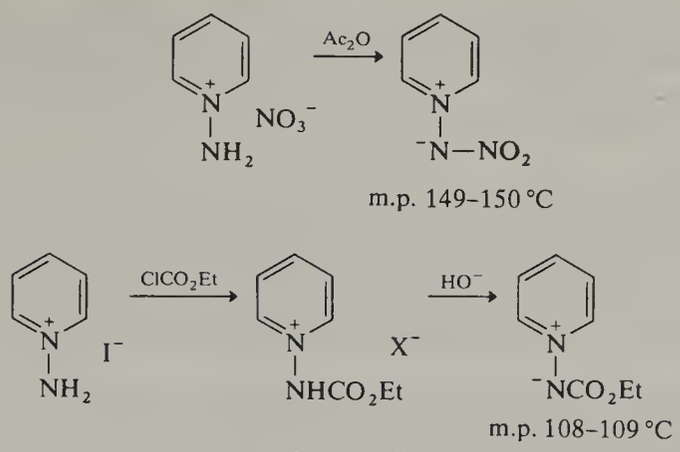
The principal interest in *N*-aminopyridinium salts and their benzo analogues is related to the fact that they can provide access to the ylide-like pyridinium imines, *e.g.* (**100**), and benzo analogues (Scheme 87) ⟨80YZ1⟩.



(100)

Scheme 87

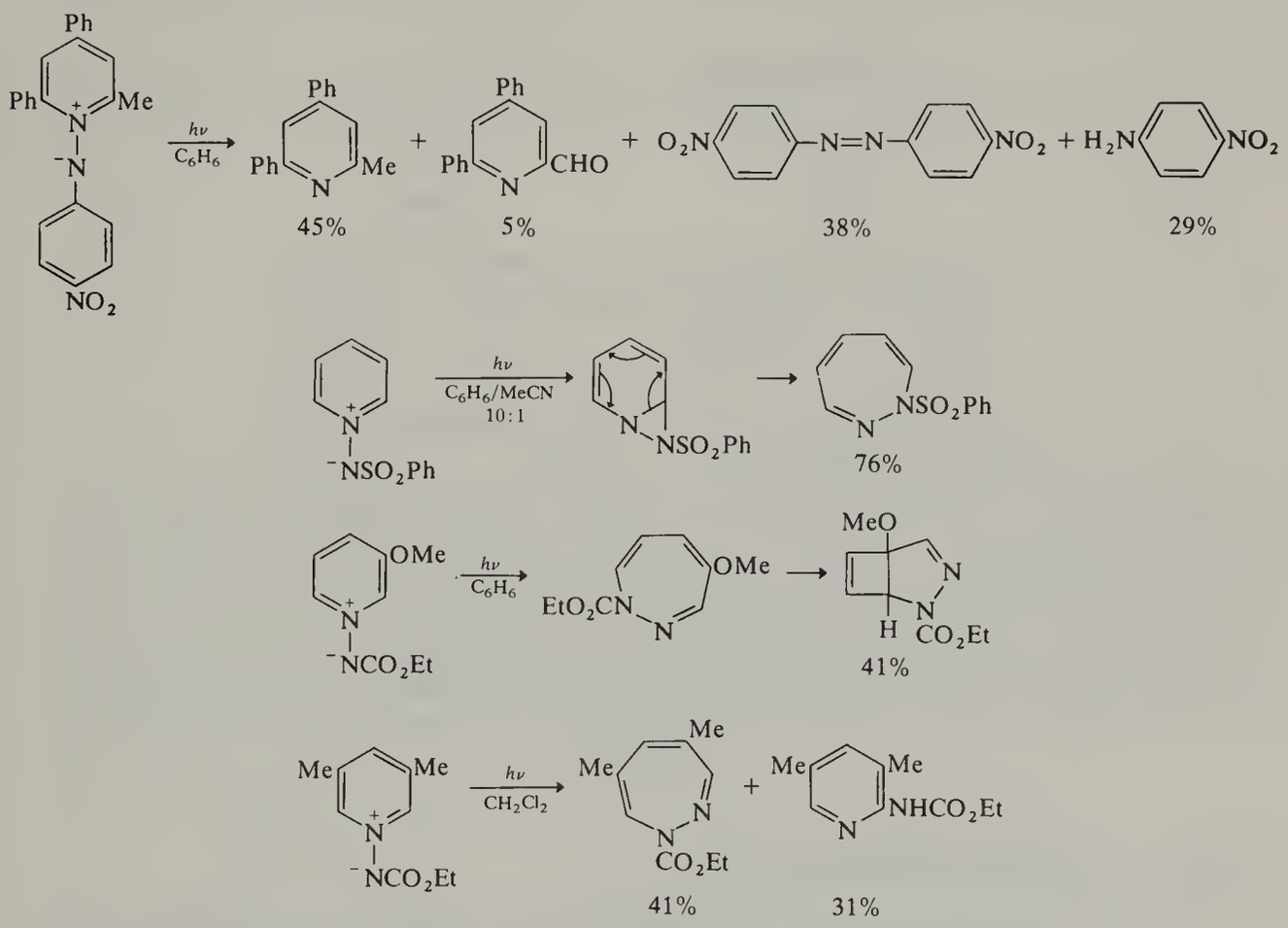
The pyridinium imines (**100**) can only be isolated when the group R can delocalize the negative charge, but an aromatic ring is sufficient for this. This contrasts with the pyridinium ylides discussed earlier (Section 2.06.3.1.2) which require more effective electron delocalization. Examples of routes to pyridine imines are shown in Scheme 88 ⟨81JCR(S)172, 70JOC433, 69TL4739, 66CPB518, 59CB2521⟩.



Scheme 88

N-Alkoxycarbonyl- and *N*-arenesulfonyl-imines can be prepared by the reaction between pyridines and nitrenes, the latter being generated from the corresponding azides ⟨72JOC2022, 64TL1733⟩. Thermolysis of pyridinium *N*-acylimines gives isocyanates and the parent heterocycle ⟨79JCS(P1)446⟩.

Under photochemical conditions, N—N bond cleavage can occur, giving the pyridine and a nitrene, and processes involving ring expansion, ring contraction and imino group migration to an unsubstituted α-position have been reported, as exemplified in Scheme 89 ⟨73JOC3311, 72JCS(P1)1020, 73BSF630, 70JOC433⟩.



Scheme 89

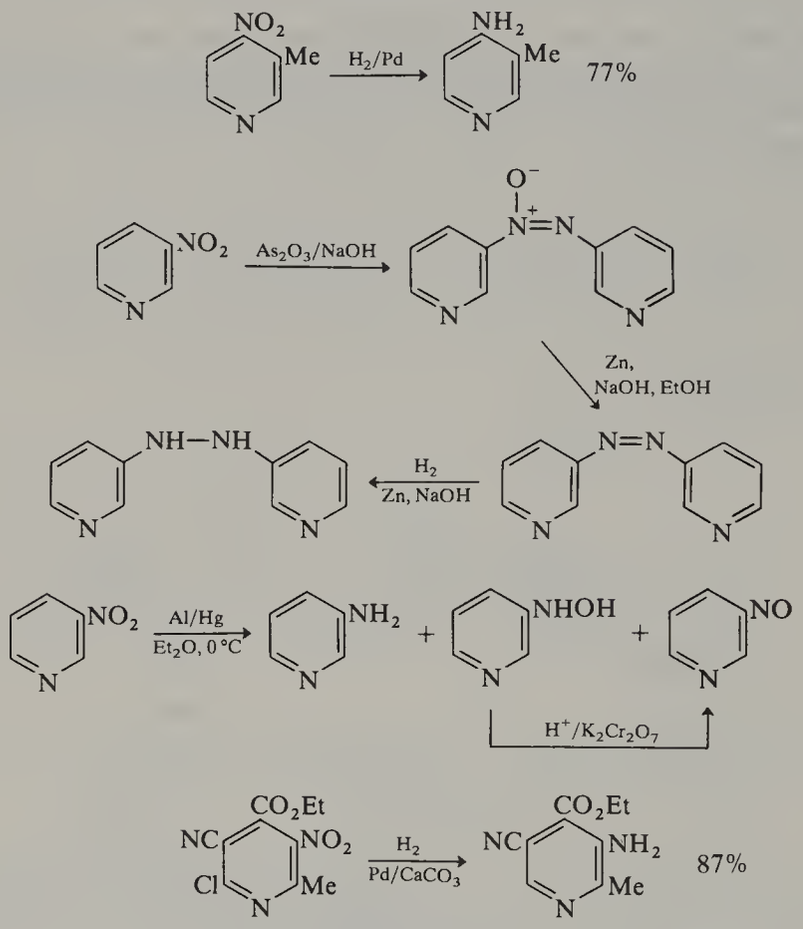
2.06.4.2 Nitro Groups

The two important processes involving the nitro group are its displacement by nucleophiles and its reduction. When the nitro group is β to the ring nitrogen its properties are comparable to those of the nitro group in nitrobenzene. However, nitro groups substituted α or γ to ring nitrogen further increase the electron deficiency of the α and γ carbons and so these positions have increased susceptibility to nucleophilic attack and subsequent loss of the

nitro group. The mobility of the nitro group is further enhanced by additional activating groups such as an *N*-oxide or electron-withdrawing substituents in the ring. In practice it is also found that ease of loss of a nitro group relates markedly to the nature of the nucleophile. Reactions involving the displacement of nitro groups are discussed in the previous chapter.

Nitropyridines, the benzo analogues and their *N*-oxides can be reduced to amino derivatives by standard methods such as catalytic hydrogenation or use of a metal and acid. Use of sodium arsenite or stannite or aqueous sodium hydroxide gives the symmetrical azopyridines. Further reduction gives the hydrazopyridines. The sodium arsenite reduction can also give azoxypyridines. Nitroacridines are reduced with tin(II) chloride to amino-9,10-dihydroacridines.

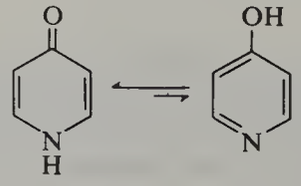
Problems can arise with the reduction of halogenonitropyridines in that the halogen is frequently removed in the process. For example, with halogeno-3-nitropyridines catalytic reduction, particularly using palladium, and use of metals and acid often but not always gives concomitant halogen loss ⟨63MI20600⟩. It has been avoided by use of tin(II) chloride, sodium hydrosulfite and by electrochemical methods ⟨B-67MI20601⟩. Some examples of nitropyridine reduction processes are shown in Scheme 90.



Scheme 90

2.06.5 *O*-LINKED SUBSTITUENTS

It is now well established that 2- and 4-pyridone and their benzo analogues exist predominantly in the oxo form, *e.g.* (**101a**), rather than the hydroxypyridine form, *e.g.* (**101b**) ⟨76AHC(S1)84; 63AHC(1)341⟩. The enaminone system NH—C=C—C=O is considerably more stable than the alternative iminoenol system N=C—C=C—OH by a factor of



(**101a**) (**101b**)

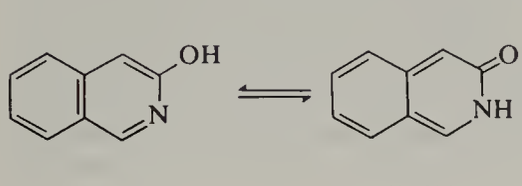
ca. 10^8 ⟨69JCS(B)299⟩. In contrast, β-hydroxypyridines and their benzo analogues usually show normal phenolic properties, as do derivatives carrying the hydroxy group on a benzo ring.

It has been recognized that there are several important factors which can swing the equilibrium from the oxo form towards the hydroxypyridine form and these have been summarized as follows. (a) Partial bond fixation due, usually, to benzene ring fusion. (b) Strongly electron-withdrawing substituents situated α to ring nitrogen. These tend to shift the equilibrium in favour of the pyridinoid form by altering the basicity of the nitrogen. (c) Substituents which stabilize one particular tautomeric form by hydrogen bonding. (d) Ring strain effects caused by the annelation of saturated rings. (e) The various effects of solvent, concentration, phase and temperature ⟨76AHC(S1)84⟩.

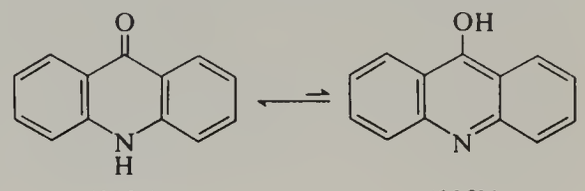
The effect of bond fixation can be seen with 3-hydroxyisoquinoline (**102a**) and its tautomer isoquinol-3-one (**102b**). Spectroscopic data, particularly UV, show the equilibrium to be finely balanced. In ethanol and in chloroform the two forms are present in comparable amounts. However, in most non-hydroxylic solvents the 3-hydroxyisoquinoline form (**102a**) predominates, but in water the isoquinol-3-one form (**102b**) is favoured ⟨69JCS(C)1729, 67JCS(B)590⟩. In the case of acridone (**103**) the two benzene rings considerably increase the relative stability of the oxo form (**103a**) compared with pyrid-4-one ⟨76AHC(S1)84⟩.

Pyrid-2- and -4-one are protonated on the oxygen atom, rather than at nitrogen, in view of the mesomeric stabilization this affords, *e.g.* (**104**) ⟨76AHC(S1)84⟩. The anion of pyrid-2-one carries the negative charge mainly on the oxygen atom ⟨66JCS(B)996⟩.

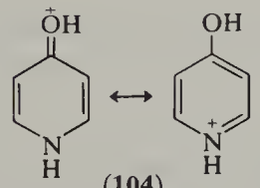
β-Hydroxypyridines, which have many properties typical of phenols, exist mainly in the hydroxy form in non-polar solvents but as zwitterion–hydroxy mixtures in water, *e.g.* (**105**).



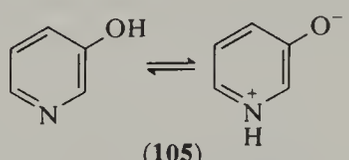
(**102a**) (**102b**)



(**103a**) (**103b**)

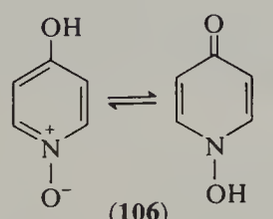


(**104**)

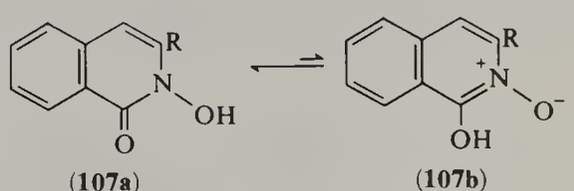


(**105**)

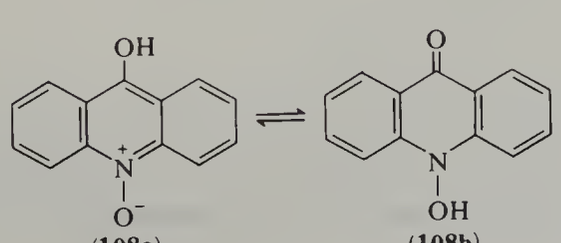
With 2- and 4-hydroxypyridine *N*-oxides, *e.g.* (**106**), the tautomeric equilibria are such that a greater proportion of the C—OH forms are present than is the case with the corresponding pyridines ⟨76AHC(S1)84⟩. Spectroscopic data for 1-hydroxyisoquinoline *N*-oxides suggests that the oxo forms (**107a**) predominate over the *N*-oxide tautomers (**107b**) ⟨66JOC2090, 63JOC2215⟩. UV and pK_a measurements show that in aqueous solution 9-hydroxyacridine *N*-oxide (**108a**) exists in equilibrium with an approximately equal amount of *N*-hydroxyacridone (**108b**) ⟨66T3227⟩. In the phenanthridine series, structure (**109**) has been assigned to *N*-hydroxyphenanthridone, based on UV and IR data ⟨67JOC1106⟩.



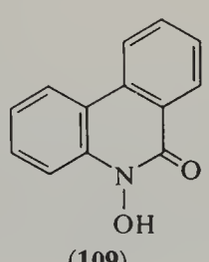
(**106**)



(**107a**) (**107b**)

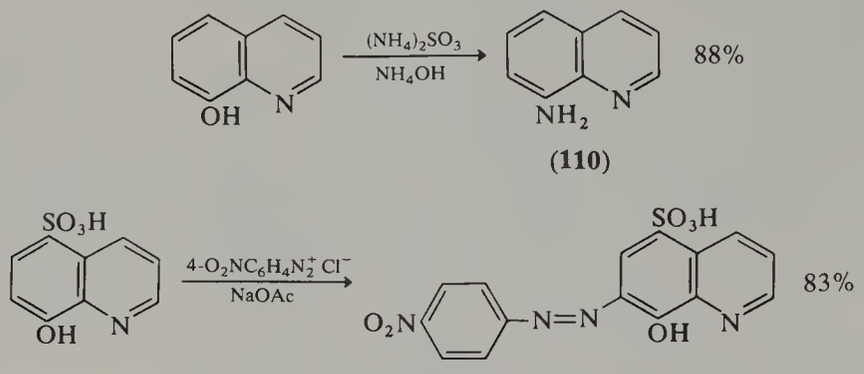


(**108a**) (**108b**)



(**109**)

As mentioned above, the benzo analogues of pyridines which carry an OH group on the benzene ring exist largely in the hydroxy form and give many of the characteristic reactions of phenols ⟨76AHC(S1)84⟩. For example, they are usually readily acylated, form nitroso derivatives and give colours with ferric chloride. They undergo the Bucherer reaction to form the corresponding amino derivatives, *e.g.* (**110**), and couple with diazonium salts in alkaline solution as shown in Scheme 91 ⟨68CB2285⟩. Quinol-4-one also gives the 3-phenylazo derivative but the 2-isomer does not couple. Both isomers give colouration with ferric chloride. 4-Hydroxyquinol-2-one is nitrosated at position 3 with nitrous acid, and also couples with diazonium salts.



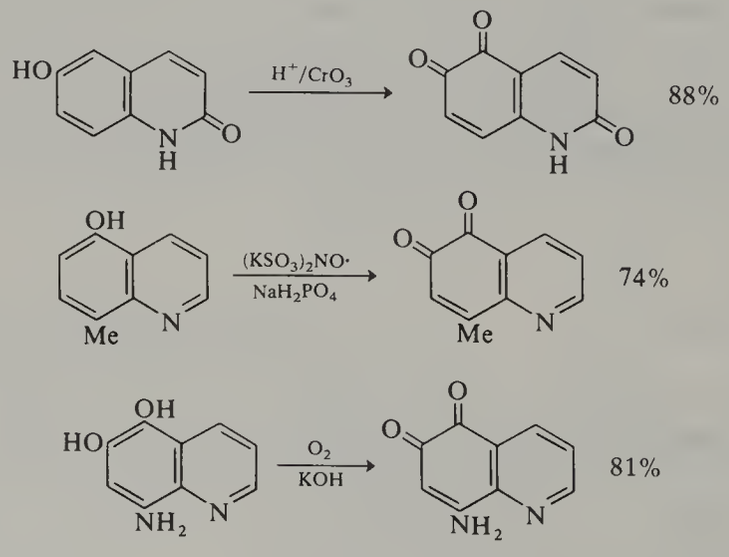
(**110**)

Scheme 91

The Reimer–Tiemann reaction with chloroform and alkali with the hydroxybenzo heterocycles gives the corresponding aldehyde. Again, the reaction is undergone by quinol-4-one, which gives the 3-formyl derivative. When carbon tetrachloride replaces the chloroform the corresponding carboxylic acids are obtained; for example, 8-hydroxyquinoline gives 8-hydroxyquinoline-5-carboxylic acid. Acids are also the product of the Kolbe–Schmidt reaction, resulting from the treatment of the alkali metal salts with carbon dioxide under pressure. For example, 6-hydroxyquinoline gives 6-hydroxyquinoline-5-carboxylic acid.

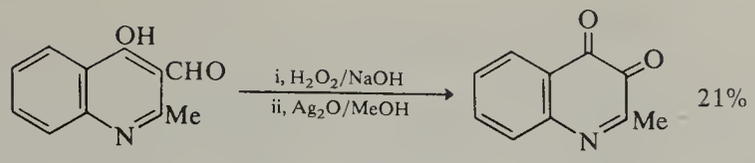
8-Hydroxyquinoline, whose chemistry has been reviewed ⟨56CRV271⟩, has found wide application as an analytical reagent, and is known as 'oxine'. It forms insoluble complexes with a great many metal ions, coordinating at O and N, and can be used for the estimation of Mg, Zn, Al, Cu, Bi, Fe, Mn, Ni and others.

Oxidation of appropriate mono- and di-hydroxyquinolines leads to quinones. This can be achieved by a variety of oxidizing agents including chromic acid and Frémy's salt (dipotassium nitrosodisulfonate, $(KSO_3)_2NO\cdot$) ⟨67CB2077, 67CB2918⟩. Examples are shown in Scheme 92. 9-Acridonequinones result from analogous oxidations of dihydroxy-9-acridones.



Scheme 92

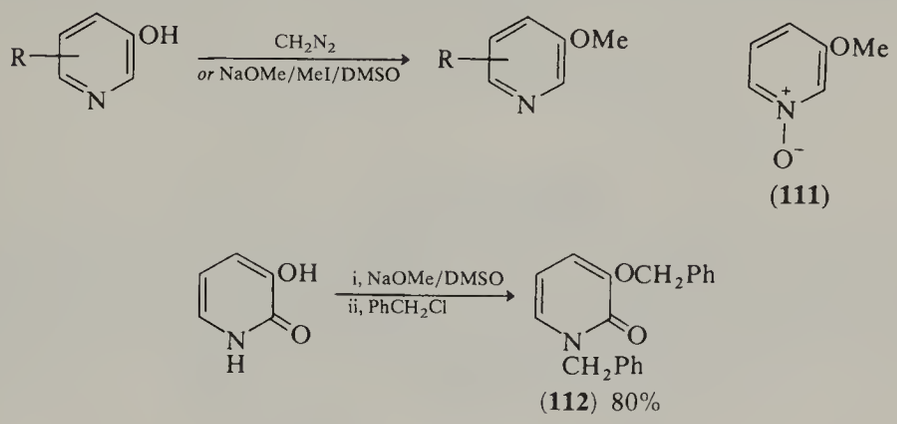
Oxidation to quinones can also proceed by involving another substituent beside hydroxyl. For example, 5-aminoquinolin-8-ol with potassium dichromate or iron(III) chloride gives quinoline-5,8-dione ⟨60JA1155⟩. *o*-Formylquinolinols give the corresponding diols and hence quinones on oxidation with Dakin's reagent, *e.g.* Scheme 93 ⟨63JOC260⟩.



Scheme 93

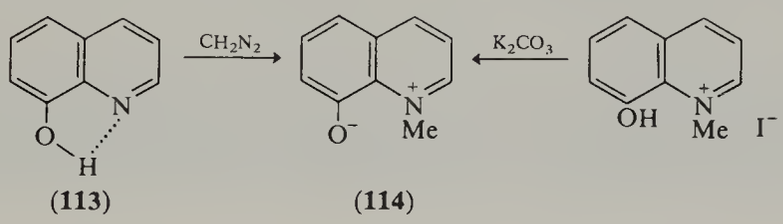
2.06.5.1 Alkylation of Hydroxypyridines, Pyridones and their Benzo Analogues

The alkylation of pyridinols and pyridones is complicated, as it may occur at either the oxygen or nitrogen atom, depending on the conditions and reagents employed. Treatment of 3-hydroxypyridine with diazomethane gives *O*-methylation and similar treatment of the *N*-oxide gives the 3-methoxy product (**111**). *O*-Alkylation can also be achieved by conversion of the 3-hydroxyquinoline into its sodium salt and addition of an alkyl halide. Dialkylation of 3-hydroxypyrid-2-one under similar conditions gives the 3-alkoxy-1-alkylpyrid-2-one (**112**; Scheme 94) ⟨69ACS1791, 57RTC58⟩.



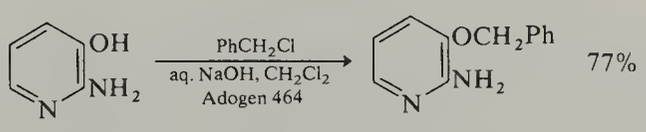
Scheme 94

8-Hydroxyquinoline (**113**) with diazomethane gives the betaine *N*-methyl-8-quinolinate (**114**) which also results from treatment of 8-hydroxyquinoline methiodide with potassium carbonate (Scheme 95) ⟨59JCS1579⟩.



Scheme 95

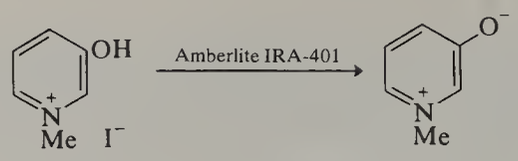
N-Alkylation of 3-hydroxypyridine results from direct treatment with an alkyl halide or dimethyl sulfate and alkali ⟨59JA5140, 57RTC58⟩. Regioselectivity depends, however, on other substituents present as well as conditions. For example, 3-hydroxy-2-nitropyridine is exclusively *O*-alkylated with dimethyl sulfate and potassium carbonate ⟨81MI20600⟩ and 2-amino-3-hydroxypyridines are exclusively *O*-benzylated with benzyl chloride and alkali in a two phase system and phase transfer catalyst (Scheme 96) ⟨81S971⟩.



Scheme 96

Treatment of the *N*-methylated product (**115**) of 3-hydroxypyridine with an ion exchange resin generates the betaine (**116**; Scheme 97) ⟨71JCS(C)874⟩. Reduction of 1-substituted 3-oxidopyridinium betaines with sodium borohydride gives hexahydro derivatives in good yields ⟨81H(16)1883⟩.

Addition of methyl iodide to 4-hydroxyisoquinoline gives the quaternary methiodide which is converted to the betaine on passage down an ion exchange column. Betaines such

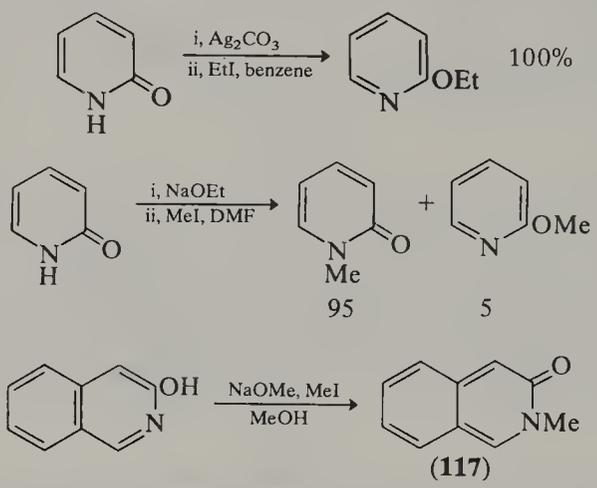


(**115**) (**116**)

Scheme 97

as 1-methyl-3-oxidopyridinium (**116**) and 2-methyl-4-oxidoisoquinolinium undergo 1,3-dipolar cycloaddition; a very extensive study of this type of process has been made by Katritzky and co-workers ⟨81JCR(S)208, 79JCS(P1)399, 76JCS(P1)2289, 72JCS(P1)2054, 71JCS(C)874⟩ as discussed in the previous chapter.

Alkylation of the silver salt of pyrid-2-ones usually gives exclusive *O*-alkylation, whereas alkylation of the sodium or potassium salt gives predominantly *N*-alkylation, *e.g.* Scheme 98. However, the course of such reactions is strongly dependent on conditions. Not only is the nature of the metal salt important but also the structure of the halide, the substituents on the pyridone ring and the solvent used ⟨77OPP5, 70JOC2517, 67JOC4040⟩.

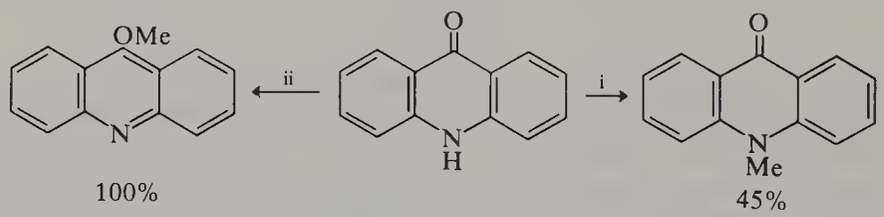


(**117**)

Scheme 98

The *N*-methyl product (**117**) from 3-hydroxyisoquinoline undergoes Diels–Alder cycloaddition across the 1,4-positions ⟨70TL1209, 69JCS(C)1729⟩.

Quinol-2- and -4-one give the *N*-methyl derivatives with methyl iodide and alkali, sometimes accompanied by the *O*-methyl isomers, depending on the conditions used. Acrid-9-one with methyl iodide or dimethyl sulfate and alkali normally gives *N*-methylacrid-9-one. Again, however, conditions can markedly affect regioselectivity; use of dimethyl sulfate in conjunction with a phase transfer catalyst gives exclusive *O*-methylation (Scheme 99) ⟨80BSF(2)345, 79S944, 79S177, 78JHC149, 76JPR515⟩.



i, MeI, $Et_3N^+CH_2Ph\ Cl^-$, KOH, H_2O, toluene; ii, Me_2SO_4, NaOH, $Et_3N^+CH_2Ph\ Cl^-$, CH_2Cl_2, H_2O

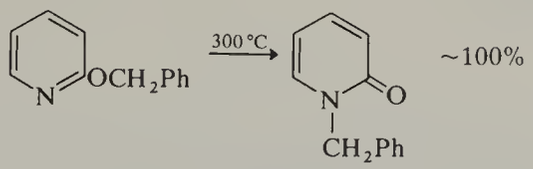
Scheme 99

Diazomethane with pyrid-2-one gives predominantly *O*-alkylation, but a mixture of *O*- and *N*-methylated products with pyrid-4-one. Other alkylating agents also give mixed products with pyrid-4-one. The quinolinols and tautomers with diazomethane give methoxyquinolines. 4-Hydroxyquinol-2-one ⟨67M100⟩, which gives a red colour with iron(III) chloride, forms 4-methoxyquinol-2-one and 2,4-dimethoxyquinoline with diazomethane. Dimethyl sulfate and alkali, however, give 4-hydroxy-1-methylquinol-2-one and 2-methoxy-1-methylquinol-4-one.

Methylation of the *N*-oxides of 2- or 4-hydroxypyridine in basic medium gives the *N*-methoxypyridone ⟨57JCS4375⟩ whereas diazomethane with the 4-isomer gives both C—OMe and N—OMe products.

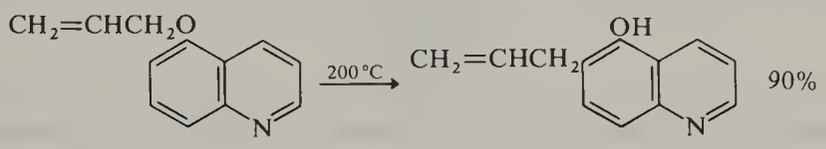
2.06.5.2 Ethers

On heating 2- or 4-alkoxypyridines rearrangement occurs to the corresponding *N*-alkylpyridone, *e.g.* Scheme 100, but the 3-ethers do not rearrange. The rearrangements are catalyzed by alkyl halides ⟨68JA1569, 65JA3365⟩. 2-Alkoxy- and 4-alkoxy-quinolines behave similarly. The ethers are very readily hydrolyzed by aqueous acid.



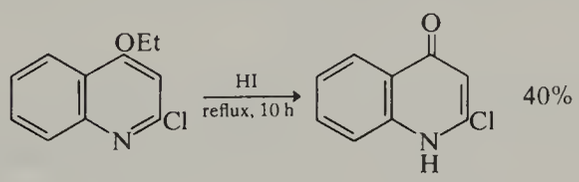
Scheme 100

Quinoline allyl ethers on heating undergo the Claisen rearrangement, giving mainly *ortho* products ⟨67JHC131, 66BSF586, 65JOC1986, 65JOC1989⟩. For example, 5-allyloxyquinoline on heating to 200 °C gives 6-allyl-5-hydroxyquinoline (Scheme 101). Zerovalent platinum complexes catalyze the conversion of 2-allyloxypyridines to *N*-allylpyridones ⟨79T3949⟩.



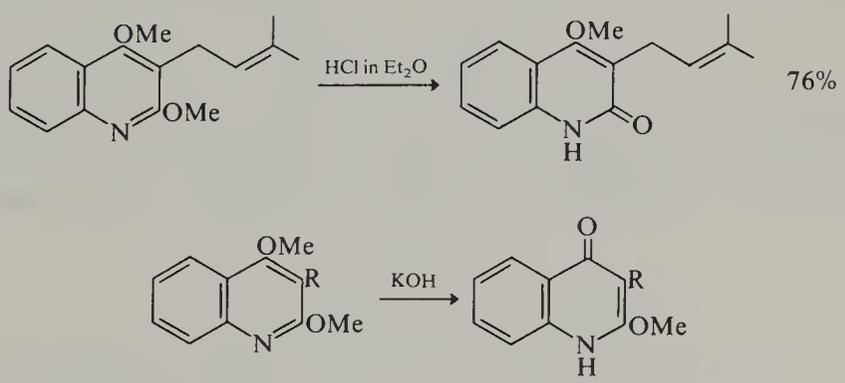
Scheme 101

Pyridyl methyl ethers can undergo alkyl–oxygen fission on treatment with methoxide ⟨70JOC3462⟩, and the alkyl ethers (and their *N*-oxides and quaternary salts) are also cleaved with aqueous acid. Ether cleavage sometimes requires prolonged heating, *e.g.* Scheme 102. The *N*-alkyl derivatives usually need more vigorous treatment to effect cleavage than the *O*-alkyl ethers.



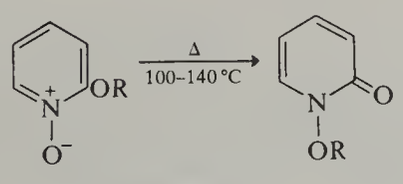
Scheme 102

Selective demethylation of 2,4-dimethoxyquinolines occurs on heating with hydrogen chloride in ether, normally giving 4-methoxyquinol-2-ones, *e.g.* Scheme 103 ⟨73JCS(P1)94⟩. If, however, alkali is used and an electron-withdrawing 3-substituent is present, as in (**118**), then the demethylation occurs at position 4 (Scheme 103) ⟨81IJC(B)543⟩.



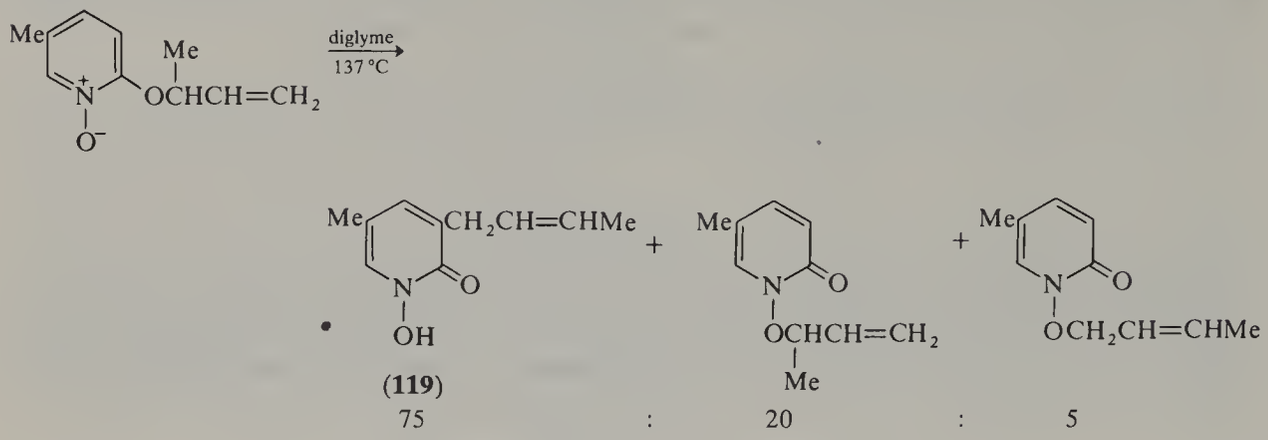
(**118**) R = CHO, CO_2Et, $CH{=}CHCO_2Et$

Scheme 103



Scheme 104

2-Alkoxypyridine *N*-oxides rearrange thermally to *N*-alkoxypyrid-2-ones (Scheme 104) ⟨72LA(765)153, 64JOC1650⟩. With 2-allyloxypyridine *N*-oxides an *ortho* Claisen rearrangement also occurs under similar conditions to give the 3-allyl-1-hydroxypyrid-2-one (*cf.* **119**) among the products (Scheme 105) ⟨68JA4361⟩.

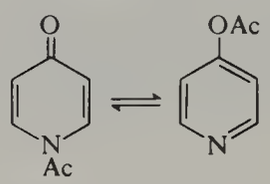


Scheme 105

2.06.5.3 Acylation of Hydroxypyridines, Pyridones and their Benzo Analogues

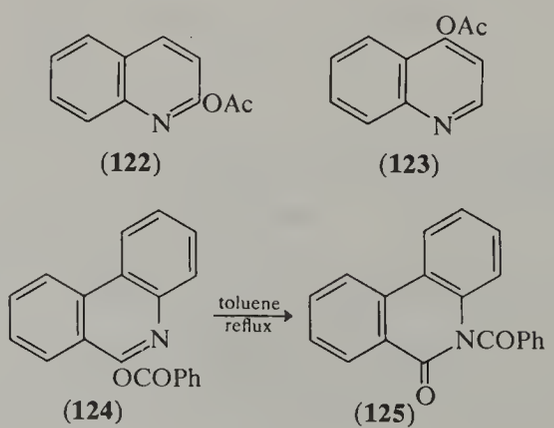
As with alkylation, the acylation processes are complex in that either or both *O*- and *N*-acylation may occur. Acetylation of pyrid-2-one under normal conditions gives the *O*-acetyl product; acetylation of the thallium salt of pyrid-2-one at −40 °C gives a mixture of isomers estimated to contain about 40% of the *N*-acetyl derivative, which on warming to room temperature rearranges almost entirely to the *O*-isomer ⟨68TL4945⟩. Benzoylation of pyrid-2-one under normal conditions gives the *O*-aroyl product, as is also the case with the 3- and 4-isomers ⟨71TL4223, 70JCS(C)2426⟩. 3-Pyridyl acetate is formed on acetylation of 3-hydroxypyridine.

Acetylation of pyrid-4-one gives crystalline *N*-acetylpyrid-4-one (**120**) which shows ν_{max} 1725 cm^{-1} (KBr) in the IR spectrum. A fresh solution in CH_2Cl_2 has an IR band at 1750 cm^{-1} but within a few minutes an equilibrium with 4-acetoxypyridine (**121**) is established and a second band appears at 1775 cm^{-1}. At room temperature in CH_2Cl_2 the two isomers are present in comparable amounts ⟨70JCS(C)2426⟩.



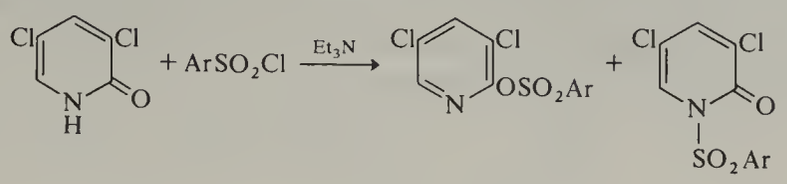
(**120**) (**121**)

Acetylation of carbostyril (quinol-2-one) and quinol-4-one gives the *O*-acetyl isomers (**122**) and (**123**) ⟨70JCS(C)2426⟩. Benzoylation of the sodium salt of phenanthridone gives the *O*-benzoyl product (**124**) which rearranges on heating to the *N*-benzoyl isomer (**125**; Scheme 106) ⟨68TL3911⟩. Acylation of acrid-9-one derivatives occurs mainly at oxygen ⟨80BSF(2)345⟩.



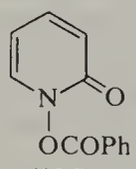
Scheme 106

Arenesulfonylation of pyrid-2-ones has been studied and both *O*- and *N*-sulfonylated products reported, *e.g.* Scheme 107 ⟨72JHC215⟩.

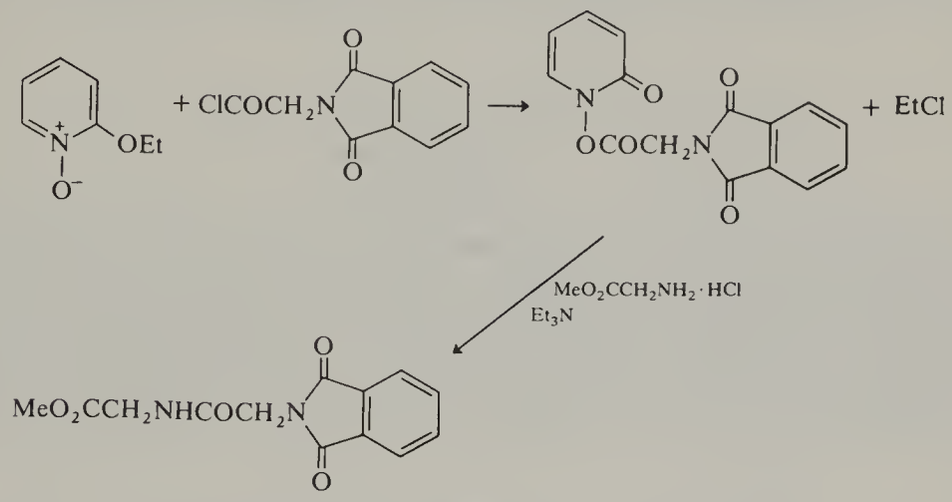


Scheme 107

1-Benzoyloxypyrid-2-one (**126**) is formed on treatment of the potassium salt of 1-hydroxypyrid-2-one with benzoyl chloride ⟨64JCS4651⟩. Analogous conversions have been effected *via* the thallium salt ⟨70JOC1672⟩. The product esters can also be made by treatment of 2-ethoxypyridine *N*-oxide with an acid chloride. The esters are reactive acylating agents and have been used in peptide synthesis, *e.g.* Scheme 108 ⟨65JA5186⟩.

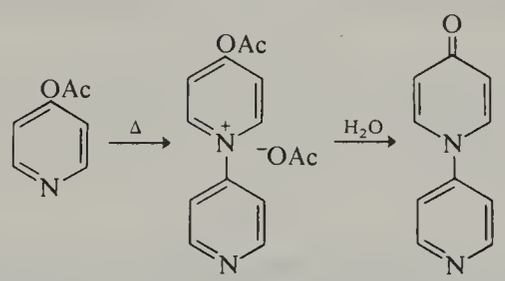


(126)



Scheme 108

As expected, acyloxy groups on electron-deficient heterocycles are usually hydrolyzed easily, particularly when at α- or γ-positions to nitrogen to give the corresponding acid and hydroxy heterocycle or tautomer. Also the benzo acetates usually undergo the Fries rearrangement with aluminum chloride to give acetyl derivatives. Self-quaternization of 4-pyridyl acetates or sulfonates occurs on heating, *e.g.* Scheme 109.

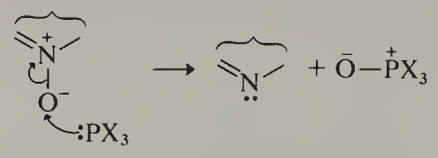


Scheme 109

2.06.5.4 *N*-Oxides and their Derivatives

The reagents most frequently used to reduce the *N*-oxides to the parent heterocycle are trivalent phosphorus compounds. These include the phosphorus trihalides, usually in chloroform or ethyl acetate, triphenylphosphine, and phosphite esters such as triethyl phosphite. Substituents which are easily reduced are not affected, although nitro groups

may be displaced by halogen in reactions with phosphorus trihalides. Clearly, reduction by a phosphorus trihalide is unsuitable when a second strongly nucleophilic substituent is present, *e.g.* amino. The mechanisms are usually written as in Scheme 110 but can be more complicated and in some cases involve radical processes ⟨62JCS1917⟩.

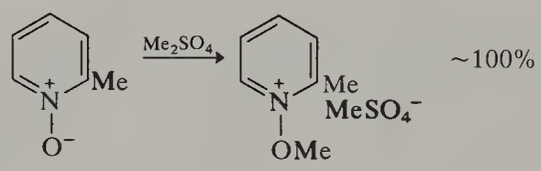


Scheme 110

Methods which are principally of use when other reducible substituents are absent include catalytic hydrogenation, use of metals and acid, iron(II) oxalate ⟨61CJC2134⟩, sodium borohydride and lithium aluminum hydride ⟨70CCC2802⟩.

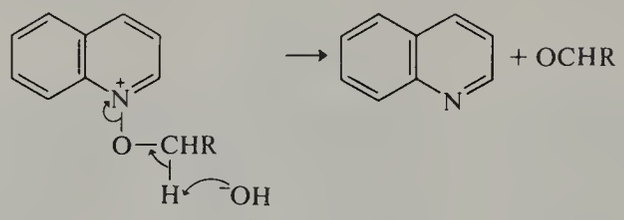
Many sulfur-containing reducing agents have been used, including diaryl sulfides ⟨68TL3791⟩, dimethyl sulfoxide ⟨69TL1015, 69TL3619, 74AJC789⟩, sulfur dioxide ⟨66JOC4267⟩, trialkylamine–sulfur dioxide complexes ⟨80S660⟩ and thiourea ⟨62JOC477⟩. Other deoxygenation reagents include trimethylsilyl chloride–sodium iodide–zinc ⟨81CL921⟩.

N-Alkoxypyridinium salts and their benzo analogues can be formed by treatment of the *N*-oxides with alkyl halides, dialkyl sulfates (*e.g.* Scheme 111) ⟨73OSC(5)269⟩, alkyl arenesulfonates, trialkyloxonium salts ⟨66CB1769⟩, and trialkyl phosphites and their thio analogues ⟨71JGU524⟩.



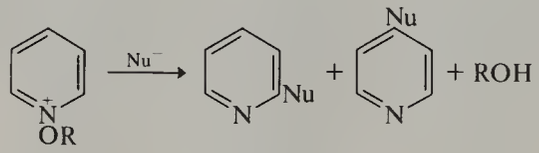
Scheme 111

N-Alkoxypyridinium salts can be nucleophilically dealkylated to give back the *N*-oxide. Hydroxide attack at the ring α-position can lead to ring opening of the carbinolamine derivative formed. Nucleophilic removal of a proton from the *N*-alkoxy side chain α-carbon results in elimination of the parent heterocycle and formation of an aldehyde, *e.g.* Scheme 112.



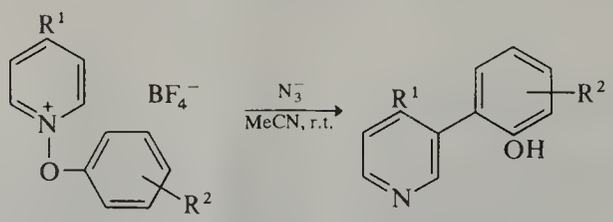
Scheme 112

N-Alkoxypyridinium salts can also undergo substitutions of the AE_a type, *e.g.* Scheme 113.



Scheme 113

Azide ion will catalyze rearrangements of *N*-(aryloxy)pyridinium salts to give 3-(*o*-hydroxyphenyl)pyridines (Scheme 114). It is suggested that azide addition to the α-position

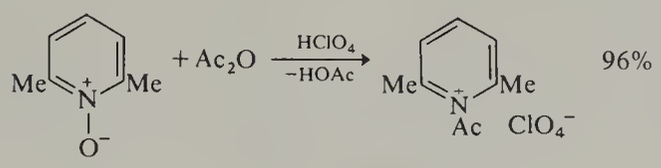


$R^1 = NO_2$, CN; R^2 = H, 3-Br, 3-Me, 4-Ph, 4-OMe

Scheme 114

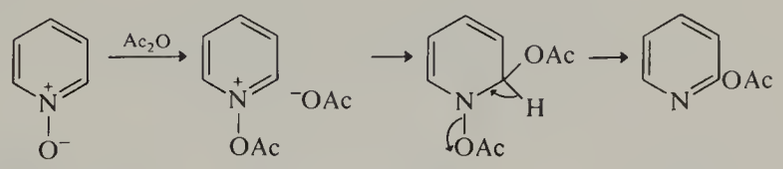
is followed by a 3,5-sigmatropic shift and elimination of HN_3. A radical pathway may also be involved ⟨79JOC464⟩. Aromatic substitutions *via* heteroaromatic *N*-oxide rearrangements have been reviewed ⟨76ACR192⟩.

N-Acyloxypyridinium salts can be isolated from the reaction of *N*-oxides with acid anhydride by the inclusion of a strong acid possessing a non-nucleophilic anion, *e.g.* $HClO_4$. Such acids will protonate the initially formed carboxylate ion and provide a stable anion for salt formation (Scheme 115) ⟨65JOC1909⟩.



Scheme 115

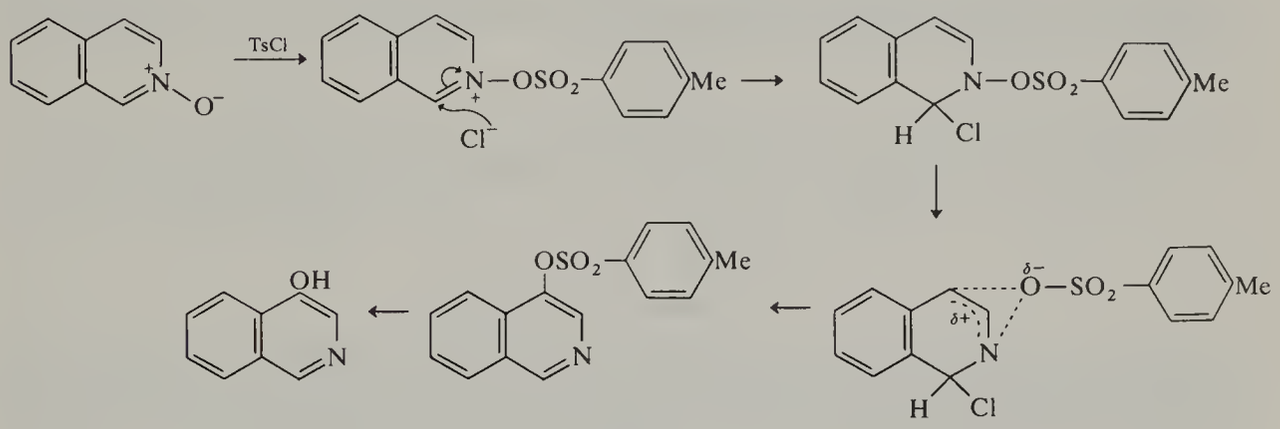
In the absence of the strong acid a different course ensues. The acetate ion attacks the *N*-acyloxypyridinium cation (**127**) at the α-position and elimination of acetic acid gives the product, 2-acetoxypyridine (**128**; Scheme 116) ⟨65T1971, 63JA958⟩. The course of the reaction under these conditions with 2- and 4-alkylpyridine *N*-oxides has been discussed earlier (Section 2.06.3.1).



(**127**) (**128**)

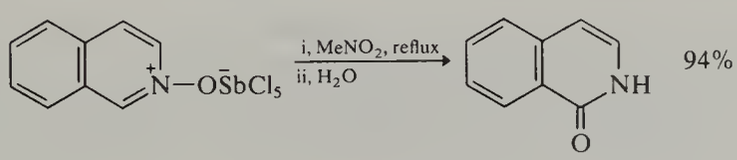
Scheme 116

A number of interesting mechanistic variations have appeared using other acylating agents, including trichloroacetic anhydride ⟨70JOC508⟩, phenylacetic anhydride ⟨69JOC2550⟩ and arenesulfonyl chlorides, *e.g.* Scheme 117 ⟨63T827⟩. The topic has been reviewed ⟨B-69MI20601⟩.



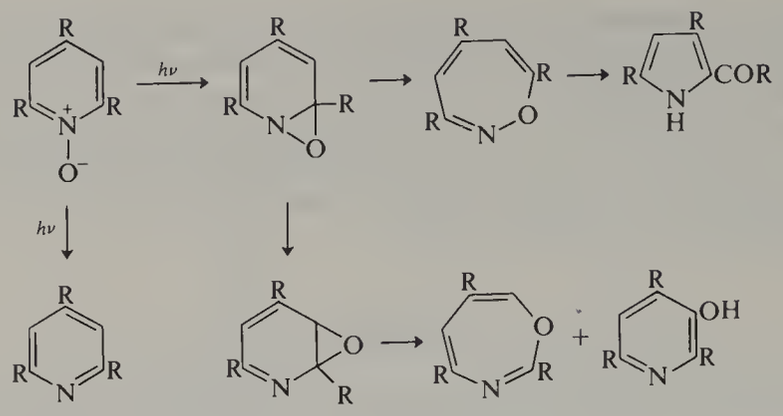
Scheme 117

Antimony pentachloride complexes of *N*-oxides of pyridine, quinoline and isoquinoline rearrange on heating to give the corresponding pyrid-2-one, carbostyril or isocarbostyril, *e.g.* Scheme 118 ⟨81T1871⟩.



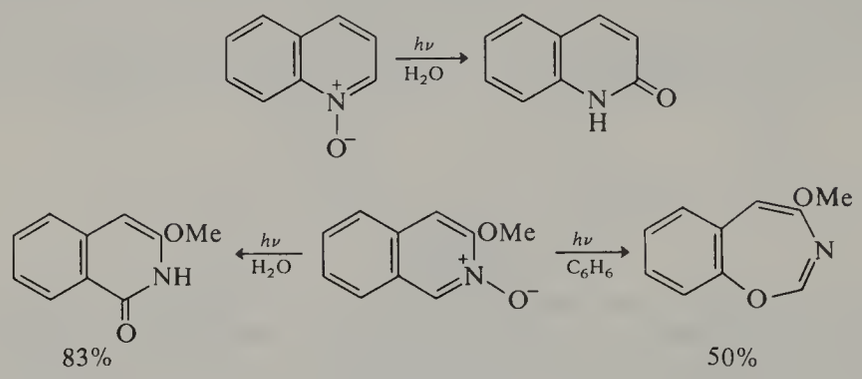
Scheme 118

The photochemical reactions of the *N*-oxides of the π-deficient heterocycles have been reviewed ⟨70CRV231⟩. In summary, they undergo a variety of reactions. Ring expansion or contraction can occur, cleavage of the N—O bond, or migration of the oxygen to a ring carbon or to a substituent on a carbon α to the nitrogen. Typical intermediates proposed in the ring transformations are illustrated in Scheme 119 ⟨70BSF1157, 68CC1321⟩.



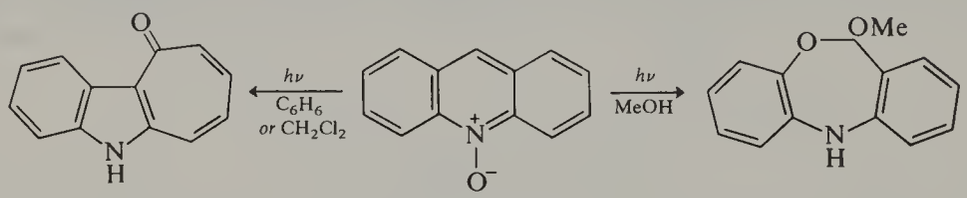
Scheme 119

The photolysis of quinoline *N*-oxides in protic media mainly leads to carbostyrils (Scheme 120) ⟨63ACS1461⟩ while in aprotic media ring expansion and contraction products are obtained ⟨69ACS2149, 71TL1311⟩. Isoquinoline *N*-oxides behave similarly (Scheme 120) ⟨80JCS(P1)2738⟩.



Scheme 120

Irradiation of acridine *N*-oxide takes a different course depending on the solvent system, as shown in Scheme 121 ⟨69LA(723)95, 68TL4519⟩.



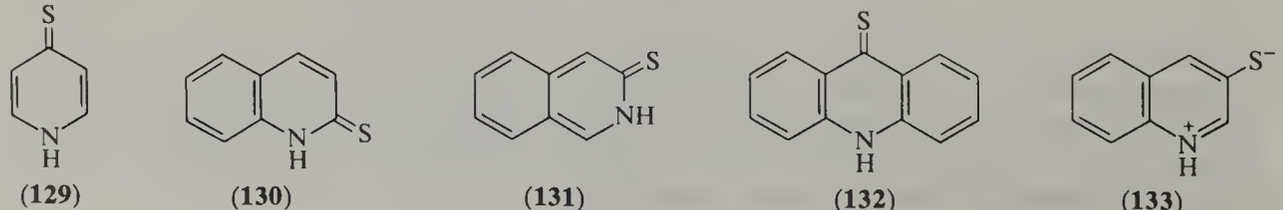
Scheme 121

Other aspects of the chemistry of the *N*-oxides, including substitution reactions, have been illustrated elsewhere in this chapter and in the previous chapter. Substantial reviews on *N*-oxide chemistry are available ⟨74HC(14-2)1, B-71MI20600, B-67MI20602⟩.

2.06.6 *S*-LINKED SUBSTITUENTS

2.06.6.1 Thiols, their Tautomers and Related Compounds

Thiol–thione tautomerism is similar to that exhibited by the oxygen analogues but with the α- and γ-thiones, *e.g.* (**129**), slightly more favoured than the corresponding α- and γ-oxo compounds. UV and other data have indicated the predominance of the thione forms of quinoline-2- and -4-thione, *e.g.* (**130**), isoquinoline-1- and -3-thione, *e.g.* (**131**), and acridine-9-thione (**132**) ⟨76AHC(S1)144⟩.

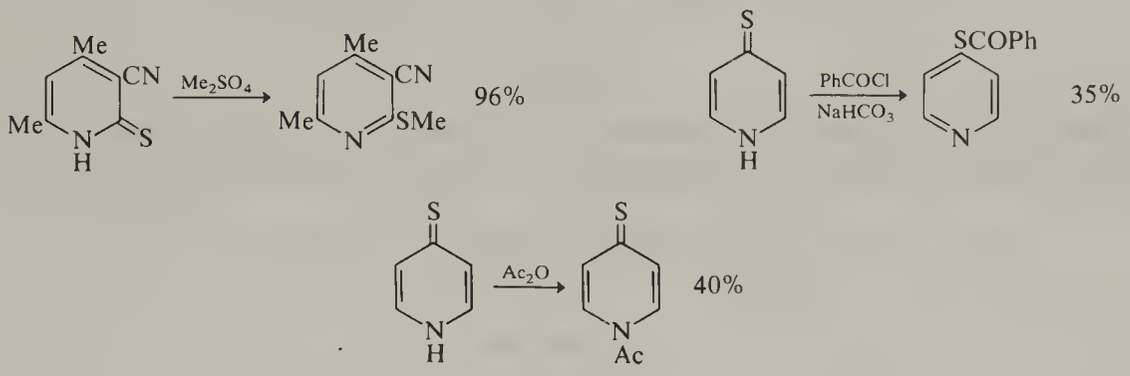


(**129**) (**130**) (**131**) (**132**) (**133**)

UV and pK_a measurements show that pyridine-3-thiol and quinoline-3-thiol occur predominantly in the zwitterion form, *e.g.* (**133**) ⟨76AHC(S1)144⟩. Quinolines carrying a mercapto group on the benzo ring exist in the zwitterion or the zwitterion extended quinone form to a larger extent than do the analogous hydroxy compounds ⟨63AHC(S1)400⟩.

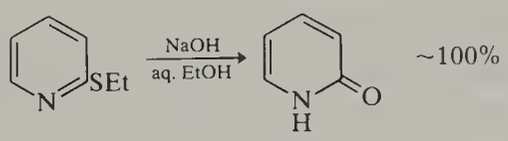
Protonation of pyridinethiones and quinoline-4-thione occurs at sulfur, giving the corresponding mercapto-pyridinium and -quinolinium cations ⟨65JCS3825, 62JCS3127⟩.

Alkylation and acylation of pyridinethiols and pyridinethiones usually occurs predominantly or exclusively on sulfur (Scheme 122) ⟨75HC(14-4)199, 59JCS2384, 58JCS3610⟩. Exceptions to this are most often observed with pyridine-4-thione; for example, although it undergoes *S*-benzoylation it is acetylated on nitrogen (Scheme 122). The quinolinethiols are methylated with methyl iodide and alkali on sulfur but the 2- and 4-isomers with dimethyl sulfate and alkali yield *N*-methyl derivatives ⟨60CB1590, 63JCS688⟩. Acridine-9-thione is converted to *S*-alkyl or *S*-acyl derivatives with alkyl or acyl halides ⟨80S850⟩.



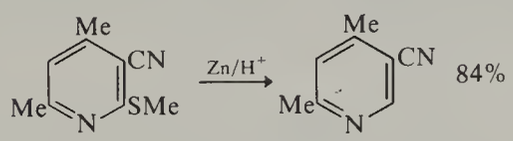
Scheme 122

Displacement of thioether substituents in pyridinium salts can be achieved with amines, and hydroxide will effect a similar substitution in pyridine thioethers, *e.g.* Scheme 123 ⟨69KGS677⟩.



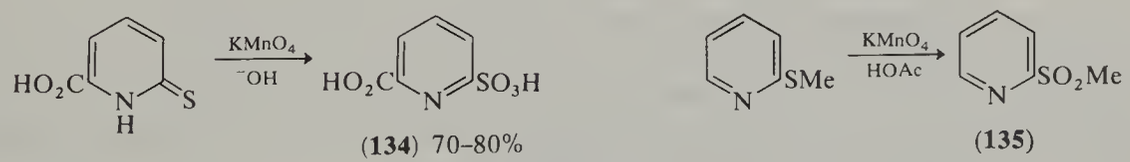
Scheme 123

Reductive removal of a thioether group can be effected by a variety of reducing agents, *e.g.* Scheme 124 ⟨60CB1590⟩.



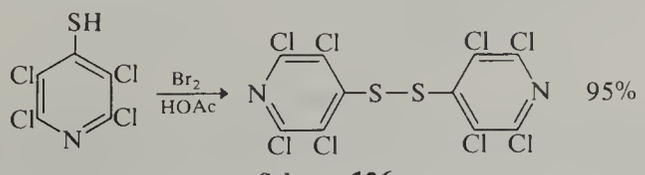
Scheme 124

The α- and γ-pyridinethiones can be oxidized to the corresponding sulfonic acids, *e.g.* (**134**), by reagents such as alkaline permanganate, nitric acid and peracids ⟨67FES1069⟩. Thioether oxidation gives the corresponding sulfone, *e.g.* (**135**; Scheme 125).



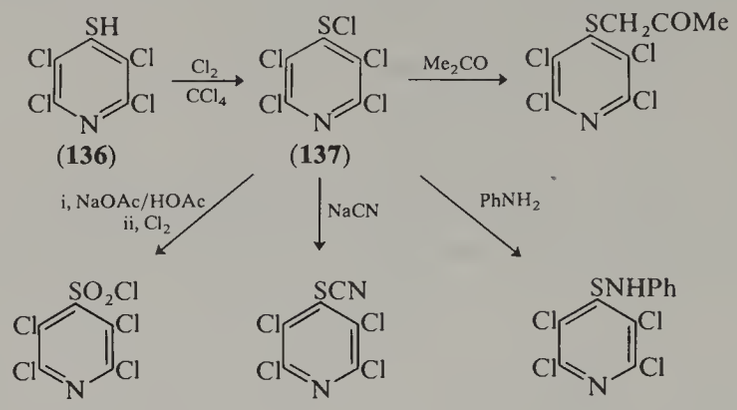
Scheme 125

Pyridinethiones and thiols are readily oxidized to the corresponding disulfides by reagents such as hydrogen peroxide, potassium ferricyanide and bromine, *e.g.* Scheme 126 ⟨70JCS(C)1530⟩. Treatment of acridine-9-thione with sulfuric acid gives acrid-9-one.



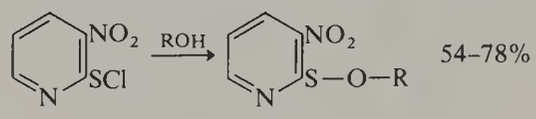
Scheme 126

Treatment of tetrachloropyridine-4-thiol (**136**) with chlorine in carbon tetrachloride gives the corresponding sulfenyl chloride (**137**) which is relatively stable. The product (**137**) can be converted into a variety of sulfur derivatives as summarized in Scheme 127 ⟨70JCS(C)1530⟩.



Scheme 127

Treatment of 3-nitro-2-pyridinesulfenyl chloride with alcohols gives 3-nitro-2-pyridinesulfenates (Scheme 128) which have been used for peptide protection ⟨81H(15)1089⟩.

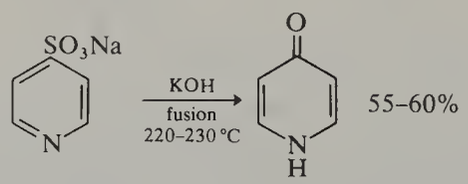


Scheme 128

2.06.6.2 Sulfonic Acids and Related Compounds

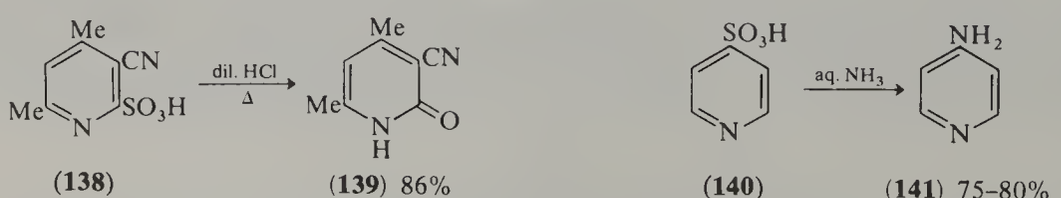
The sulfonic acids are comparatively weak and exist as zwitterions. They can be esterified with an alcohol and hydrogen chloride for example, but treatment of pyridinesulfonic acids with methyl iodide or dimethyl sulfate and alkali gives *N*-methylation.

The sulfonate salts of the π-deficient heterocycles will undergo many reactions typical of arenesulfonates, such as displacement by hydroxide, on fusion with alkali (*e.g.* Scheme 129), or by cyanide on fusion with potassium or sodium cyanide. Also, the sulfonation of pyridine is reversible; when pyridine-3-sulfonic acid is heated with 100% sulfuric acid and mercury(II) sulfate at approximately 330 °C a mixture is obtained containing mainly pyridine ⟨58RTC963⟩.



Scheme 129

The α- and γ-sulfonates will also undergo displacement reactions which occur because of the electron withdrawal from the α- and γ-positions by the ring nitrogen, reactions not undergone by sulfonates at the β-position. For example, aqueous mineral acid will convert the pyridine-2-sulfonic acid (**138**) into the pyridone (**139**). Similarly, heating the 4-sulfonic acid (**140**) with aqueous ammonia gives (**141**), a reaction which fails with the 3-substituted isomer of (**140**; Scheme 130) ⟨60CB1590, 58RTC963⟩.

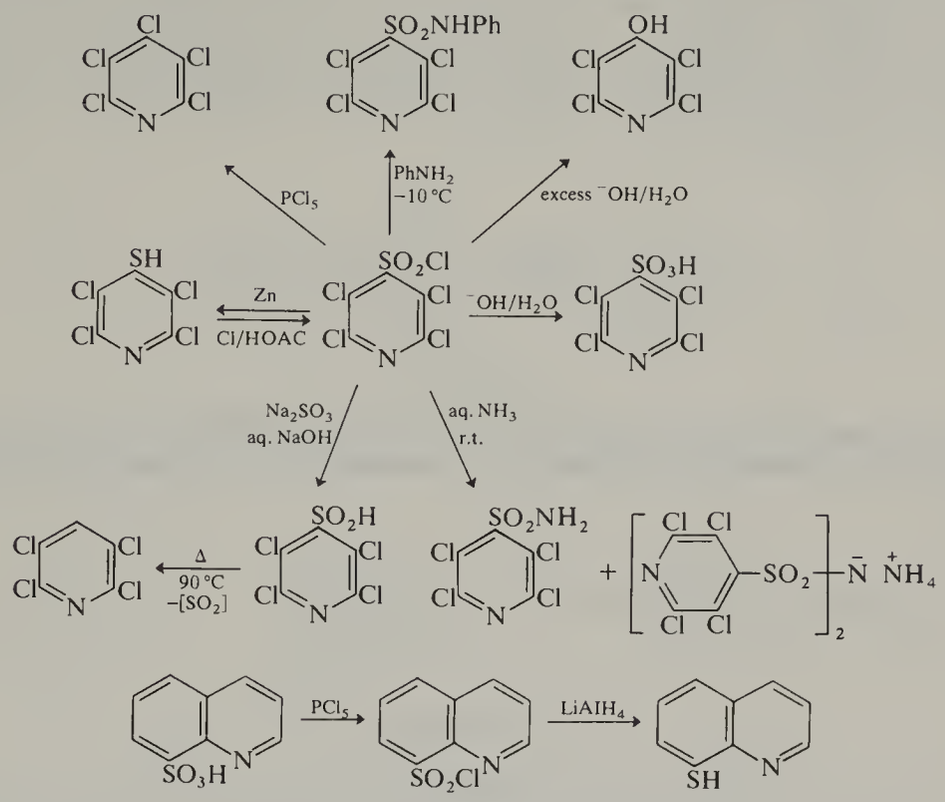


(**138**) (**139**) 86% (**140**) (**141**) 75–80%

Scheme 130

Pyridine-3-sulfonic acid is converted to the sulfonyl chloride with phosphorus pentachloride and the 2-isomer results from treatment of the corresponding sodium sulfonate

with benzotrichloride. Pyridinesulfonyl chlorides have also been prepared by oxidation of the corresponding thiols with hypochlorite or chlorine. A large variety of products can be obtained from the sulfonyl chlorides and examples are shown in Scheme 131 ⟨70JCS(C)1530, 63CJC1646⟩.



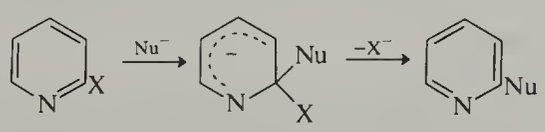
Scheme 131

2.06.7 HALOGEN SUBSTITUENTS

2.06.7.1 Nucleophilic Displacement

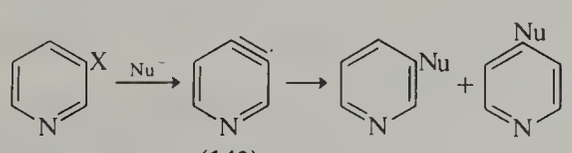
The α-, β- and γ-halogeno substituents in pyridines and their benzo analogues are each more susceptible to nucleophilic substitution than is the case for halobenzenes because of the overall electron deficiency of the heteroaromatic ring. Furthermore, halogen substituents α and γ to nitrogen are usually more reactive than β-halogens and this is particularly so in pyridinium type systems.

The majority of reactions involving loss of halogen are the addition–elimination (*AE*) type, in which the nucleophile adds at the carbon carrying the halogen, followed by elimination of halide. This occurs most readily when the halogen is α or γ to ring nitrogen, *e.g.* Scheme 132.



Scheme 132

The other common mechanism involving loss of halogen is the elimination–addition (*EA*) type in which, usually, a strong base attacks at hydrogen with elimination of adjacent halogen leading to a hetaryne, *e.g.* pyridyne (**142**). The halogen is normally at an unactivated position, *i.e.* β (Scheme 133) ⟨82T427⟩.

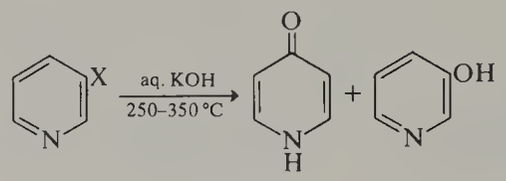


(142)

Scheme 133

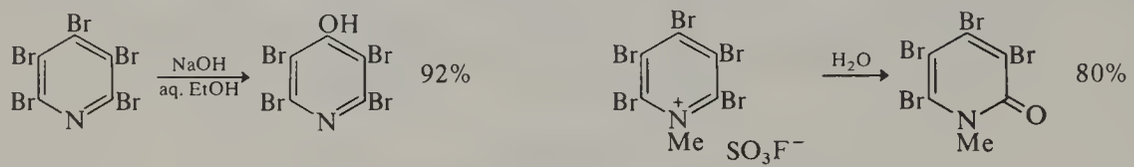
2.06.7.1.1 Oxygen and Sulfur Nucleophiles

Displacement of halogen by oxygen nucleophiles is extremely common. Hydrolysis of 2- and 4-halopyridines occurs with relative ease. Either aqueous base or acid may be used, the latter being more efficient due to protonation of ring nitrogen assisting nucleophilic attack. Substitution of a β-halogen requires higher temperatures and the aryne mechanism competes with direct substitution. Involvement of 3,4-pyridyne leads to a mixture of 3-hydroxypyridine and pyrid-4-one (Scheme 134). The 3:4 isomer ratio decreases in the order Cl > Br > I ⟨71JOC1455⟩.



Scheme 134

Hydrolysis of pentahalogenopyridines usually proceeds initially at position 4, whereas *N*-alkylated derivatives are first substituted at position 2, *e.g.* Scheme 135 ⟨73JCS(P1)2839, 70JCS(C)1523⟩.



Scheme 135

Alkoxide ions also displace α- and γ-halogens relatively readily and the reaction will also proceed with β-isomers; there seem to be fewer reports of pyridyne intermediates ⟨74RTC166, 70JOC3462⟩. As expected, 2- and 4-halogenopyridinium salts and *N*-oxides react more readily with oxygen nucleophiles than do the corresponding uncharged halogenopyridines.

In general, 2-halogenoquinolines show greater reactivity than the 4-isomers. For example, 2,4-dichloroquinoline gives 4-chloro-2-ethoxyquinoline with ethanolic potassium hydroxide. However, the ratio of 2- to 4-substitution products can be reversed in some cases by variation of the reaction conditions. In the isoquinoline series, halogen at the 1-position is more susceptible to substitution than at the 3-position; 1,3-dichloroisoquinoline with sodium ethoxide gives 3-chloro-1-ethoxyisoquinoline. 6-Chlorophenanthridine, although unreactive towards sodium hydroxide, is converted into 6-methoxyphenanthridine with sodium methoxide.

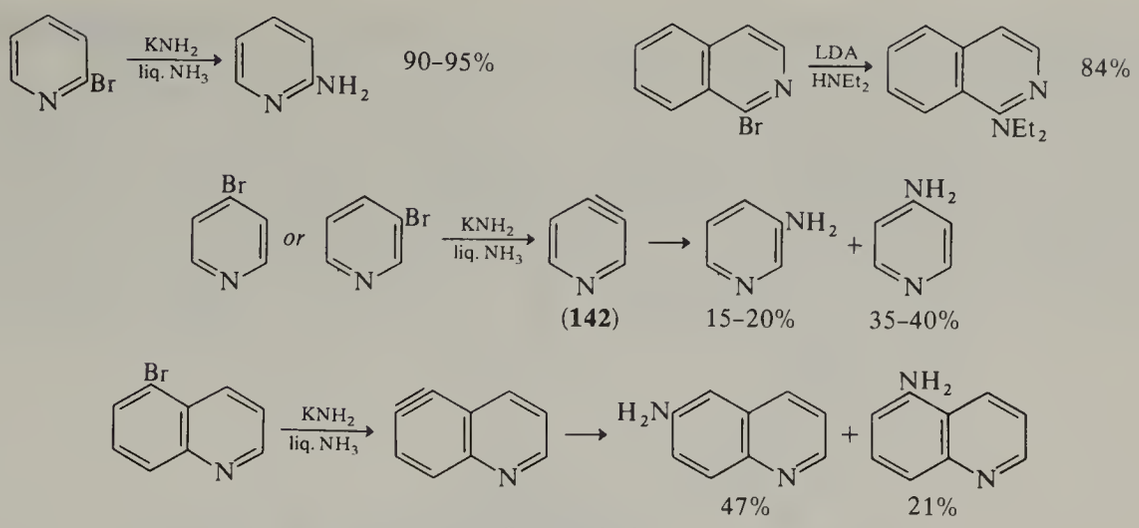
Analogous substitution reactions take place with alkane- and arene-thiolate anions ⟨73JCS(P1)1689⟩, and pyridine-2- and -4-thiones are usually prepared by use of sodium or potassium hydrogen sulfide or thiourea ⟨74JCS(P1)2300⟩.

2.06.7.1.2 Nitrogen nucleophiles

Ammonia and amines will displace activated halogens, *i.e.* those sited α or γ to the ring nitrogen, or *ortho* or *para* to an electron withdrawing group. The process is facilitated by a positively charged heteroatom and so catalysis by acids, zinc chloride, *etc.* and copper sulfate is common. Copper sulfate even assists the substitution of β-halogens. Weaker nucleophiles such as arylamines usually require higher temperatures and copper bronze has been used as catalyst. As expected, the substitution processes with pyridinium salts or *N*-oxides proceed more readily ⟨60JCS4953⟩. Loss of *N*-oxide oxygen can also occur.

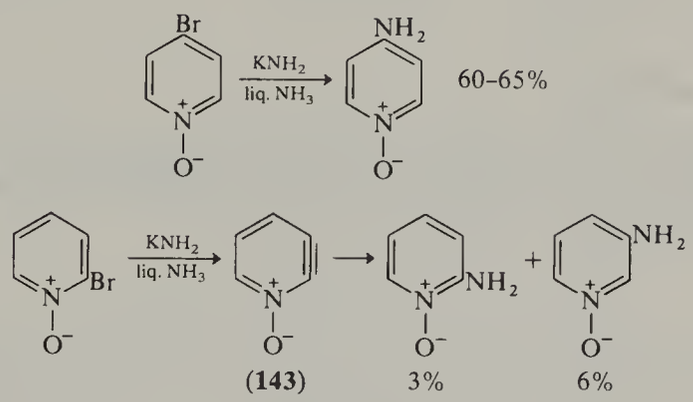
Pyridine itself will substitute α- and γ-halogenopyridines, giving *N*-(2- or 4-pyridyl)pyridinium salts. Self-quaternization of halogenopyridines can also occur and is most common with 4-fluoropyridines ⟨58BSF424⟩.

Use of an amide ion to replace halogen can proceed by an *AE* or *EA* mechanism. Direct substitution (*AE*) of halogen α to ring nitrogen is usually observed ⟨69CB1161, 74RTC195⟩. β-Halogenopyridines usually react by the pyridyne (*EA*) mechanism, but the two mechanisms compete in substitutions of 3-fluoropyridine and of 4-halogenopyridines. Some examples are shown in Scheme 136 ⟨82T427, 75S733⟩.



Scheme 136

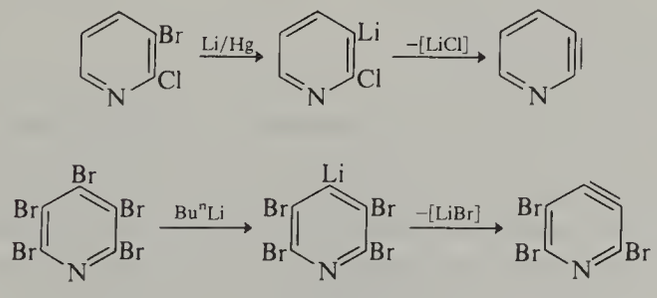
With pyridine *N*-oxides the situation is reversed in that amide ion reacts at the 4-position by the *AE* mechanism but at the 2-position by the *EA* mechanism, albeit in poor yield (Scheme 137) ⟨67RTC655⟩.



Scheme 137

It can be seen from examples in Scheme 136 and 137 that nucleophilic addition to the hetarynes (**142**) and (**143**) leads to unequal amounts of two products. Since in the addition step the nucleophile gives initially a pyridyl anion, the orientation of addition is such that the more stable anion will be preferred. The order of pyridyl anion stabilities is 3 > 4 > 2 whereas for anions of the corresponding *N*-oxides it is 2 > 3 > 4 and the observed orientations are in accord with this ⟨69JOC1405, 69JA2590, 67CC55⟩. The situation is changed by an alkoxy group *ortho* to the dehydro bond in that it directs the incoming nucleophile to the *meta* position, presumably for steric reasons and by stabilizing the anion on the adjacent centre by inductive electron withdrawal.

Pyridynes are also commonly generated from *ortho*-dihalogenopyridines by lithium exchange processes, *e.g.* Scheme 138, and processes not involving halogenopyridines, *e.g.* thermal decomposition of pyridinediazonium carboxylates.

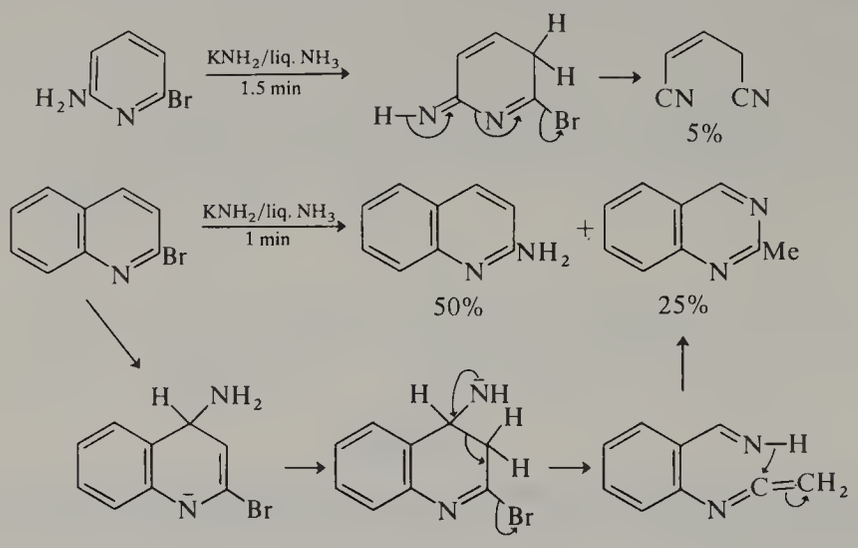


Scheme 138

Reviews of hetaryne chemistry are available ⟨82T427, 71AG(E)20, B-67MI20604, 65AG(E)543, 65AHC(4)121⟩.

The final group of reactions involving amide ion attack on halogenopyridines and their benzo analogues concerns processes which give ring openings. In some remarkable cases rearrangement and closure can follow: these follow the *ANRORC* mechanism (*A*ddition

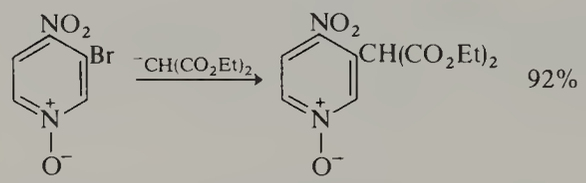
of *N*ucleophile, *R*ing *O*pening, *R*ing *C*losure). An example of a simple ring opening and of an *ANRORC* process is shown in Scheme 139 ⟨73TL1887, 69RTC1391, 67RTC187⟩.



Scheme 139

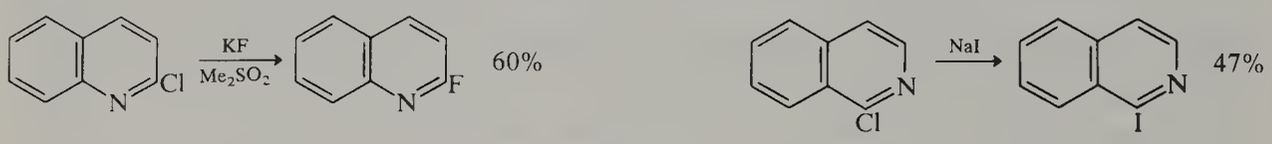
2.06.7.1.3 Other nucleophiles

Stabilized carbanions will substitute α- and γ-halogenopyridines and their benzo analogues. Substitution at the β-position is much less common and requires the presence of suitable activating groups, *e.g.* Scheme 140 ⟨73BCJ3144⟩.



Scheme 140

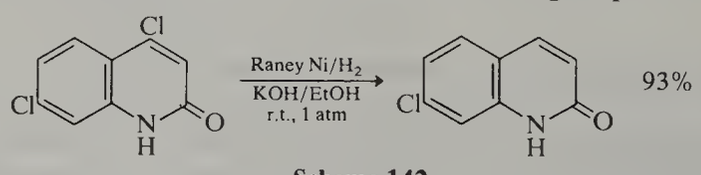
Halogen exchange reactions can occur easily at the α- and γ-positions, *e.g.* Scheme 141 ⟨62RTC1058, 67YZ1342⟩, particularly if the ring nitrogen carries a positive charge. The principal value in such processes is in the preparation of polyfluorinated pyridines. Pentachloropyridine is converted into pentafluoropyridine by use of potassium fluoride at elevated temperatures, the exchange proceeding the most slowly at β-positions ⟨64JCS3573⟩.



Scheme 141

2.06.7.2 Reductive Dehalogenation

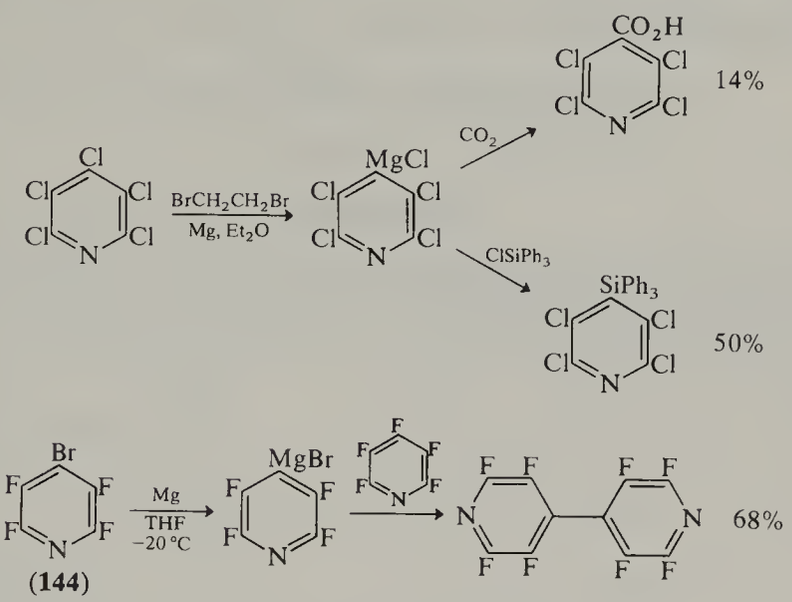
Reductive removal of halogen can be effected by palladium-catalyzed hydrogenolysis. Also, halogens sited at α- and γ-positions to nitrogen can be reduced selectively with zinc and acid, and with hydriodic acid and phosphorus. Lithium aluminum hydride has been used to achieve selective reduction of polychloropyridines. For example, the main product at room temperature from pentachloropyridine is 2,3,6-trichloropyridine ⟨70JCS(C)1375⟩. An example of selective reduction in the quinoline series, using Raney nickel, is shown in Scheme 142. Further hydrogenation removes the 7-chloro group.



Scheme 142

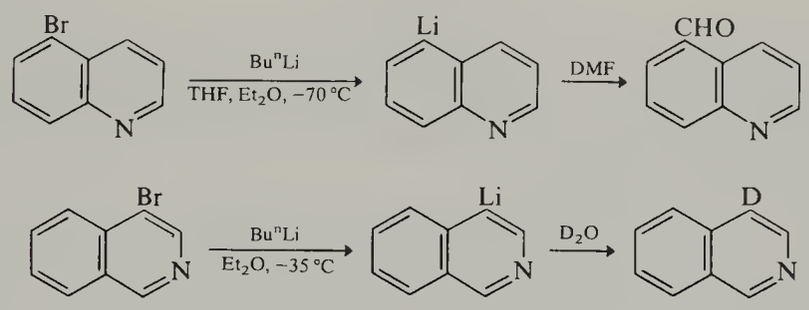
2.06.8 METALS

Halogenopyridines under normal conditions do not readily form Grignard reagents. The reagents can be prepared, however, by the entrainment method, which involves adding a small quantity of ethyl bromide or dibromoethane to 2- or 3-bromopyridine (for example) and magnesium in dry ether. Modest yields of pyridylmagnesium bromides result ⟨65RTC439, 68JOM(13)15⟩. Polyfluorohalopyridines, *e.g.* (**144**), have, however, been converted directly into Grignard reagents with magnesium ⟨65JCS5040⟩. Some reactions are shown in Scheme 143 ⟨68JOM(12)299⟩.



Scheme 143

Halogeno-quinolines and -isoquinolines cannot be successfully converted into Grignard reagents but lithium derivatives can be formed from bromo compounds and butyllithium, using low temperatures to prevent addition to the azomethine double bond (Scheme 144) ⟨79JCS(P1)266, 69JHC243⟩.

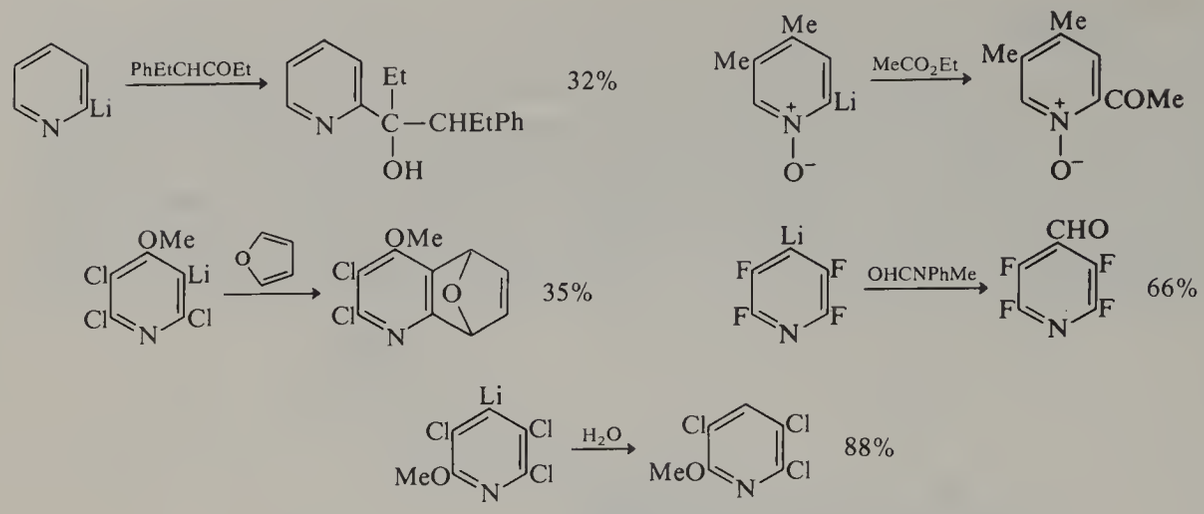


Scheme 144

Pyridyllithium reagents are not formed by interaction of halogenopyridines with lithium metals but by halogen–metal exchange with an alkyllithium, usually *n*-butyllithium. Again the reaction is carried out at low temperature to minimize competing processes. Direct metallation, though relatively unusual, has recently been observed with some halopyridines and with other substrates; for example, 2-fluoropyridine with LDA gives lithiation at the 3-position, *i.e. ortho* to the fluoro group ⟨81JOM(215)139, 81JOC4494, 80TL4137, 73JCS(P1)1125, 81JOC3564, 81S127⟩.

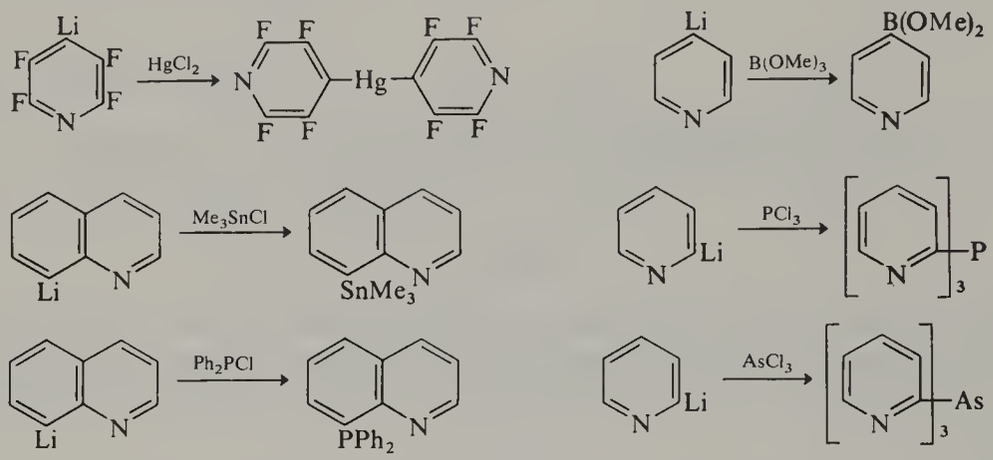
2-Pyridyllithium can be converted into 2-pyridylmagnesium bromide by reaction with magnesium bromide. However, it is the pyridyllithiums, rather than the pyridyl Grignard reagents, which have found most use as synthetic intermediates. It was mentioned earlier (Section 2.06.7.1.2, Scheme 138) that pyridyllithium compounds carrying a halogen *ortho* to the metal can eliminate lithium halide to generate a pyridyne.

Pyridyllithium compounds undergo a wide range of reactions, for example with esters, aldehydes, ketones, nitriles and carbon dioxide. The subject has been reviewed ⟨74HC (14-2)489⟩. Some examples are shown in Scheme 145 ⟨72JOC3584, 71JCS(C)1227, 70JMC359, 69JCS(C)1908, 69JCS(C)1700⟩.



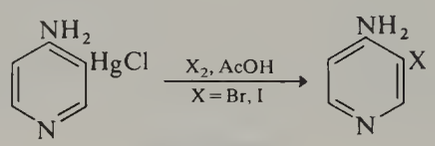
Scheme 145

Pyridyllithiums and their benzo analogues can be used for the introduction of other metals, and non-metals, on to the ring, such as mercury, boron, phosphorus, tin and arsenic (Scheme 146) ⟨80JOC1514, 67TL1705, 65RTC439⟩.



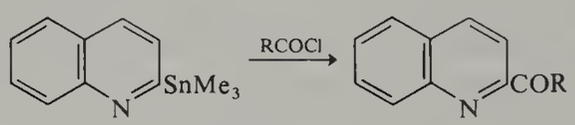
Scheme 146

Pyridyl-phosphorus and -arsenic compounds have also been made by nucleophilic displacement reactions with, for example, 3-pyridinediazonium salts ⟨74HC(14-2)489⟩. Organomercury derivatives can be converted into bromides and iodides by standard methods, *e.g.* Scheme 147 ⟨59JPR(8)156⟩.



Scheme 147

Trimethylstannyl-pyridines and -quinolines have been used for the introduction of an acyl group into the nucleus. The reaction occurs most readily with the 2-isomers, *e.g.* Scheme 148 ⟨82H(19)41⟩.



Scheme 148

2.07

Pyridines and their Benzo Derivatives: (iv) Reactivity of Non-aromatics

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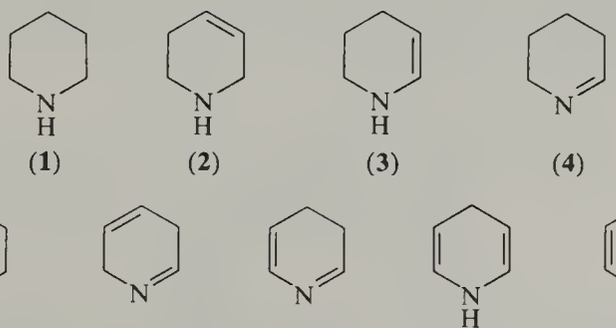
State University of New York at Stony Brook

2.07.1 GENERAL SURVEY OF REACTIVITY

The simple non-aromatic pyridines discussed in this Section are represented by nine structures (**1**)–(**9**). These are the fully saturated piperidine (**1**), the tetrahydropyridines (**2**)–(**4**) and the dihydropyridines (**5**)–(**9**). In this section (**2**), (**3**) and (**4**) will be referred to as Δ^3-, Δ^2- and Δ^1-piperideine as well as 1,2,3,6-, 1,2,3,4- and 2,3,4,5-tetrahydropyridine. The former designation is rather archaic but less cumbersome and it has also been used by other authors of the review literature in this area ⟨74HC(14-S1)1⟩. The latter designation is used by *Chemical Abstracts*.



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

(**5**) (**6**) (**7**) (**8**) (**9**)

The reduced pyridines have been periodically reviewed. The most recent of these was written by Lyle and covers the literature through 1973 ⟨74HC(14-S1)1⟩. There is an excellent review available on dihydropyridines by Eisner and Kuthan which was published in 1972 ⟨72CRV1⟩. Although this review covers all dihydropyridines, it is primarily concerned with

the 1,2- and 1,4-dihydropyridines for which a larger body of literature exists. The Δ^3-piperideines were reviewed in 1970 ⟨70AHC(12)43⟩ by Ferles and Pliml.

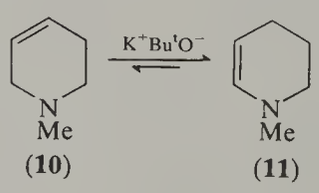
In addition to the reviews completely devoted to the reduced pyridines, there are a number of articles which discuss these ring systems in connection with other subjects. In a 1966 article by Blaha and Cervinka ⟨66AHC(6)147⟩ on cyclic imines and enamines there are several references to Δ^1- and Δ^2-piperideines. The monograph 'Photochemistry of Heterocyclic Compounds' edited by Buchardt has a chapter on the photoisomerization of six-membered heterocycles ⟨B-76PH1⟩ which contains many examples of the reduced pyridines. 'Rodd's Chemistry of Carbon Compounds' has many sections devoted to reduced pyridine derivatives ⟨B-76MI20700⟩ and their benzo analogs ⟨B-76MI20701, B-76MI20702, B-76MI20703⟩.

Except for piperidine, the reduced pyridines contain at least one double bond and are generally characterized by high reactivity. These heterocycles are not stabilized by aromaticity and most contain polarized double bonds ranging from the electron-deficient imine to the electron-rich enamine. Because of this reactivity, synthetic routes to most of the reduced pyridines have been limited and their chemistry has not been extensively studied. In fact, much of the knowledge of these reactive ring systems has been obtained only in recent years. Because many of these compounds are proving to be valuable intermediates for organic synthesis, the study of the reduced pyridines is proving to be one of the more rapidly developing fields of heterocyclic chemistry.

2.07.2 THERMAL AND PHOTOCHEMICAL REACTIONS INVOLVING NO OTHER SPECIES

When considering the thermal chemistry of isomeric compounds such as the tetra- and di-hydropyridines, the question of their relative stability naturally arises. In the piperideine series (**2**), (**3**), and (**4**) it is generally assumed that the Δ^1-isomer is the most stable. The Δ^1-piperideine is frequently generated under conditions that would allow tautomerism to the Δ^2-isomer. This is not a surprising situation since imines, because of the greater strength of the carbon–nitrogen π-bond, are generally more stable than their enamine tautomers. It has also been assumed that the Δ^2-piperideine (enamine **3**) is more stable than the Δ^3-isomer (allyl amine **2**). It is well known that structures are more stable with heteroatoms containing lone pairs of electrons attached directly to a double bond. The primary reason for this greater stability is generally believed to be the stabilization that results from the interaction of the lone pair of electrons with the double bond. Although the relative stabilities of the σ-frameworks may also be involved, the roles that these two factors play have not been evaluated.

The equilibria among all the piperideines has not been directly determined. However, it is known that the *N*-methyl-Δ^3-piperideine (**10**) rearranges to the Δ^2-isomer (**11**) when treated with strong base ⟨78T3027⟩. By measuring the amount of the Δ^3-isomer remaining after equilibration it has been estimated that the Δ^2-isomer is more stable by at least 16.7 kJ mol^{-1} at 91.6 °C ⟨80JOC1336⟩. This value is larger than is generally assumed for enamine resonance energy. The magnitude of the above value and reactivity of the Δ^2-piperideine are probably a result of structural constraints imposed by the ring that favor a strong interaction between the lone pair of electrons on nitrogen and the double bond. This feature is characteristic of all the endocyclic enamines present in the reduced pyridines and is one that sets them apart from the acyclic analogs.

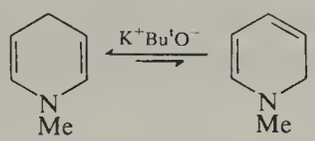


(**10**) (**11**) (1)

The relative stabilities of the dihydropyridines have also attracted attention over the years. Because of the reactivity of the dihydropyridines much of the research concerning the relative stabilities has been of a theoretical nature ⟨78JA4946, 81CCC2068⟩. Although the stability series is a sensitive function of the method of calculation, there is agreement that the 1,4-dihydropyridine is more stable than the 1,2-isomer. There is disagreement with

respect to the relative stabilities of the 6π-electron (**8** and **9**) and the 4π-electron (**5**, **6** and **7**) dihydropyridines.

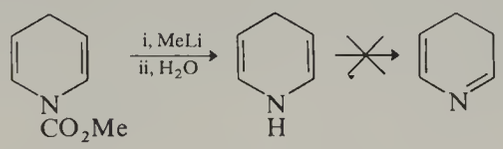
Direct experimental data regarding this problem are sparse. Over the years many investigators have been led to believe that the 1,4-dihydropyridine ring system is more stable than the 1,2-isomer. Direct equilibration of the *N*-methyl derivatives (**12**) and (**13**) gave an energy difference between these two structures of 9.58 kJ mol^{-1} at 91.6 °C ⟨72JA5926⟩.



(2)

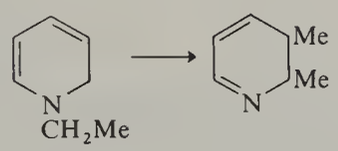
(**12**) (**13**)

Indirect evidence suggests that the 1,4-dihydropyridine is more stable than its 3,4-isomer and that the 2,3-dihydropyridine is more stable than the 1,2-isomer. The 1,4-dihydropyridine (**8**) shows no tendency to tautomerize to the 3,4-dihydropyridine (**7**) even when present in a basic aqueous environment ⟨74JOC560⟩, indicating that (**8**) is a relatively stable enamine. It is also known that 1,2-dihydropyridines rearrange in the gas phase to 2,3-dihydropyridines ⟨78JA6696⟩, suggesting that the latter is a more stable ring system (equation 3). Clearly, more experimental work is needed to resolve the problem regarding the relative stabilities of the dihydropyridines.



(**8**) (**7**)

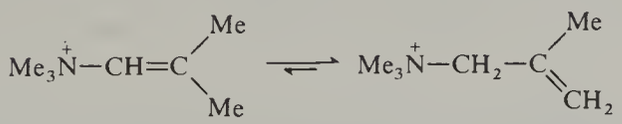
Scheme 1



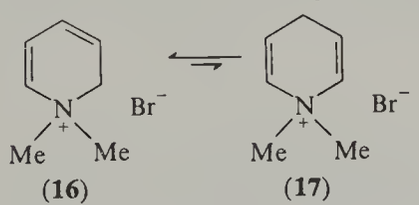
(3)

(**14**) (**15**)

The equilibrium for unsaturated amines favors the allyl rather than the vinyl derivative when the nitrogen atom is in the quaternary amine salt form (equation 4) ⟨66JA3376⟩. It has also been assumed that the *N*,*N*-dimethyl-1,2-dihydropyridinium bromide (**16**) is more stable than the 1,4-isomer (**17**) since complete deuterium exchange can be accomplished without isomerization ⟨66JA3376⟩.

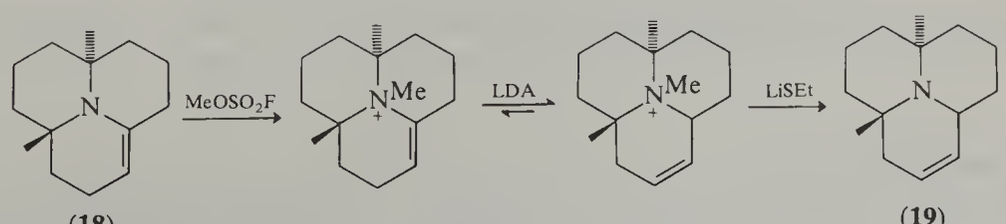


(4)



(**16**) (**17**)

The quaternization of the nitrogen atom in these unsaturated amines alters considerably the position of the equilibrium. This fact has been taken advantage of in the synthesis (Scheme 2) of the ladybug alkaloid coccinellin ⟨79TL1991⟩.

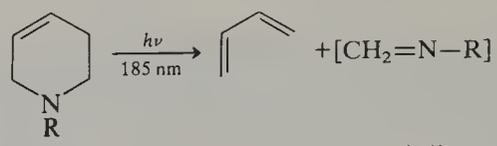


(**18**) (**19**)

Scheme 2

2.07.2.1 Piperideines

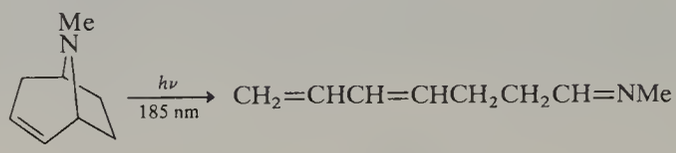
Piperidine and its simple derivatives lack significant absorption in the UV region, and as a consequence there is little information available on the photochemical behavior of these compounds. The Δ^3-piperideines (1,2,3,6-tetrahydropyridines) also lack strong absorption above 200 nm but they have recently been studied in the vacuum UV region. Irradiation of these compounds at 185 nm results in a retro Diels–Alder reaction ⟨79TL1955⟩. For example, the parent compound (**20a**) and the simple *N*-methyl derivative (**20b**) both give butadiene and products derived formally from the imine (**21**). Interestingly, irradiation of the tropane derivative (**22**) results in an intramolecular retro Diels–Alder reaction to give the imine (**23**).



(5)

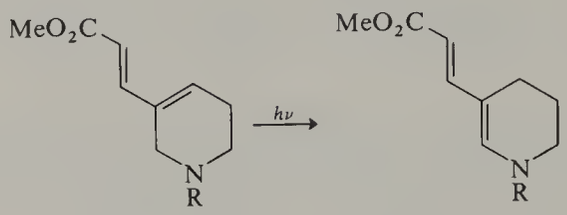
(**20a**) R = H
(**20b**) R = Me

(**21**)



(6)

(**22**) (**23**)

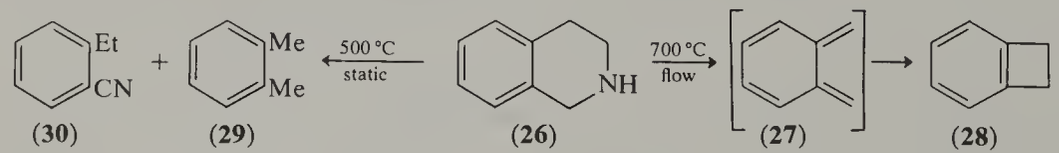


(7)

(**24**) (**25**)

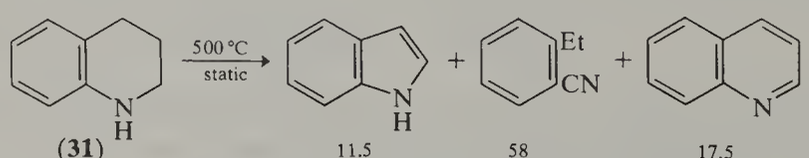
There is a report of a 1,2,3,6-tetrahydropyridine (**24**) undergoing a photochemical rearrangement to the enamine isomer (**25**) ⟨B-80MI20700⟩. This isomerization has synthetic possibilities but its generality will have to await further study.

Taking the lead from mass spectral studies, the thermal chemistry of tetralin and heterocyclic analogs has been explored ⟨70JCS(B)1727⟩. Heating 1,2,3,4-tetrahydroisoquinoline (**26**) in a flow apparatus resulted in a retro Diels–Alder reaction to give *o*-quinodimethane (**27**). Although this compound was trapped with dienophiles, its existence was usually inferred by the isolation of benzocyclobutene as the major product. In a static system the thermochemistry was more complicated. Heating (**26**) at 500 °C in a pyrolysis tube gave *o*-xylene (**29**) and *o*-ethylbenzonitrile (**30**). Only a trace of the benzocyclobutene (**28**) was observed.



(8)

(**30**) (**29**) (**26**) (**27**) (**28**)



(9)

(**31**) 11.5 58 17.5

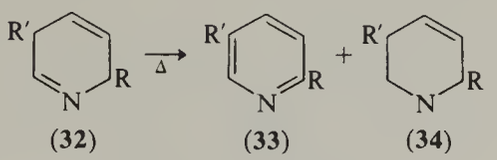
relative molecular abundances

The isomeric tetrahydroquinoline (**31**) shows no tendency to undergo a retro Diels–Alder reaction. The products of its thermal reactions were the result of more complicated processes.

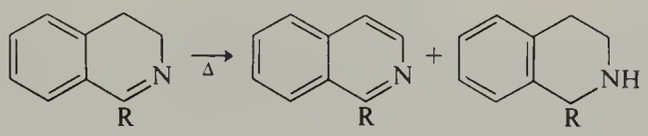
2.07.2.2 Dihydropyridines

Dihydropyridines are known to disproportionate into pyridines and tetrahydropyridines ⟨72CRV1⟩. This reaction is more common than is reported. It probably is the primary source

of pyridine and tetrahydropyridines that are frequently observed as impurities when working with dihydropyridines. For example, distillation of a series of 2,5-disubstituted 2,5-dihydropyridines (**32**) resulted in disproportionation to (**33**) and (**34**) ⟨78JOC3227⟩. This reaction is known among the benzo derivatives as well. Distillation of dihydroisoquinolines at atmospheric pressure frequently results in disproportionation (equation 11) ⟨B-76MI20701, B-76MI20702, B-76MI20703⟩.

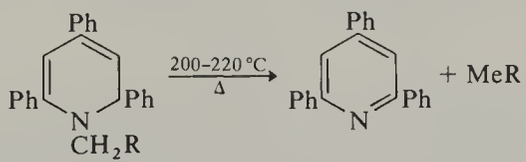


(**32**) (**33**) (**34**) (10)

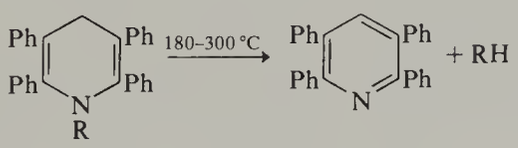


(**35**) (**36**) (**37**) (11)

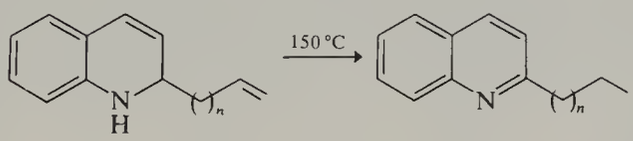
The tendency of dihydropyridines to be converted into pyridines on heating has been developed as a synthetic method for the replacement of the amino group by hydrogen. Heating either 1,2- ⟨79JCS(P1)442⟩ or 1,4-dihydropyridines ⟨79CC300⟩ gave the pyridine derivatives and reduced nitrogen substituents. The 1,4-dihydropyridines were more synthetically useful since a wider range of nitrogen substituents could be reduced (equations 12 and 13). Preliminary studies on the mechanism of this reaction indicate that the 1,2-dihydropyridine derivative decomposes by a free radical pathway.



(**38**) R = aromatic or allyl (**39**) (12)



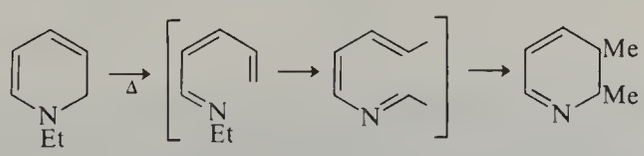
(**40**) R = aromatic, alkyl, CH_2Ar (**41**) (13)



$n = 0, 1$ (14)

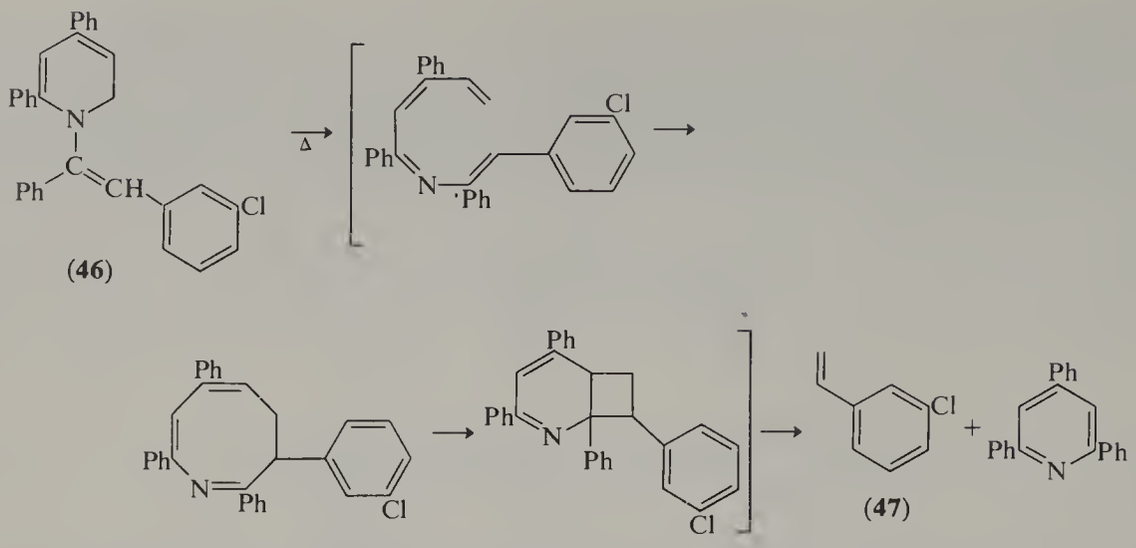
A related reaction has been observed with alkenyl substituted 1,2-dihydroquinolines. Heating these compounds results in oxidation of the heterocycle with corresponding reduction of the double bond. A radical mechanism was also postulated to be operating in this reaction (equation 14) ⟨75JOC2288⟩.

Dihydropyridines with conjugated double bonds have the possibility, by analogy to the cyclohexadienes, of ring opening to the open chain trienes at high temperature. Heating *N*-ethyl-1,2-dihydropyridine (**42**) in the gas phase resulted in the formation of 2,3-dimethyl-2,3-dihydropyridine (**45**) ⟨78JA6696⟩. This reaction has been postulated to proceed through the imine (**43**) which undergoes a 1,7-hydrogen shift followed by electrocyclic ring closure to give the 2,3-dihydropyridine (**45**).



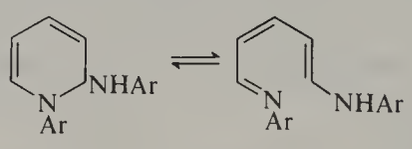
(**42**) (**43**) (**44**) (**45**) (15)

A similar thermal ring opening reaction has been postulated for the conversion of *N*-vinyl-1,2-dihydropyridine (**46**) to styrene (**47**) and triphenylpyridine. Ring opening to an acyclic polyene was also proposed (equation 16). This appears to be a general reaction of *N*-vinyl-1,2-dihydropyridines ⟨82JOC492⟩.



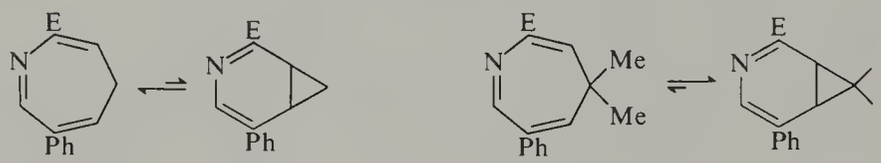
(46) (16) (47)

Related to the above are the reactions of pyridinium ions with nucleophiles. It has been known for many years that pyridinium ions can undergo ring-opening reactions with primary amines ⟨70JA5641⟩. Studies on the mechanisms of these reactions indicate that the interconversion of the dihydropyridine (**48**) with the acyclic dianils (**49**) of glutacondialdehyde is a key step in these reactions.



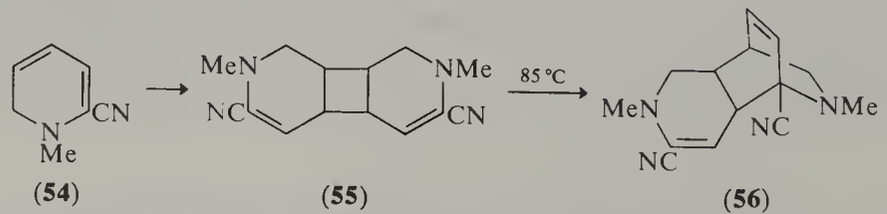
(48) (49) (17)

The bicyclic 3,4-dihydropyridines (**51**) and (**53**) illustrate that the electrocyclic ring opening is sensitive to substituents ⟨80TL599⟩. The 3,4-dihydropyridine (**51**) has been observed to be in equilibrium with the azepine (**50**). Consistent with the analogous carbocyclic system, norcaradiene–cycloheptatriene, the monocycle (**50**) is the predominant species present in this equilibrium. In contrast, the dimethyl derivatives (**52**) and (**53**) exist almost exclusively in the 3,4-dihydropyridine form. A greater steric interaction between these methyl substituents in (**52**) was given in explanation of these observations.



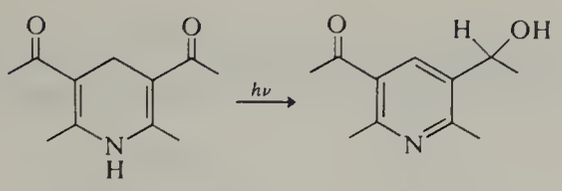
(**50**) E = CO_2Me (**51**) (**52**) (**53**)

An unusual thermal dimerization has been reported for the cyano-1,2-dihydropyridines. The preparation of (**54**), by the sodium borohydride reduction of the corresponding pyridinium ion, gave only the [2+2] dimer (**55**) ⟨75JOC559⟩. Heating this compound to 85 °C resulted in isomerization to the [2+4] dimer (**56**). This type of dimer appears to be restricted to the cyano-substituted dihydropyridines ⟨74HCA1204⟩.

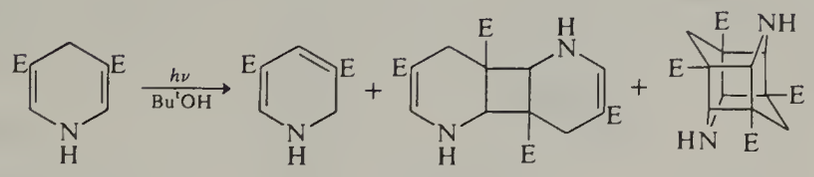


(**54**) (**55**) (**56**) (18)

Studies on the photochemical reactions of dihydropyridines have proven to be interesting. There are a number of 1,4-dihydropyridines that are known to disproportionate when irradiated (equation 19) ⟨B-76PH240⟩. Analogous intramolecular reductions have also been observed by other workers ⟨55JA447⟩. In contrast to these results, the 1,4-dihydropyridine (**59**) rearranged to its 1,2-dihydro isomer (**60**). Further irradiation resulted in dimerization. Interestingly, the photodimer (**61**) cyclized to the cage compound (**62**).

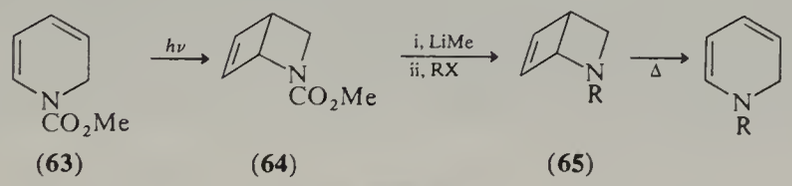


(57) (58) (19)



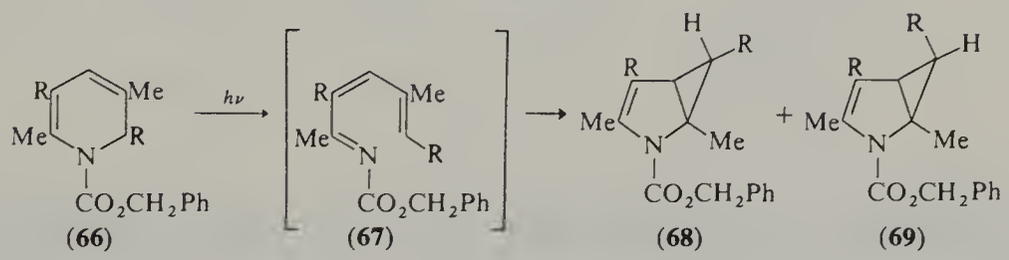
(59) E = CO_2Et (60) (61) (62) (20)

The simple 1,2-dihydropyridine (**63**) cyclizes to the 2-azabicyclo[2.2.0]hexene (**64**) derivative upon irradiation ⟨79JA6677⟩. This reaction is the basis of a general synthetic route to dihydropyridines that are difficult to prepare by other means (Scheme 3). Dihydropyridines with more complicated substitution patterns, *i.e.* (**66**), undergo a photochemical rearrangement to valence isomers (**68**) and (**69**) ⟨71T2957⟩. The 1-azahexatriene (**67**) is believed to be an intermediate in this reaction (equation 21).



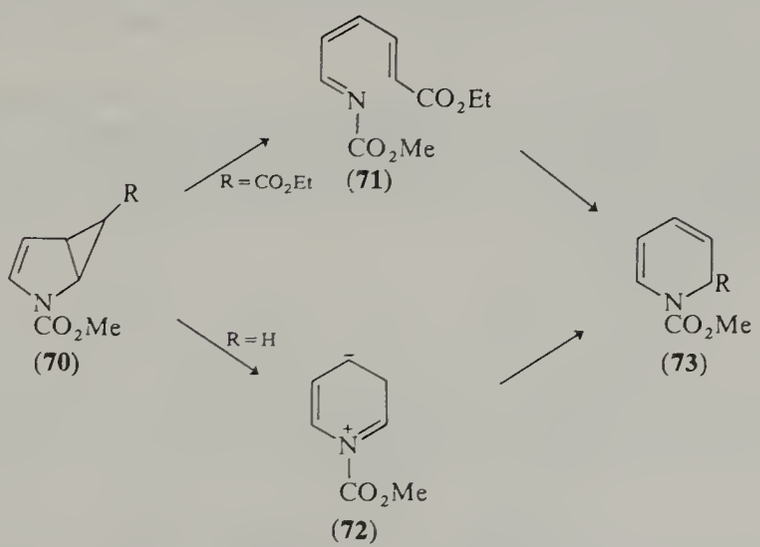
(63) (64) (65)

Scheme 3



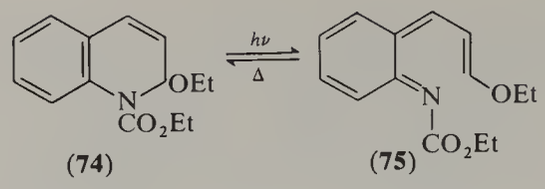
(66) (67) (68) (69) (21)

In connection with the above work, it should be noted that the 2-azabicyclo[3.1.0]hexene ring system can also be prepared by carbenoid addition to *N*-methoxycarbonylpyrrole. Thermally it rearranges to the dihydropyridine but the mechanistic pathway depends upon the substituent attached to the cyclopropane ring (equation 22) ⟨72JA6495⟩.

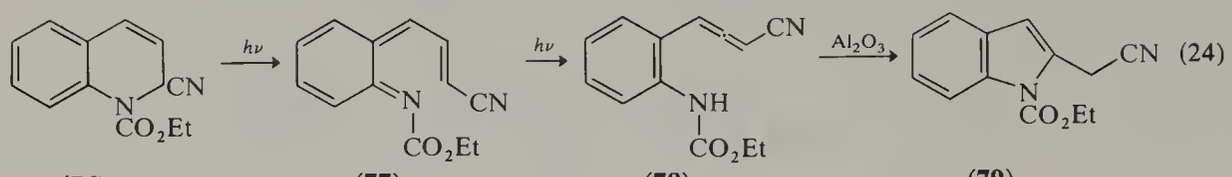


(70) (71) (72) (73) (22)

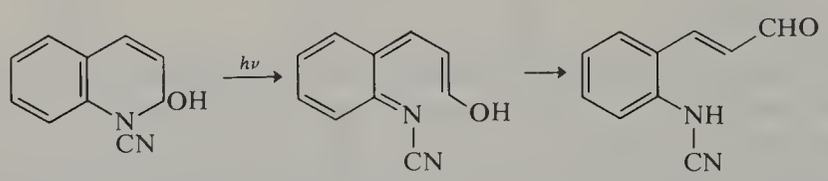
There are a number of 1,2-dihydroquinolines that are known to ring open when irradiated at low temperature. For example, irradiation of (**74**) at −196 °C in an EPA matrix results in the development of a pink color attributed to (**75**). Warming to room temperature causes reversion to (**74**). This cycle can be repeated several times with high conversions ⟨72JCS(P2)17⟩. The appropriate choice of substituents can result in transformations that have potential synthetic utility (equations 24 and 25) ⟨69JA6513, 73CC922⟩.



(74) (75) (23)

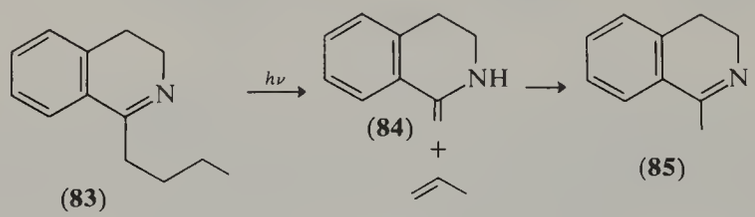


(76) (77) (78) (79) (24)



(80) (81) (82) (25)

The photochemistry of Δ^1-piperideines has been little studied but should yield some interesting results. In contrast to acyclic imines, which are photochemically relatively inert compared to carbonyl compounds, the cyclic analogs are considerably more reactive. It has been suggested that cyclic imines cannot become deactivated by twisting about the carbon–nitrogen double bond ⟨77CRV37⟩. An imine example of a Norrish type II fragmentation is given in equation (26) ⟨77CSR43⟩.



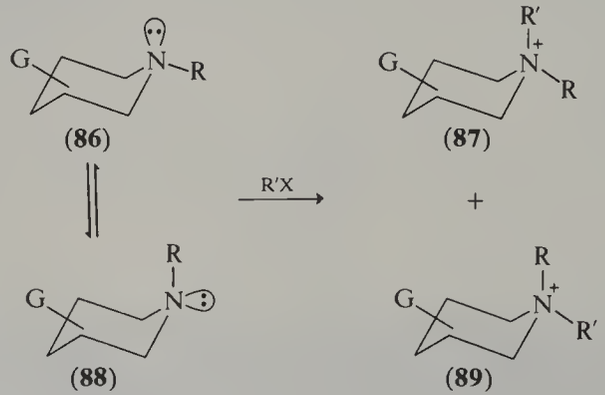
(26)

2.07.3 REACTIONS WITH ELECTROPHILES AND OXIDIZING AGENTS

2.07.3.1 Piperidines

The piperidines are saturated amines and their reactions are in accord with those generally observed for this functional group ⟨B-79MI20700⟩. This section will primarily be concerned with reactions that are of interest because the nitrogen comprises one of the atoms making up the six-membered ring.

The quaternization of amines is an extensively studied reaction in organic chemistry. The quaternization of piperidine can follow two distinct stereochemical pathways, axial or equatorial alkylation ⟨70MI20700⟩. Since the Curtin–Hammett principle is valid in this reacting system it is important to recognize that the product ratio of (**87**) to (**89**) does not directly reflect the ratio of (**86**) to (**88**).

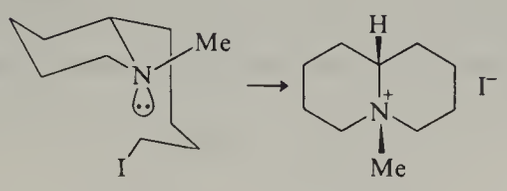


(27)

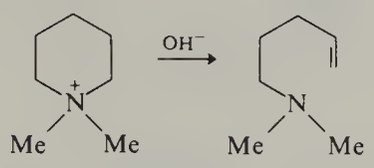
G = biasing group, reference group or fused ring

Overall, there is a slight preference for axial quaternization of piperidine derivatives (equation 28). The degradation of amines *via* these quaternary ammonium salts (Hofmann

elimination) has been used extensively in the past for structure elucidation. It is still an important synthetic method ⟨60OR(11)317⟩ that can be used for the synthesis of unsaturated amines that are difficult to obtain by other means (equation 29).



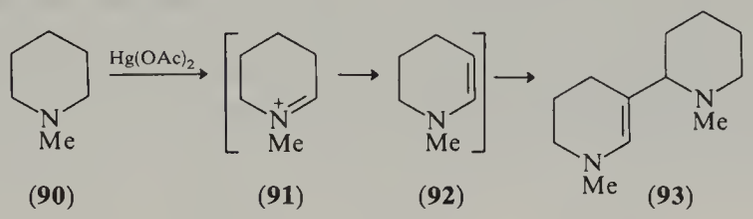
major product (28)



(29)

The reaction of piperidine derivatives with electrophilic and oxidizing agents has been an effective method for functionalizing the positions adjacent to the nitrogen atom. This can be a useful synthetic process and a number of these methods are presented below.

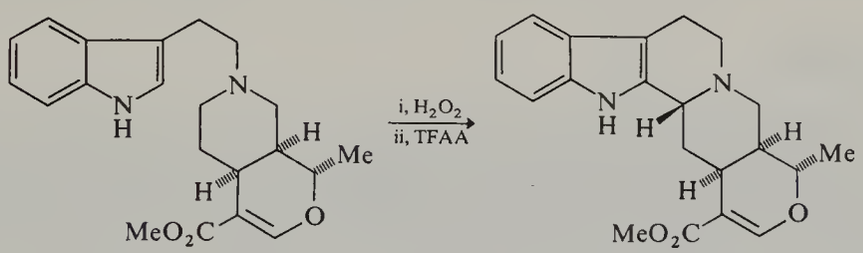
The mercury(II) acetate oxidation of tertiary amines is frequently used to introduce unsaturation into piperidine derivatives. The iminium ion is believed to be an intermediate in this reaction. These ions can give the enamine or react further with nucleophiles to give more complex heterocyclés (Scheme 4).



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

Scheme 4

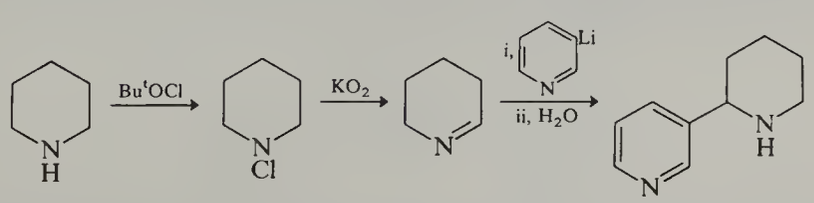
A related process shown to have value in alkaloid synthesis is the modified Polonovski reaction ⟨78MI20700⟩. Treatment of (**94**) with hydrogen peroxide followed by trifluoroacetic anhydride gave akuammigine (**95**) (Scheme 5). The analogous reaction using mercury(II) acetate gave the epimeric tetrahydroalstonine, suggesting that these two reactions do not proceed through the same intermediate. It was proposed that the modified Polonovski reaction involved the iminium ion whereas the reactive intermediate in the mercury(II) acetate oxidation was the α-acetoxy amine.



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

Scheme 5

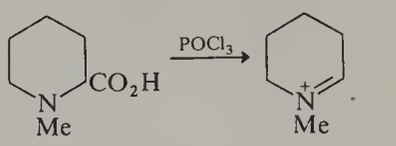
Piperidines can also be functionalized *via* the *N*-chloro derivatives. These are known to give imines when treated with base ⟨76S745⟩. Although there is little regiochemical control, the reaction provides a useful entry into the simple Δ^1-piperideines (Scheme 6) ⟨80JOC1515⟩.



(**96**) (±)-Anabasine (44%)

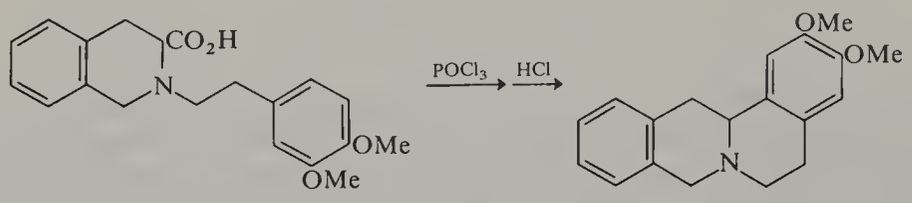
Scheme 6

The degradation of α-aminocarboxylic acids has proven to be a useful method for the preparation of iminium salts. For example, treatment of *N*-methylpipecolic acid (**97**) with phosphorus oxychloride gave 94% of the iminium salt (**98**) (Scheme 7) ⟨76JA7448⟩. The synthetic utility of this approach is illustrated by the synthesis of tetrahydroberberine (Scheme 8) ⟨78JOC2115⟩. The advantage of this method for the preparation of iminium salts is that the position of the carbon–nitrogen double bond can be controlled.



(**97**) (**98**) (94%)

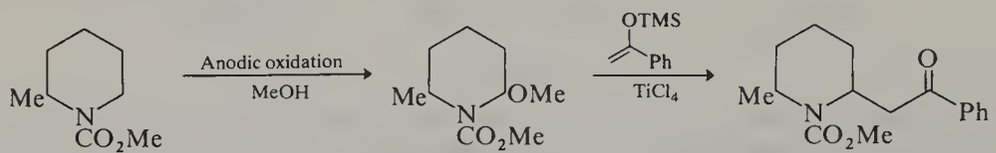
Scheme 7



(**99**) (**100**) 79%

Scheme 8

The electrolytic oxidation of *N*-methoxycarbonylpiperidines provides an interesting and potentially valuable method for the functionalization of piperidine derivatives ⟨81JA1172⟩. Anodic oxidation of piperidine (**101**) gave (**102**) which reacted, presumably through the acyl imine, with enol ethers to form a carbon–carbon bond α to the nitrogen atom (Scheme 9). The regiochemical control in this reaction is illustrated by the exclusive oxidation at the less substituted carbon atom ⟨55JA439⟩.



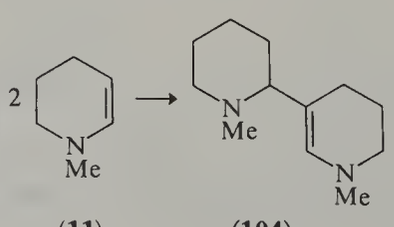
(**101**) (**102**) 70% (**103**) 74%

Scheme 9

It can be seen from the above discussion that the oxidation of piperidines can be a useful and often mild method for the preparation of carbon-substituted piperidines.

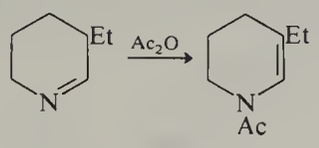
2.07.3.2 Piperideines

The Δ^1- and Δ^2-piperideines contain the imine and enamine functional groups respectively. The chemistry of these ring systems is interrelated, as is the chemistry of the imines and enamines. There is a much larger literature available on imines and enamines than on Δ^1- and Δ^2-piperideines ⟨B-79MI20701, B-79MI20702⟩. This information can be used to a large extent to predict the behavior of the analogous unsaturated heterocycles. However, it is important to recognize that the heterocyclic imines and enamines appear to be more reactive than their acyclic counterparts. For example, Δ^1-piperideine (**4**) has not been fully characterized. It is usually prepared *in situ* from one of a number of precursors. One of the simplest Δ^2-piperideines capable of isolation is the *N*-methyl derivative (**11**). In spite of several attempts ⟨78T3027⟩ this compound has only recently been characterized ⟨80JOC1336⟩. It is very reactive, rapidly dimerizing even simply in the presence of a glass surface (equation 30).

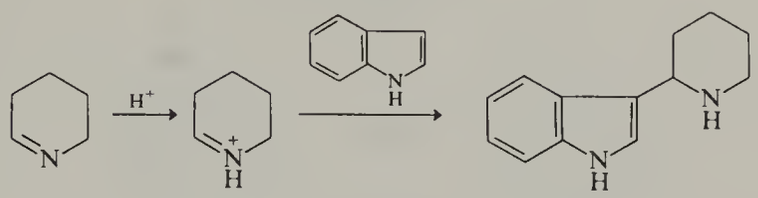


(**11**) (**104**) (30)

The imine group of Δ^1-piperideines, although very reactive, behaves as a typical carbon–nitrogen double bond. The π-bond is electron deficient and is not susceptible to attack by electrophilic reagents. However, the lone pair of electrons on nitrogen is basic and does react with electrophilic reagents. For example, acylation of imine (**105**) produces the enamide (**106**) ⟨72LA(759)84⟩. Protonation of Δ^1-piperideines occurs on nitrogen giving a reactive iminium compound. The reaction of these compounds with nucleophiles can provide a useful synthesis of 2-substituted piperidines (equation 32) ⟨55JA1860⟩.

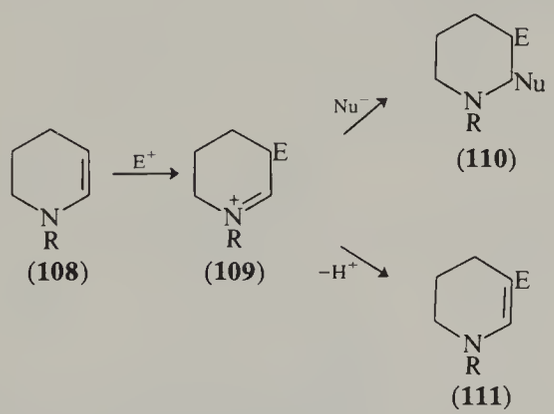


(**105**) (**106**) (31)



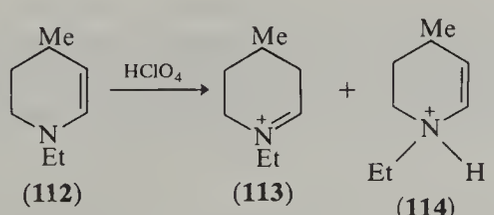
(**107**) 40–55% (32)

The Δ^2-piperideines are enamines and the carbon–carbon double bond is electron rich due to a π-interaction with the nitrogen lone pair of electrons. As a consequence this double bond is very reactive with respect to electrophilic addition. The resulting iminium ion (**109**) can either lose a proton to give another Δ^2-piperideine (**111**) or react with a nucleophile to give a piperidine derivative (**110**). This reactivity is typical of enamines but takes on special significance with these heterocycles since they can be valuable intermediates for alkaloid total synthesis ⟨77ACR193, 68ACR78⟩. In fact, analogous reactions are believed to be involved in alkaloid biosynthesis ⟨B-79MI20703⟩.



(**108**) (**109**) (**110**) (**111**) (33)

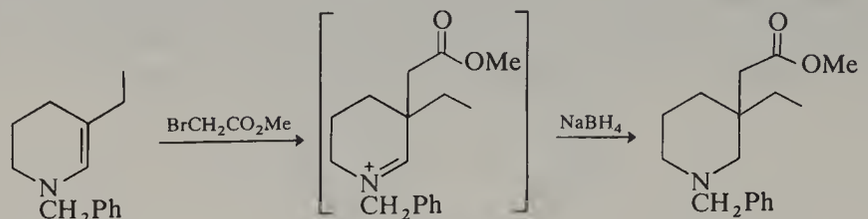
Electrophilic addition to Δ^2-piperideines can occur on either the nitrogen or the β-carbon atom of the double bond. These enamines are ambident nucleophiles and their reactivity is consistent with behavior of similar species. Electrophilic attack can occur on either the nitrogen or β-carbon atom. As the 'hardness' of the electrophile increases so does the relative rate of reaction on nitrogen ⟨B-73MI20700⟩. For example, kinetic protonation of enamines is believed to occur on nitrogen giving the vinylamine derivative whereas the thermodynamic product is the carbon-protonated iminium ion ⟨B-69MI20700⟩. Both carbon and nitrogen protonation have been observed to occur with the endocyclic enamines, Δ^2-piperideines (equation 34) ⟨57JA5279⟩.



(**112**) (**113**) (**114**) (34)

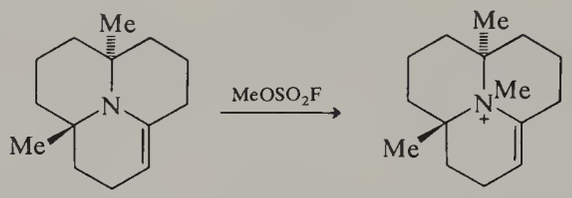
In general, alkylations as well as some acylations of enamines using halides as the leaving group occur predominantly on carbon ⟨B-69MI20700⟩. For example, treatment of Δ^2-piperideine (**115**) with methyl bromoacetate followed by sodium borohydride reduction

gave the piperidine (**117**) as the major product ⟨69JA2342⟩. However, as the 'hardness' of the alkylating agent is increased so is the probability of *N*-alkylation. For example, *N*-methylation of piperideine (**118**) has been accomplished using the relatively hard methylating agent methyl fluorosulfonate ⟨79TL1991⟩.



(**115**) (**116**) (**117**) 22%

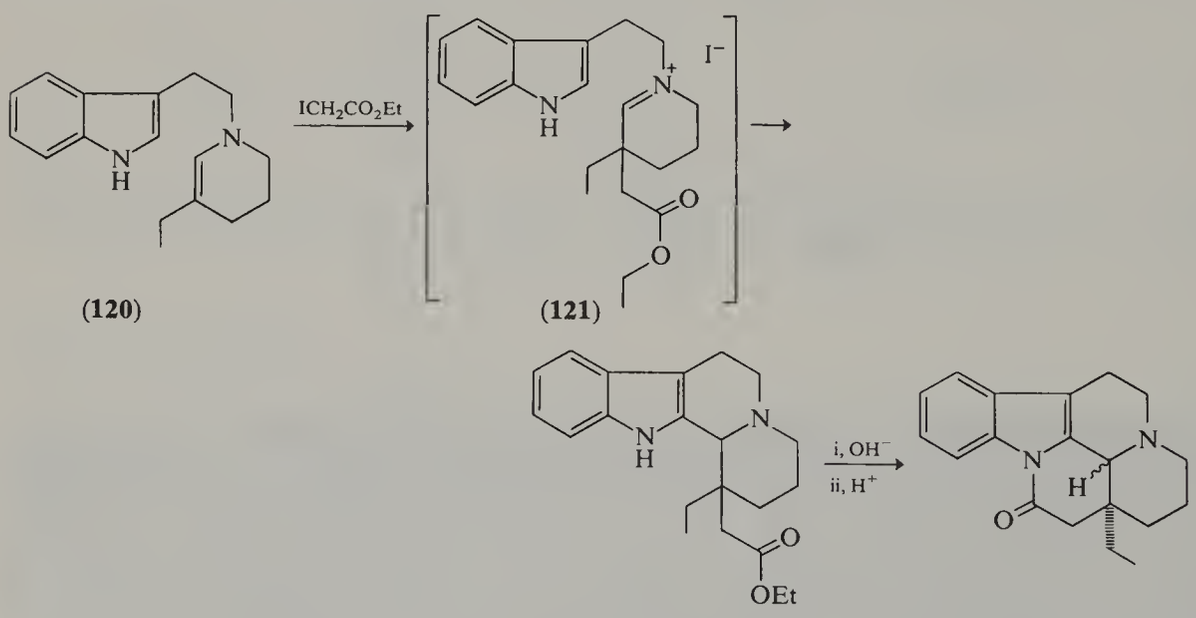
Scheme 10



(**118**) (**119**) 86%

Scheme 11

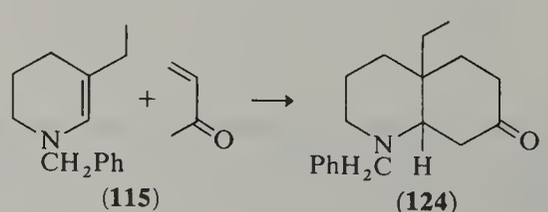
The iminium ions produced by the *C*-alkylation of Δ^2-piperideines can have synthetic utility for the formation of additional carbon–carbon bonds. This concept is illustrated (Scheme 12) by the synthesis of vincamone and its epimer from piperideine (**120**). Treatment of enamine (**120**) with ethyl iodoacetate gave iminium ion (**121**) which cyclized to (**122**) under the reaction conditions. Completion of the synthesis was accomplished by base followed by acid treatment ⟨82TL177⟩.



(**120**) (**121**) (**122**) (**123**) Vincamone and epivincamone

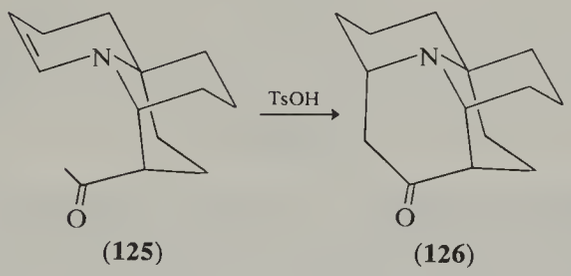
Scheme 12

The reaction of Δ^2-piperideine (**115**) with methyl vinyl ketone to give (**124**) is another example of how initial electrophilic attack on the enamine double bond can be used in heterocyclic synthesis ⟨77ACR193⟩. This overall process is an enamine analog of the Robinson annelation and is a useful approach to the perhydroquinoline ring system.

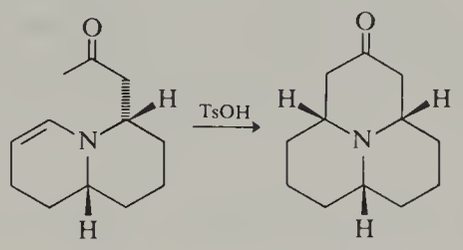


(**115**) (**124**) (35)

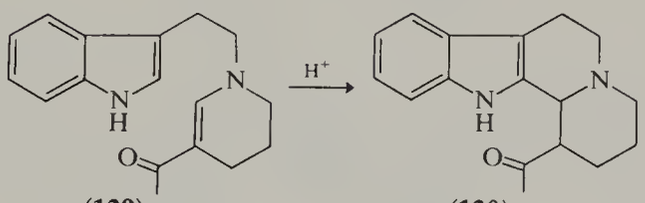
The addition of acid to Δ^2-piperideine results in an iminium ion that readily reacts with nucleophilic species. This reaction has been particularly useful for the formation of carbon–carbon bonds in alkaloid total synthesis. For example, key steps in the total synthesis of (±)-porantherine (equation 36) ⟨74JA6517⟩, coccinelidine (equation 37) ⟨77H(7)685⟩ and eburnamonine (equation 38) ⟨65JA1580⟩ were acid-catalyzed ring closures between Δ^2-piperideine derivatives and enols. Even the weakly nucleophilic carbon–carbon double bond can participate in this type of reaction ⟨80JA5955⟩, as has been demonstrated by a recent total synthesis of a morphinan derivative (Scheme 13).



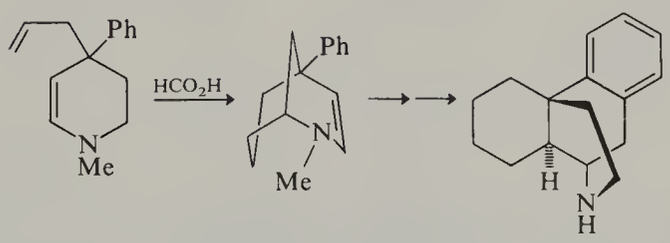
(125) (126) (36)



(127) (128) (37)

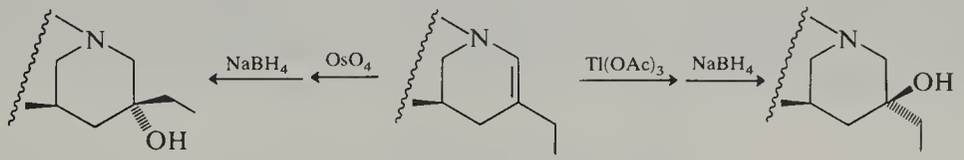


(129) (130) (38)



Scheme 13

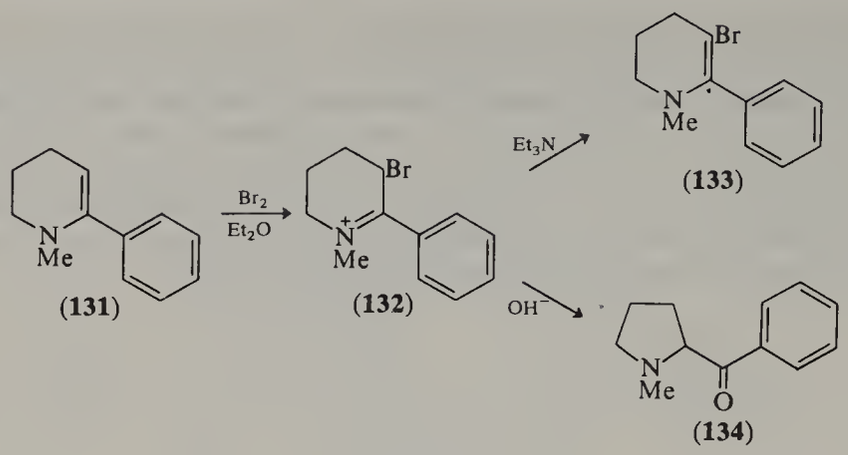
Two interesting approaches for the stereospecific oxidation of the enamine bond of Δ^2-piperideine have been reported in connection with studies on the synthesis of vinblastine derivatives (Scheme 14) ⟨79JA2243⟩.



Scheme 14

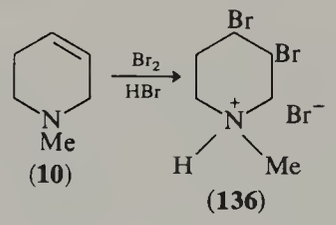
The bromination of Δ^2-piperideine (**131**) has been reported to give iminium ion (**132**). Treatment of this ion with triethylamine gave the bromoenamine (**133**), while treatment with hydroxide ion resulted in a rearrangement to give the pyrrolidine (**134**; Scheme 15) ⟨76TL2437⟩. The presence of the 2-aryl substituent undoubtedly stabilized the iminium ion facilitating these reactions.

The Δ^3-piperideines are the most stable isomers of the tetrahydropiperidines. The nitrogen atom and the double bond are isolated by saturated carbon atoms and might be expected to have little influence on each other. This is particularly true of the nitrogen atom; *N*-alkylations and -acylations of Δ^3-piperideines occur without difficulty.

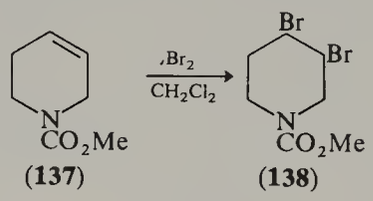


Scheme 15

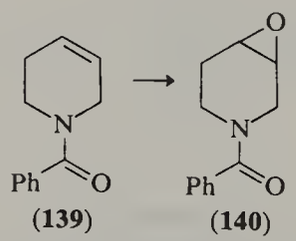
The addition of electrophilic reagents to the carbon–carbon double bond may encounter some interference from the nitrogen lone pair. The nucleophilicity of the nitrogen atom can be suppressed by protonation or acylation. For example, bromination of *N*-methyl-Δ^3-piperideine (**10**) under acidic conditions ⟨47CCC71⟩ and bromination of the carbamate (**137**) ⟨82UP20700⟩ gave (**136**) and (**138**) as relatively stable dibromide derivatives. Also, the oxidation of (**139**) was reported to give the epoxide (**140**) without complications ⟨62MI20700⟩.



(39)

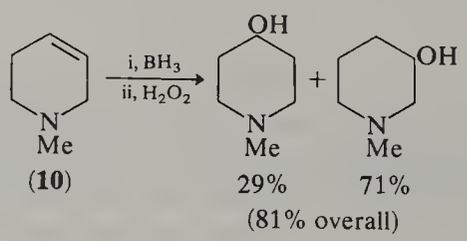


(40)



(41)

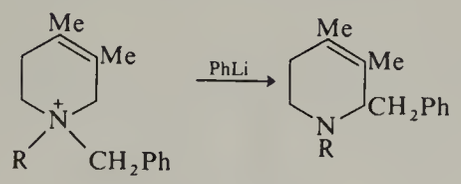
The nitrogen atom in Δ^3-piperideines would be expected to influence the addition of unsymmetrical reagents to the double bond. Although this effect has not been extensively studied, the results on the hydroboration–oxidation of a number of *N*-substituted Δ^3-piperideines show a preference for the piperidin-3-ol (Scheme 16) ⟨70JOC802⟩. Initial coordination of borane with the nitrogen atom was proposed and the observed regiochemistry is believed to be the result of electronic factors ⟨70TL1133⟩.



Scheme 16

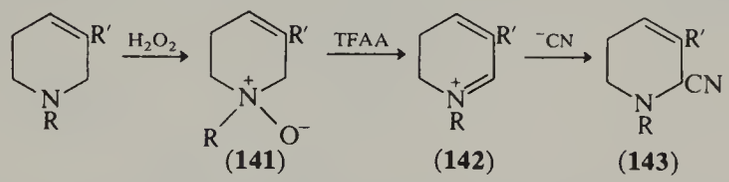
The double bond of Δ^3-piperideines can be used to activate and control the functionalization of the six-membered ring. For example, studies on the synthesis of the benzomorphans require 2-benzyl-Δ^3-piperideine derivatives. One approach to these compounds has been

by the Stevens rearrangement of the quaternary salts (Scheme 17). This reaction proceeds by a regiospecific removal of the allylic proton by the strong base ⟨77CRV1⟩.



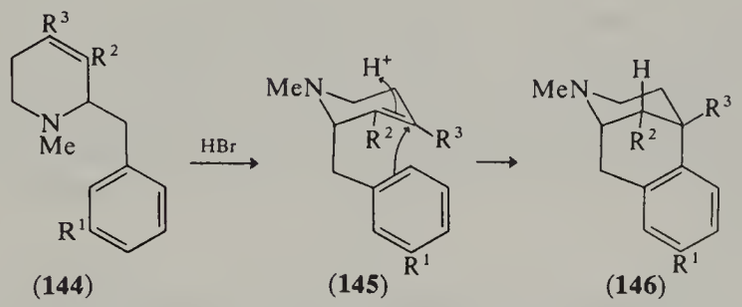
Scheme 17

Another example is provided by the application of the modified Polonovski reaction to Δ^3-piperideines. Treatment of amine oxides (**141**) with trifluoroacetic anhydride results in the formation of iminium ion (**142**). These compounds can behave as useful synthetic intermediates, reacting with a number of nucleophiles such as cyanide ion ⟨80JA1064⟩.



Scheme 18

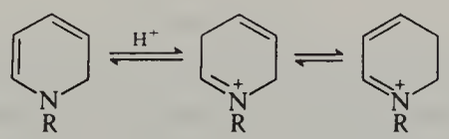
The acid-catalyzed cyclization of Δ^3-piperideines has proven to be a valuable approach to the benzomorphans (equation 42) ⟨77CRV1⟩. This is a general reaction and, with simple alkyl substitution on the double bond, *anti* addition to the double bond gives the predominant if not exclusive product. This has led to speculation that the reaction occurs in a concerted fashion.



(42)

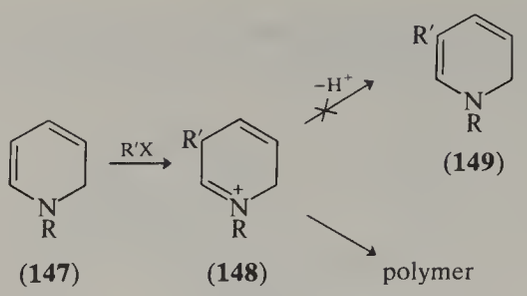
2.07.3.3 Dihydropyridines

In principle, 1,2-dihydropyridines are susceptible to electrophilic attack at the nitrogen atom and the positions β and δ to the nitrogen atom. The experimental evidence suggests that the β-carbon is the kinetic site of protonation, giving the 2,5-dihydropyridinium ions. It is believed that these compounds slowly rearrange to the thermodynamically more stable 2,3-dihydropyridinium ion (equation 43). The *N*-protonated 1,2-dihydropyridine may play a role in these reactions. These pyridinium ions have proven useful for regiospecific syntheses of the precursor substituted tetrahydropyridines for the Grewe benzomorphan synthesis ⟨63JOC1869⟩.



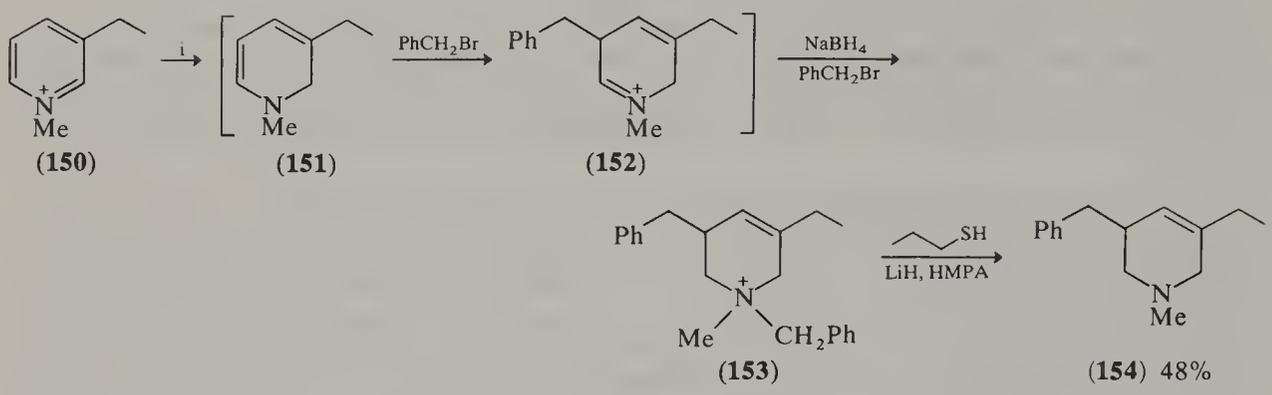
(43)

The direct alkylation of dihydropyridines to produce alkyl-substituted dihydropyridines has not proven to be a very successful reaction. Although initial alkylation at the β-position probably occurs, the intermediate 2,5-dihydropyridinium ions (**148**) apparently induce polymerization of the unreacted dihydropyridine. To overcome this problem a two-phase system has been developed ⟨74JA7364⟩. The alkylated product (**152**) is reduced and *N*-alkylated under the reaction conditions. This method may have application to the synthesis of 3,5-substituted tetrahydropyridine and pyridine derivatives (Scheme 20).



(147) (148) (149) polymer

Scheme 19

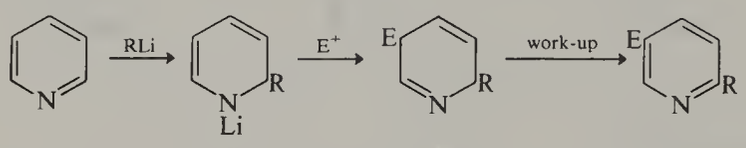


(150) (151) (152) (153) (154) 48%

i, $NaBH_4$, Et_2O, $MeOH–H_2O$, NaOH, $PhCH_2Br$

Scheme 20

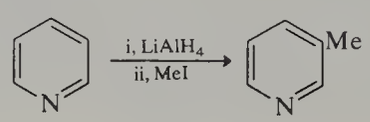
The reaction of the 1-lithio derivatives of 1,2-dihydropyridines with a number of electrophiles occurs β to the nitrogen atom and has been shown by several groups to be a useful pyridine synthesis (Scheme 21) ⟨76JHC789⟩. The lithio derivatives are prepared by the reaction of a suitable substituted pyridine with an organolithium reagent. A variety of organolithium reagents (*e.g.* RLi, R = Me, Ph, Bu^n) and electrophilic reagents (*e.g.* alkyl halides ⟨78JOC3227⟩, epoxides ⟨75CJC2305⟩, disulfides ⟨75JOC569⟩) have been used in this reaction. The 2,5-dihydropyridines (**156**) have been postulated as intermediates and in certain cases they have been isolated ⟨78JOC3227, 81JOC4494⟩. More electrophilic alkylating agents, *e.g.* $ClCO_2Me$, AcCl and $ClP(O)(OEt)_2$, give predominantly the *N*-substituted product ⟨74JOC3565⟩.



(155) (156) (157)

Scheme 21

The reduction of pyridine is known to give a mixture of 1,2- and 1,4-dihydroaluminate derivatives. Alkylation of this mixture has provided a simple entry into 3-substituted pyridines (Scheme 22) ⟨71JA1294⟩.



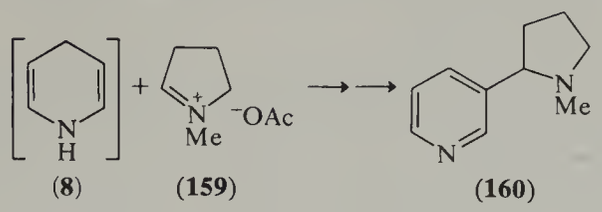
(158) 86%

Scheme 22

The 2,5-, 2,3- and 3,4-dihydropyridines have received very little study regarding their reactivity toward electrophilic reagents. This is undoubtedly due to their instability and the low number of authentic derivatives that are known.

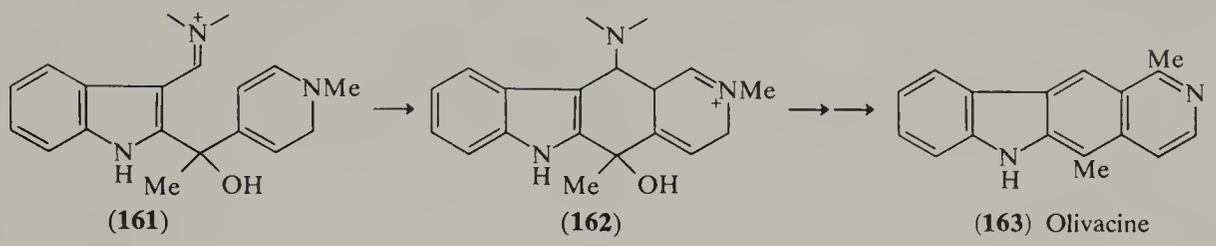
The reaction of iminium ions with dihydropyridines is a method, suggested from biosynthetic studies, for the formation of carbon–carbon bonds to these six-membered heterocycles. The 1,4-dihydropyridine (8), a presumed intermediate from the reaction of ammonia with glutaraldehyde, reacts with the cyclic iminium ion (**159**) to give, after oxidation, nicotine (**160**) ⟨72CC1091⟩. Another example of this reaction has provided a total synthesis of olivacine (**163**). The 1,2-dihydropyridine ring system in (**161**), generated from its chromium tricarbonyl complex, was observed to undergo an intramolecular cyclization

with the iminium group to give (**162**) ⟨81H(16)1469⟩. The compound was not isolated but was further elaborated to the alkaloid olivacine (**163**).



(**8**) (**159**) (**160**)

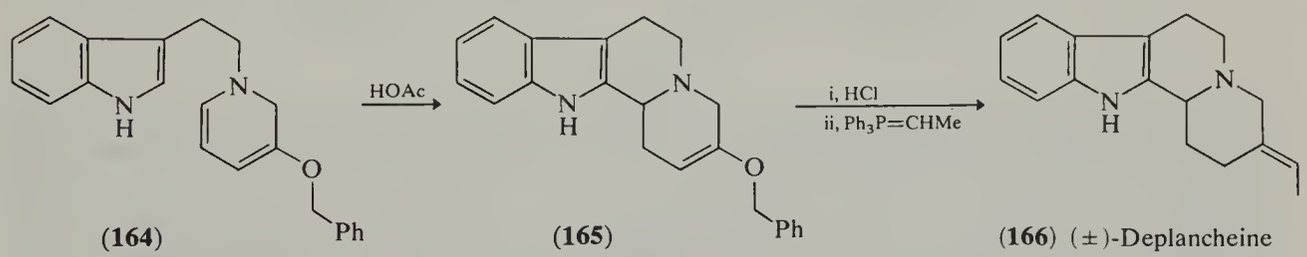
Scheme 23



(**161**) (**162**) (**163**) Olivacine

Scheme 24

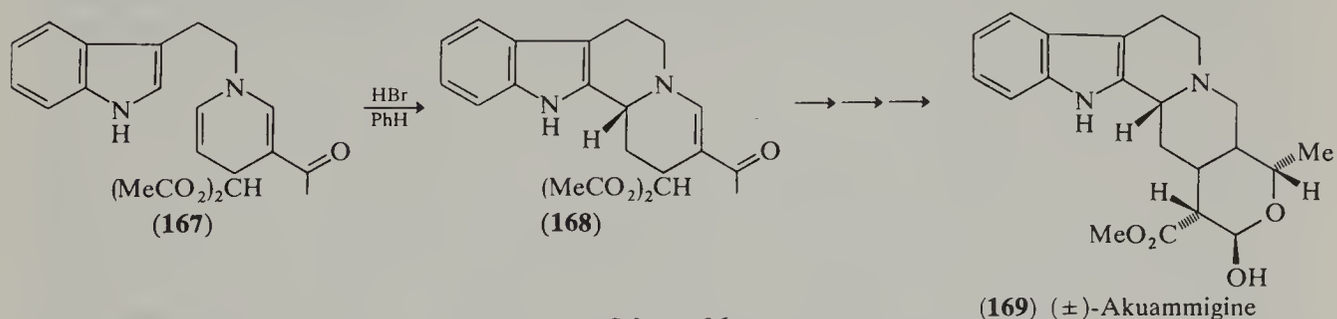
Although the reaction of dihydropyridinium ions produced by the electrophilic attack of dihydropyridines has promise in organic synthesis, this reaction has not been extensively exploited. Some examples of their potential are provided by the acid-catalyzed reactions with indoles ⟨80TL2341⟩. An application of this reaction for an efficient synthesis of (±)-deplancheine is shown in Scheme 25. An interesting feature of this reaction was the use of the alkoxy-substituted dihydropyridine as a carbonyl precursor.



(**164**) (**165**) (**166**) (±)-Deplancheine

Scheme 25

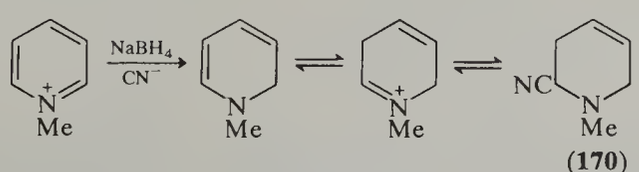
The 1,4-dihydropyridine ring system has also been used in a similar fashion for efficient syntheses of the yohimboid and ajmalicinoid alkaloid ring systems. Thus, 1,4-dihydropyridine (**167**) has been cyclized to (**168**) using HBr in benzene. This indoloquinolizidine could then be converted to akuammigine (**169**) in three steps, providing an overall very short route to this alkaloid ⟨70JOC2809, 76JA3645⟩.



(**167**) (**168**) (**169**) (±)-Akuammigine

Scheme 26

Cyclic iminium ions are well known to react cleanly with cyanide ion. This has often been used as a chemical method to characterize reactive enamines ⟨57JA5279⟩. The reaction can also be used with 1,2-dihydropyridines to provide stable derivatives of this reactive

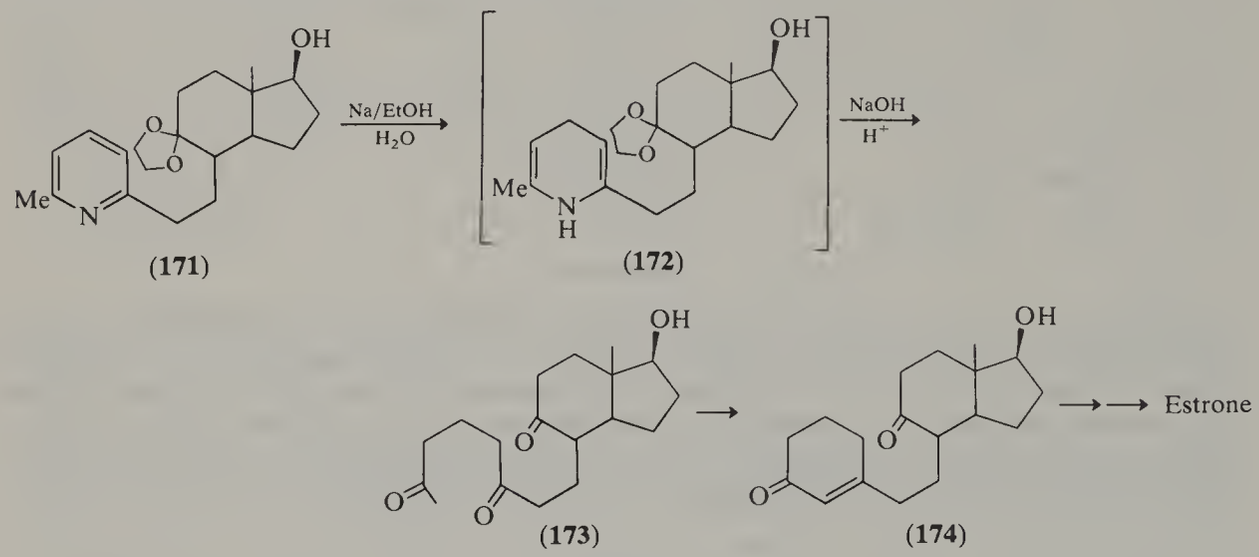


(**170**)

Scheme 27

ring system. Since loss of cyanide ion can occur under basic or acidic conditions, the cyanotetrahydropyridines (**170**) can be considered as protected or masked 1,2-dihydropyridines (Scheme 27) ⟨64JOC1647⟩.

The acid-catalyzed hydrolysis of dihydropyridines to give amines and carbonyl compounds is a reaction that workers in the field generally try to avoid. However, this reaction can have advantages in organic synthesis. The recognition that 1,4-dihydropyridines are synthetic equivalents of 1,4-dicarbonyl compounds has effectively been exploited in steroid synthesis. Reduction of pyridine (**171**) gave the 1,4-dihydropyridine (**172**) which was not isolated but directly hydrolyzed to the diketone (**173**). Cyclization of (**173**) gave the enone (**174**) which was readily converted into the steroid estrone ⟨75JA5282⟩.

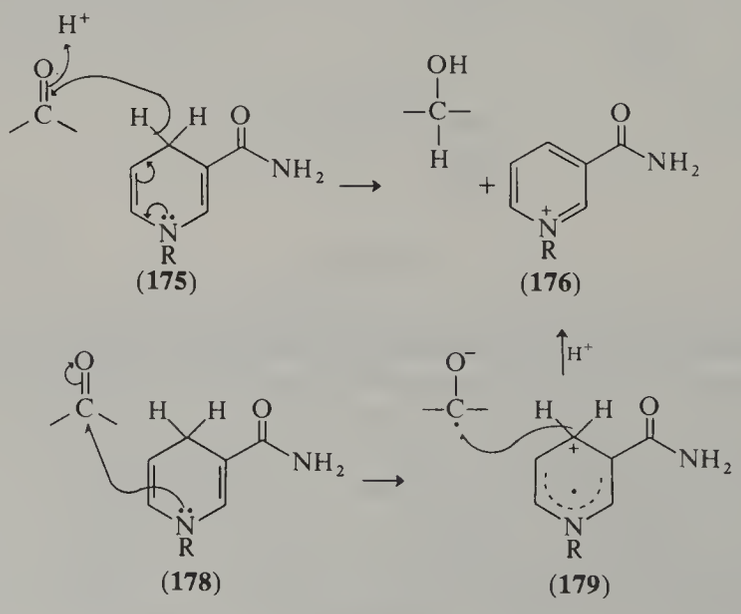


Scheme 28

The dihydropyridines are very susceptible to oxidation to pyridine derivatives. They readily decompose in the presence of a number of oxidizing agents to pyridines. The oxidation of 1,2- and 1,4-dihydropyridines can be suppressed by electron-withdrawing groups in conjugation with the lone pair of electrons on nitrogen. Most of the information in the literature is concerned with dihydropyridines that have these stabilizing substituents ⟨72CRV1⟩.

The oxidation of 1,2- and 1,4-dihydropyridines has been extensively studied. This is due in large part to the occurrence of the 1,4-dihydropyridine ring system in the reduced forms of the coenzymes nicotinamide adenine di- and tri-phosphate (NADH and NADPH). These redox couples are responsible for a number of biological oxidations and reductions ⟨B-70MI20701⟩.

The research on NADH and its analogs has proceeded along two major lines ⟨B-78MI20701⟩. Groups have been involved with the elucidation of the mechanistic details of dihydropyridine



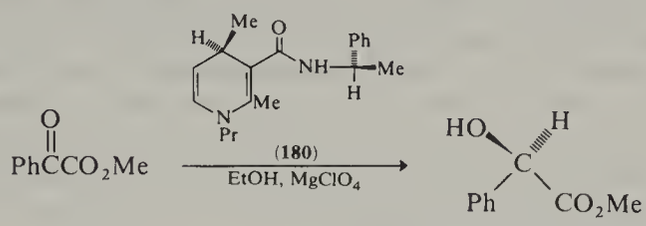
Scheme 29

reductions and the development of dihydropyridines that mimic NADH reductions. Considerable progress has been made in both of these areas.

The mechanism of 1,4-dihydropyridine reductions is actively being pursued ⟨B-78MI20702⟩. A mechanism involving hydride transfer is attractive because of its simplicity ⟨80JA4198⟩. However, many workers in the area prefer an electron transfer as the first step ⟨79JA7402⟩. The hydride mechanism can be completed by the transfer of a proton followed by an electron or by the transfer of a hydrogen atom (Scheme 29). It is unlikely that the mechanistic question will be resolved in the near future. It may be that the mechanistic pathway that these reactions follow is very sensitive to both the structure of the dihydropyridine and the compound being reduced.

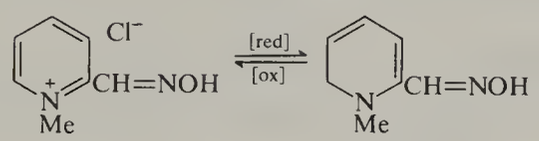
Biomimetic reductions using 1,4-dihydropyridines have been mainly successful with molecules that have high oxidation potentials ⟨B-78MI20701⟩. Undoubtedly the range of functional groups capable of reduction will grow larger as more research is done. Already it has been observed that polarization of carbonyl groups through hydrogen bonding and metal ion coordination has facilitated their reduction ⟨71CC552, 79JA7059⟩.

Considerable success has been obtained in enantiospecific reductions using chiral 1,4-dihydropyridines. For example, keto ester (**181**) is reduced by the dihydropyridine (**180**) with a high degree of optical purity ⟨79JA7036⟩. At present this is a very active area of research.



(44)

(**181**) (**182**) opt. yield 97.6%

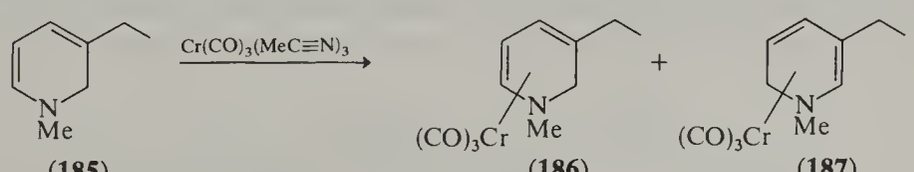


(45)

(**183**) (**184**)

The dihydropyridine–pyridinium ion redox couple has been used effectively to assist in the delivery of drugs across the blood–brain barrier ⟨81MI20700⟩. The first example of this interesting concept was provided by *N*-methylpyridinium-2-carbaldehyde oxime chloride (2-PAM), the drug of choice for treatment of organophosphate poisoning ⟨76JMC102⟩. The active drug 2-PAM does not cross the blood–brain barrier. However, the lipoidal reduced form [pro-2-PAM (**184**)] readily penetrates this barrier whereupon it is oxidized to the active pyridinium form. Undoubtedly this interesting concept of using the dihydropyridine–pyridinium redox couple to solve problems of drug delivery will be further exploited.

An interesting area of dihydropyridine chemistry has proven to be the synthesis and reactions of their metal carbonyl complexes. The 1,2- and 1,4-dihydropyridines are known to form metal complexes with both chromium and iron tricarbonyl. The first work was carried out on the chromium tricarbonyl complexes where the dihydropyridine is presumably behaving as a six-electron ligand. These compounds can be prepared by treating the dihydropyridine with a suitable chromium tricarbonyl precursor such as trisacetonitrile chromium tricarbonyl ⟨79CJC300⟩. The formation of the complex (**187**) is presumably the result of a 1,5-hydrogen shift induced by the metal. Although these complexes are relatively stable, the dihydropyridine can be liberated by treatment with a competing ligand such as pyridine. These results have led some workers to develop these complexes as a protected form of the very reactive 1,2-dihydropyridines (equation 46) ⟨79CJC300⟩.

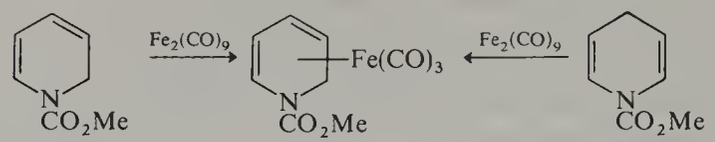


(46)

(**185**) (**186**) (**187**)

It has been claimed that attempts to prepare iron and nickel carbonyl complexes of 1,2- and 1,4-dihydropyridines resulted in reduction of the metal ⟨67AG(E)988⟩. This problem has been avoided by using dihydropyridines with electron withdrawing groups on the nitrogen

atom. The reaction of either *N*-methoxycarbonyl-1,2- or -1,4-dihydropyridine diiron nonacarbonyl gave the iron tricarbonyl complex of the 1,2-dihydropyridine (equation 47) ⟨75JOM(96)95⟩.



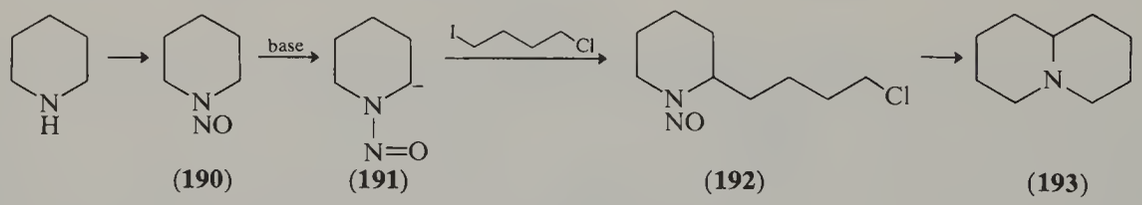
(63) (189) (188) (47)

The chemistry of these complexes is proving to be interesting and will undoubtedly have a future impact on dihydropyridine chemistry ⟨80TL1589, 79H(12)1269, 79H(12)1517⟩.

2.07.4 REACTIONS WITH NUCLEOPHILES AND REDUCING AGENTS

2.07.4.1 Piperidines

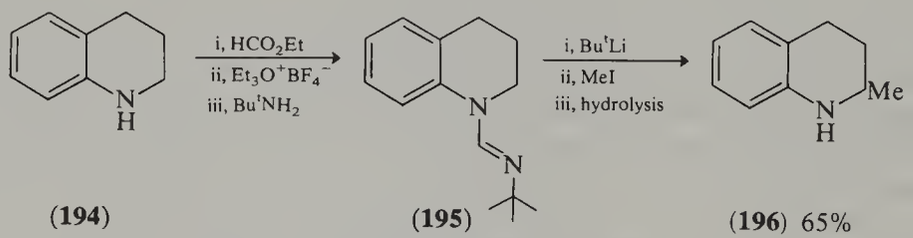
Simple piperidines, being secondary amines, are not very reactive toward nucleophilic species. However, effort has been devoted to modifying the nitrogen atom to enhance the acidity of the protons on the α-carbon atom. Reasonable success has been obtained with *N*-nitrosoamines ⟨75AG(E)15⟩. The nitroso group enhances the acidity of the α-hydrogen to such an extent that it can be removed with strong base such as lithium diisopropylamide. This anion and analogous species readily react with nucleophiles (alkyl halides, aldehydes, ketones). Removal of the *N*-nitroso substituent results in overall alkylation of the piperidine ring at the position adjacent to the nitrogen atom. The use of this method for the synthesis of quinolizidine (**193**) is illustrated in Scheme 30.



(190) (191) (192) (193)

Scheme 30

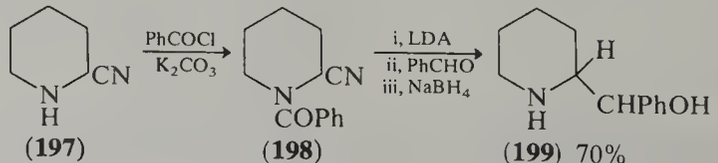
A similar result has been achieved using heterocyclic formamidine derivatives (Scheme 31) ⟨81TL5119⟩. In addition to alkyl halides, aldehydes were also suitable electrophiles in this reaction.



(194) (195) (196) 65%

Scheme 31

Both of the above reactions represent examples of dipole-stabilized carbanions. Use of these anions is becoming increasingly important in synthetic heterocyclic chemistry ⟨78CRV275⟩. The cyano group has also been used to stabilize anions adjacent to a heterocyclic nitrogen atom ⟨79TL771⟩. In the example shown, the cyano group was introduced by the addition of HCN to the Δ^1-piperideine. Generation of the anion using lithium diisopropylamide followed by benzaldehyde gave a 70% yield of the amino alcohol (**199**). This reaction is reasonably stereospecific, the ratio of the *erythro* to the *threo* diastereomer being 85/15.

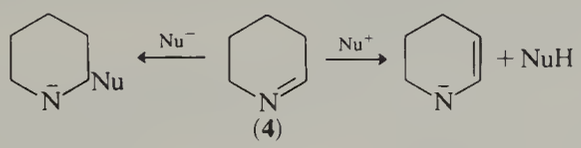


(197) (198) (199) 70%

Scheme 32

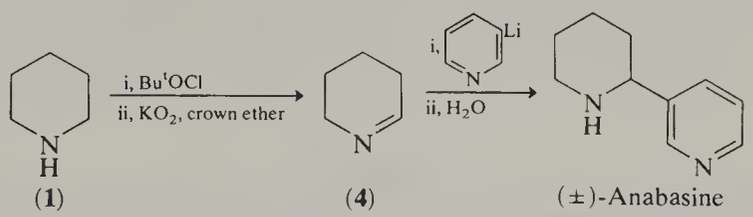
2.07.4.2 Piperideines

The Δ^1-piperideines, in contrast to the Δ^2- and Δ^3-isomers, are usually very reactive toward nucleophilic reagents. Depending upon the nature of the nucleophile, two reaction pathways are possible (equation 48). The nucleophile can add to the imine carbon or the nucleophile can abstract the α-hydrogen. Since both of the resulting anions can undergo further reactions, Δ^1-piperideines have potential for the synthesis of complex six-membered ring heterocycles.



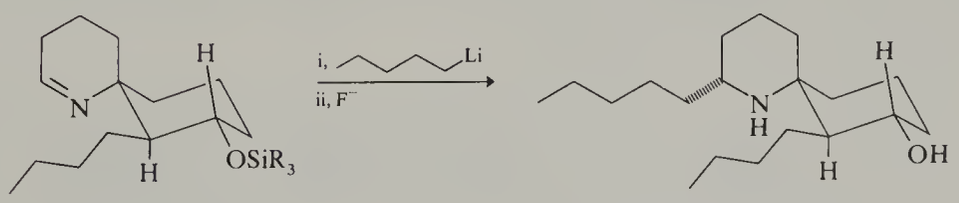
(4) (48)

Although the carbon–nitrogen double bond in Δ^1-piperideines is susceptible to attack by a wide range of nucleophilic species, it is the carbon nucleophiles that offer the most potential in synthetic chemistry. Alkyl- and aryl-lithium reagents have been reported to add to the imine bond to give 2-substituted piperidines. Using 3-pyridyllithium this reaction has been applied to the synthesis of the tobacco alkaloid (±)-anabasine ⟨80JOC1515⟩ and perhydrohistrionicotoxin (Scheme 34) ⟨75JA430⟩. Grignard reagents give no arylation or alkylation of Δ^1-piperideine. This is behavior typical of imines in general ⟨B-70MI20702⟩. The major difficulty with the addition of organometallic reagents to imines is the competing removal of the α-proton.



(1) (4) (±)-Anabasine

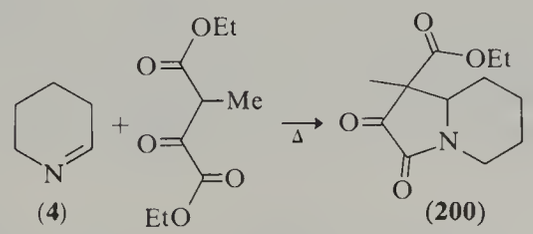
Scheme 33



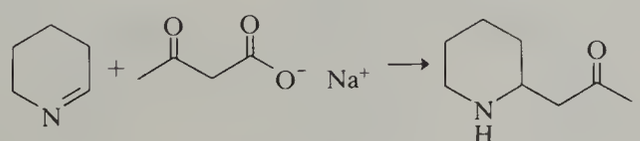
Perhydrohistrionicotoxin

Scheme 34

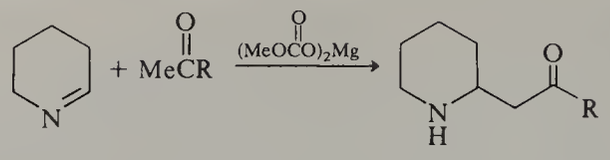
A number of workers have successfully added enols and enolates to the imine bond of Δ^1-piperideines. The indolizine (**200**), a useful intermediate in a β-lactam synthesis, was prepared according to equation (49) ⟨75JOC1264⟩. The addition of enolates to Δ^1-piperideines has frequently been used in biomimetic alkaloid synthesis. For example, pelletierine can be prepared by treating Δ^1-piperideine with sodium acetoacetate (equation 50) ⟨76S745⟩. The same overall transformation can be achieved using the ketone and methylmagnesium carbonate as a base. An advantage of this latter approach is that trimerization of the Δ^1-piperideine can be suppressed by maintaining a low pH (equation 51) ⟨74S284⟩.



(4) (200) (49)

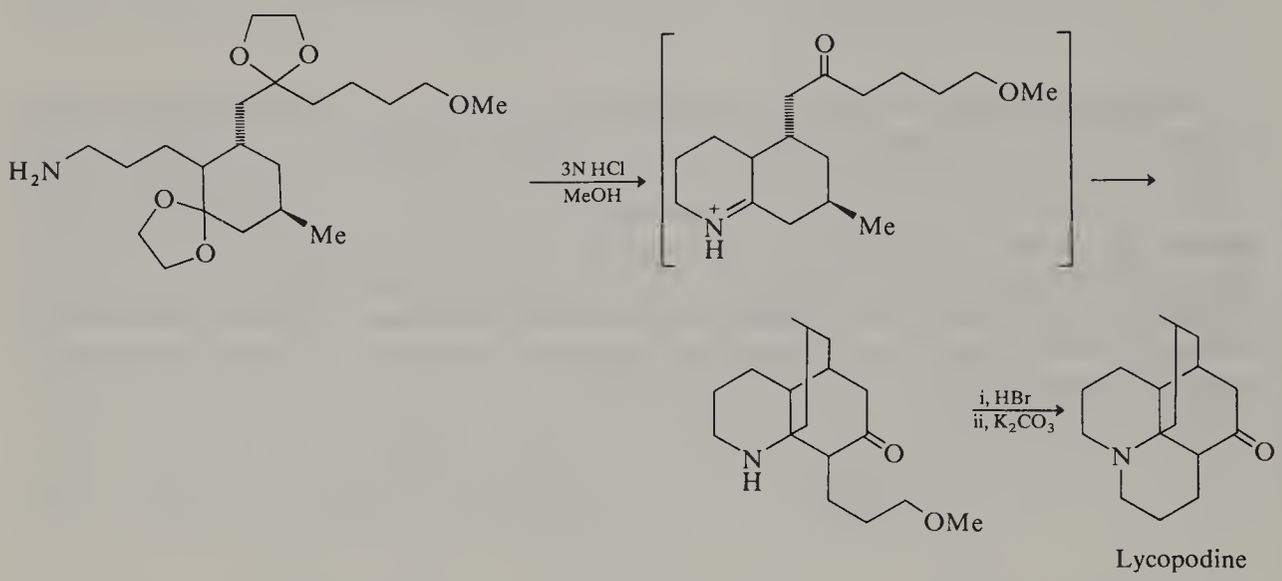


(4) (201) Pelletierine (40–50%) (50)



(4) (202) 35–75% (51)

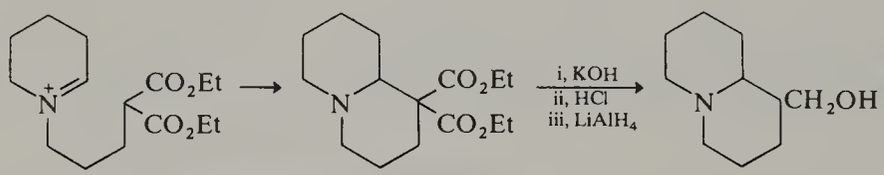
The reactions shown in equations (49)–(51) are reminiscent of the Mannich reaction. An example of where this approach was used to great advantage for the synthesis of lycopodine ⟨82JA1054⟩ is illustrated in Scheme 35. In this sequence the Δ^2-piperideine was not isolated but was prepared as a reactive intermediate.



Lycopodine

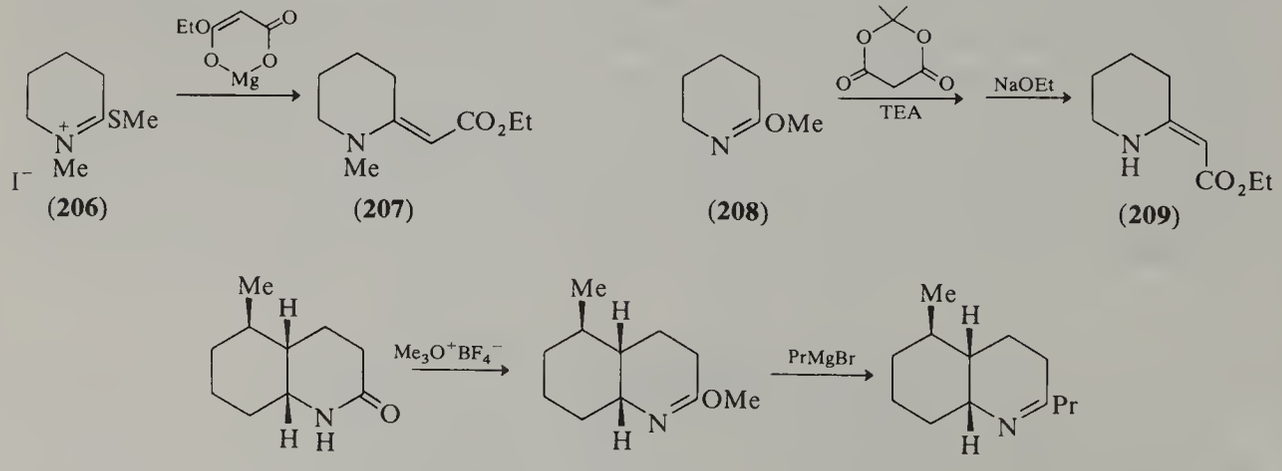
Scheme 35

Analogous reactions involving the more reactive iminium ions have also been observed. For example, a lupinine synthesis involved (**203**) as a reactive intermediate ⟨60JA502⟩. The decarboxylation of the diacid was relatively nonstereospecific giving, after reduction, a mixture of (±)-lupinine and (±)-epilupinine.



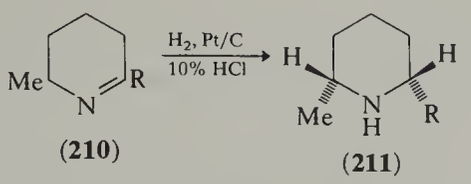
(**203**) (**204**) (**205**) Lupinine (52)

There has been interest in elaborating the piperidine ring from the lactam (Scheme 36). Most of these approaches involve converting the lactam into a 2-substituted Δ^1-piperideine followed by reaction with the carbon nucleophile ⟨81JOC3671, 79JOC3089, 77H(8)633⟩. This has the advantage that it involves less reactive Δ^1-piperideines which are generally prepared from the corresponding amides.



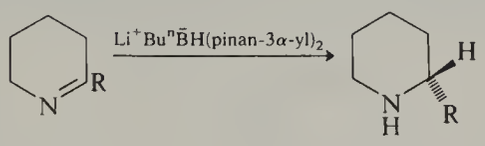
Scheme 36

The carbon–nitrogen double bond of Δ^1-piperideines is susceptible to reduction. This can be useful for the stereospecific introduction of ring substituents. An illustration is the preparation of *cis*-2,6-disubstituted piperidines (**211**) by catalytic hydrogenation of the corresponding Δ^1-piperideine (**210**) ⟨77T1569⟩.



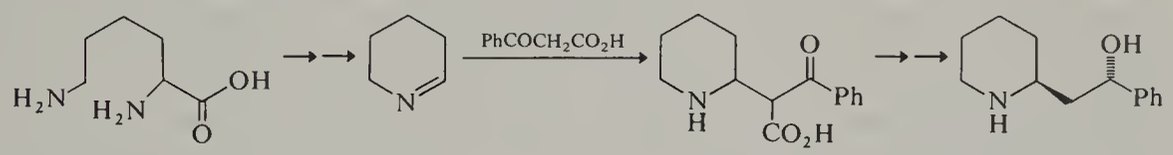
(**210**) (**211**) (53)

The polarized carbon–nitrogen double bond can also be reduced enantiospecifically using chiral hydrides ⟨71JCS(C)2560⟩. Although only modest asymmetric inductions were observed, this method holds promise for the synthesis of chiral piperidines (equation 54).



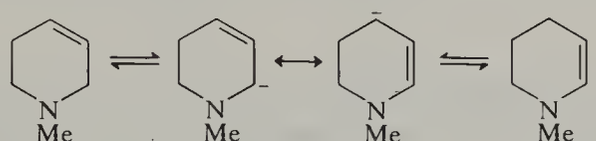
(**212**) (**213**) Predominant enantiomer (54)

It is clear that the reactions of these cyclic imines with nucleophiles are useful methods for elaborating the piperidine ring system. It is not surprising that these reactions also have their biosynthetic analogs. The vast majority of alkaloids containing the piperidine ring are believed to involve Δ^1-piperideine ⟨B-79MI20703, B-80MI20701, B-80MI20702⟩ as a biosynthetic intermediate. The Δ^1-piperideine originates from the amino acid L-lysine. Thus, the biosynthesis of a simple alkaloid such as sedamine (**216**) can be envisaged as proceeding through the Δ^1-piperideine (**4**).



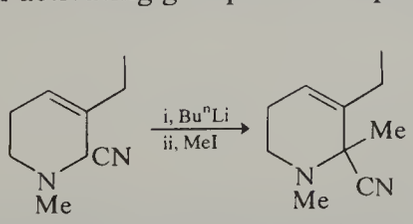
(**214**) (**4**) (**215**) (**216**) Sedamine

The π-systems of the Δ^2- and Δ^3-piperideines are not reactive toward nucleophilic reagents. The Δ^3-piperideine contains an isolated double bond whereas the Δ^2-piperideine contains the electron-rich enamine functional group. However, treatment of either piperideine (**10**) or (**11**) with strong base (potassium *t*-butoxide) apparently does generate a small equilibrium concentration of the anion (**217**), as is evidenced by the equilibration of the Δ^3-piperideine (**10**) to the more stable Δ^2-isomer (**11**) ⟨78T3027⟩. The Δ^2-piperideine is favored to such an extent that this reaction can be used preparatively ⟨80JOC1336⟩.



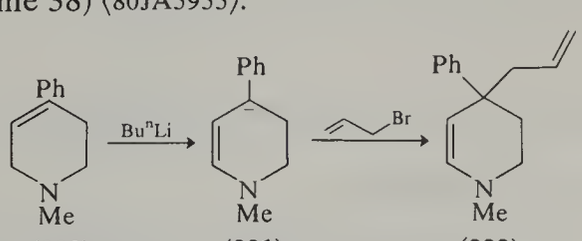
(**10**) (**217**) (**11**) (55)

The Δ^2- and Δ^3-piperideines can readily be metalated with strong base if there is an electron-withdrawing group in conjugation with the anion. The 2-cyano-Δ^3-piperideine (**218**) was metalated using *n*-butyllithium at 30 °C and alkylated to give the substituted piperideine (**219**) ⟨80JA1064⟩. This overall approach is analogous to Stork's acyl anion equivalent ⟨79TL771⟩. It appears that metalation of Δ^3-piperideines can even occur with weak activating groups such as phenyl (Scheme 38) ⟨80JA5955⟩.



(**218**) (**219**)

Scheme 37

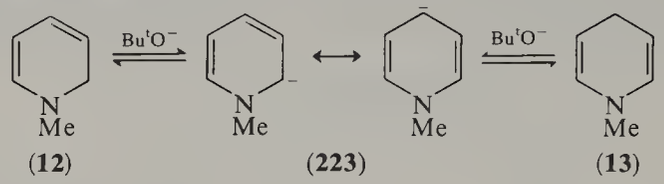


(**220**) (**221**) (**222**)

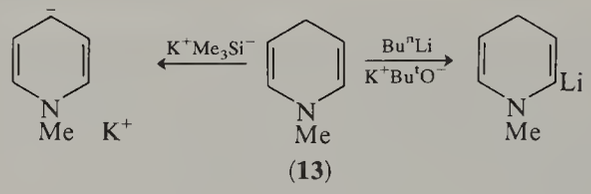
Scheme 38

2.07.4.3 Dihydropyridines

The π-systems of 1,2- and 1,4-dihydropyridines, like the Δ^2- and Δ^3-piperideines, are unreactive toward nucleophilic reagents. However, strong bases are also able to extract a proton from the ring. The equilibration of the *N*-methyl-1,2- and -1,4-dihydropyridines with potassium *t*-butoxide in DMSO undoubtedly involves the anion (**223**). The *N*-methyl-1,4-dihydropyridine can be metalated at the allylic position if a very strong base ($K^+ {}^-SiMe_3$) is employed (Scheme 39) ⟨79AG(E)489⟩. Removal of the allylic proton produces an eight electron π-system. If the base is changed to *n*-butyllithium and potassium *t*-butoxide, then metalation, although in low yield, occurs at the vinyl position adjacent to the nitrogen atom. The position and yield of the metalated compounds were inferred by the products resulting from the reaction with trimethylsilyl chloride.

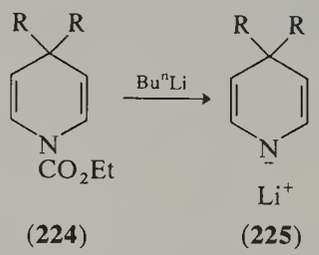


(56)



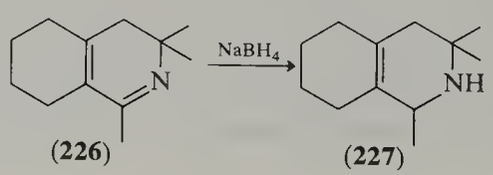
Scheme 39

There has been some interest in the 4-hydridopyridyl anions regarding the question of homoaromaticity ⟨79JA4488, 81JOC715⟩. These compounds are most easily prepared by the reaction of *n*-butyllithium with the carbamate (equation 57) ⟨79JA4488⟩. However, this method did not work for the preparation of the parent ring system (R = H), which is surprising since treatment of the carbamate with methyllithium followed by water is a known method of preparation of 1,4-dihydropiperidine ⟨72JOC1321⟩. The anion of the parent system was prepared using potassium *t*-butoxide in DMSO ⟨81JOC715⟩. Studies of these anions by NMR spectroscopy indicate that the anions are planar and show no delocalization of the electrons involving the saturated ring carbon atom.



(57)

The 2,3-, 2,5- and 3,4-dihydropyridines all contain a highly polarized carbon–nitrogen double bond and should be reactive toward nucleophilic reagents. From the limited information in the literature, this appears to be the situation. The 2,3-dihydropyridine is readily reduced by sodium borohydride (equation 58) ⟨64JHC13⟩. Hydride addition occurs in a 1,2 rather than 1,4 sense.



(58)

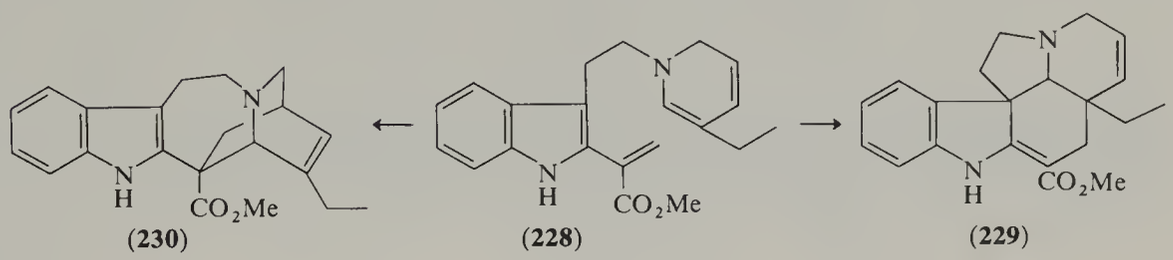
2.07.5 CYCLOADDITION REACTIONS

2.07.5.1 Piperideines

The cycloaddition reactions of the reduced pyridines have proven to be an exciting area of research. A number of the reduced pyridines are capable of undergoing cycloaddition

reactions. In particular, the electron rich Δ^2-piperideines and the 1,2-dihydropyridines are reactive partners in a number of cycloaddition reactions. Some of this research has been stimulated by studies in alkaloid biosynthesis. The chemistry described in this section will be better appreciated if a few of the ideas that have arisen from these biosynthetic studies are briefly presented ⟨74MI20700⟩.

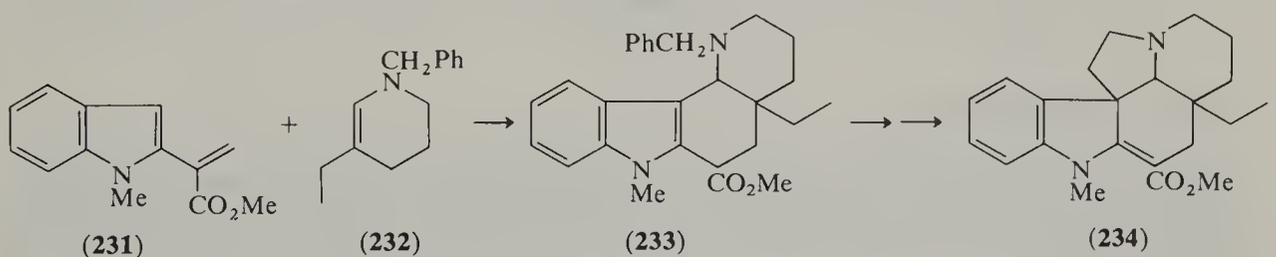
The biosynthetic and chemical interrelationships among various classes of indole alkaloids have led to the suggestion that a common intermediate, dehydrosecodine (**228**), is involved in these transformations. Although there has been some controversy regarding the evidence supporting this intermediate ⟨74MI20701⟩, the idea provides an interesting basis for a synthetic approach to the indole alkaloids. For example, dehydrosecodine (**228**) can be related *via* cycloaddition reactions to both tabersonine (**229**) and catharanthine (**230**; Scheme 40). In the first of these reactions the dihydropyridine is behaving as the dienophile whereas in the second it is the diene in a Diels–Alder reaction. Although this is an attractive proposal, all attempts to prepare and characterize dehydrosecodine have failed.



(**230**) (**228**) (**229**)

Scheme 40

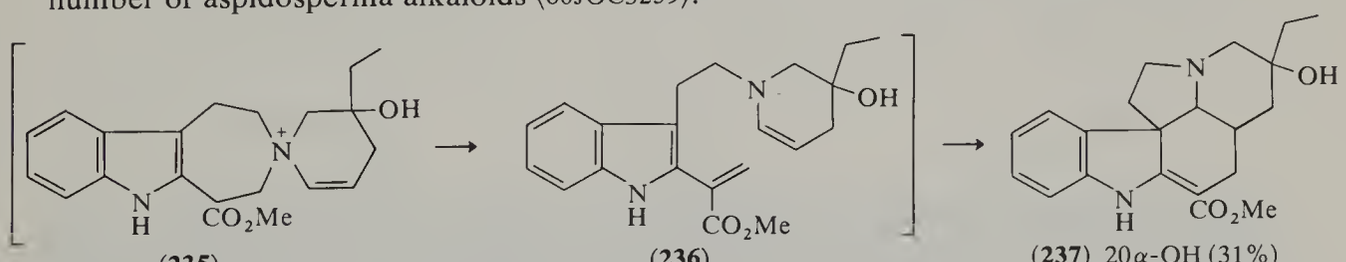
The Δ^2-piperideines are capable of behaving as dehydrosecodine analogs in alkaloid synthesis. One of the first successful applications of this approach is provided by the total synthesis of the aspidosperma alkaloid minovine (**234**; Scheme 41) ⟨73JA7146⟩.



(**231**) (**232**) (**233**) (**234**)

Scheme 41

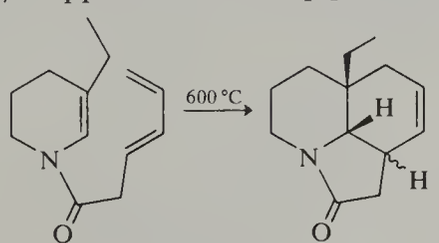
A closer analogy to dehydrosecodine (**228**) has been developed using Δ^2-piperideines (*e.g.* **236**). These compounds are not isolated but are produced by the fragmentation of salt (**235**). This elegant method is illustrated in Scheme 42 by the synthesis of racemic pandoline (**237**) and its C_{20} epimer. This reaction has provided an efficient route to a number of aspidosperma alkaloids ⟨80JOC3259⟩.



(**235**) (**236**) (**237**) 20α-OH (31%)
20β-OH (32%)

Scheme 42

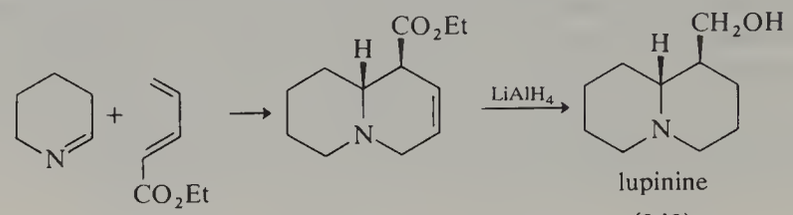
The intramolecular cycloaddition reaction of enamides has recently been exploited in alkaloid synthesis ⟨81JOC3763⟩. Application of Δ^2-piperideine derivatives resulted in the



(**238**) (**239**) 1 : 1 mixture of epimers (43%) (59)

synthesis of the fused indolizidine (**239**) ⟨79JA3294⟩, a key intermediate in aspidosperma alkaloid synthesis. This reaction is remarkable because the diene is not activated by substituents. The cycloaddition reactions of Δ^2-piperideines will undoubtedly increase in importance as new methods for their preparation are developed.

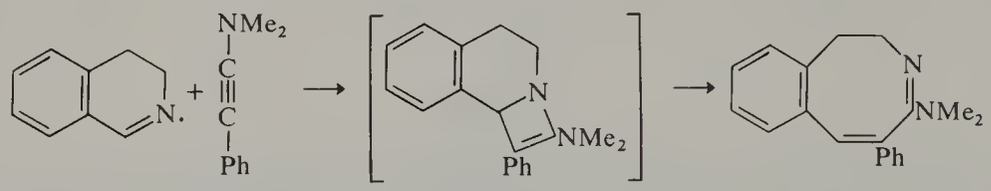
The Diels–Alder reaction using the double bond of a Δ^1-piperideine as the dienophile is relatively rare. The potential of this reaction is illustrated by the synthesis of lupinine (**242**) ⟨79H(12)949⟩, where the quinolizidine ring was formally constructed by a Diels–Alder reaction involving Δ^1-piperideine and the ester (**240**; Scheme 43).



(**240**) (**241**) (**242**)

Scheme 43

The double bond of Δ^1-piperideines is known to participate in [2+2] cycloaddition reactions, particularly with electron rich π-systems (Scheme 44) ⟨70CB573⟩.

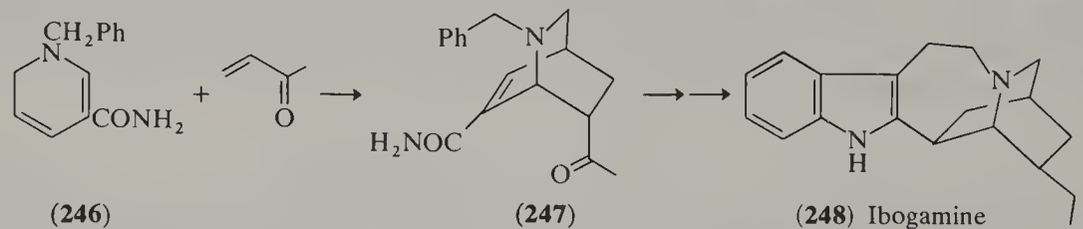


(**243**) (**244**) (**245**) 75%

Scheme 44

2.07.5.2 Dihydropyridines

It has been known since 1939 that the 1,2-dihydropyridine ring system is capable of behaving as a four-electron component in the Diels–Alder reaction ⟨39LA(538)195⟩. This reaction produces the isoquinuclidine ring system and has proven to be the method of choice for the synthesis of this heterocyclic ring system. For example, a classic synthesis of ibogamine (**248**) used the Diels–Alder reaction of 1,2-dihydropyridine (**246**) to construct the isoquinuclidine portion of this alkaloid (Scheme 45) ⟨66JA3099⟩.

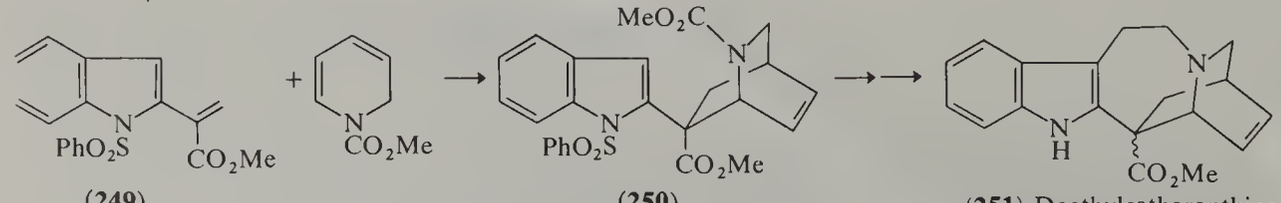


(**246**) (**247**) (**248**) Ibogamine

Scheme 45

It was suggested in the discussion of Section 2.07.5.1 that an intramolecular Diels–Alder reaction between a dihydropyridine and α-indolyl acrylate could be an efficient route to indole alkaloids. Although this has proven to be a successful reaction with Δ^2-piperideines (Section 2.07.5.1), all attempts, most of which have not been reported in the literature, to apply this concept to dihydropyridines have been unsuccessful ⟨81JOC3293⟩.

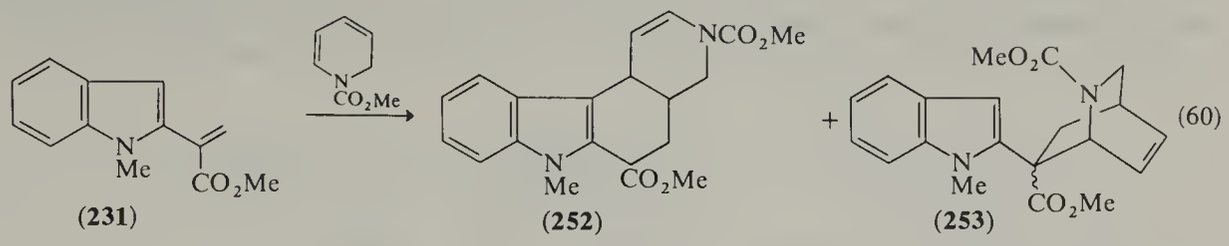
A biomimetic and very efficient route (Scheme 46) to the iboga alkaloid deethylcatharanthine has recently been developed using an intermolecular Diels–Alder reaction ⟨80JOC3382, 81JOC4836⟩.



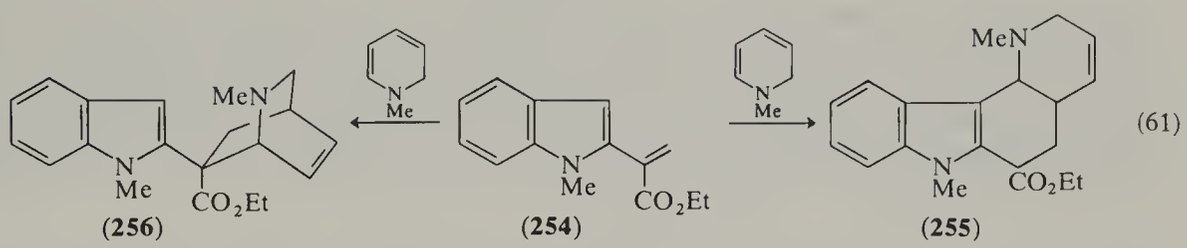
(**249**) (**250**) (**251**) Deethylcatharanthine

Scheme 46

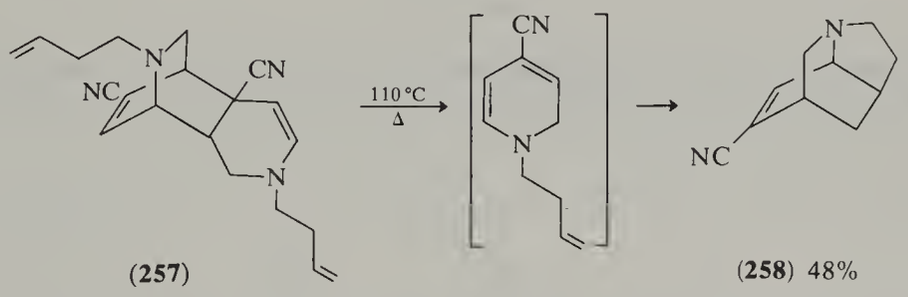
Similar strategies have been pursued by other workers. The reaction of indolyl acrylate (**231**) is of interest because of the formation of (**252**) in addition to the expected isoquinuclidine (**253**) ⟨81CC37⟩. Although (**252**) was formed in low yield, it is unusual because cycloadditions involving the 3,4-double bond of the dihydropyridine are rare ⟨81CC37⟩.



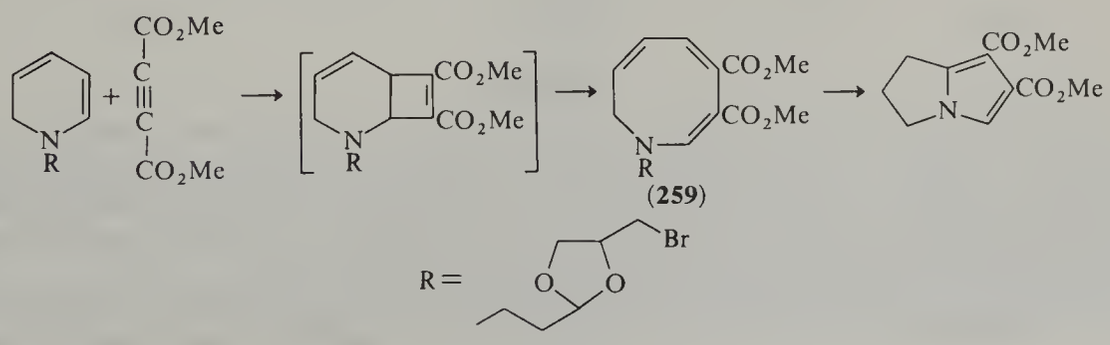
Previous biosynthetic studies have suggested that the diene and enamine double bonds can both participate in Diels–Alder reactions with indolyl acrylates. However, electron-withdrawing groups on the nitrogen suppress its enamine character, and reactions of the dihydropyridine as a diene predominate. If an electron-withdrawing group is not present on the nitrogen the dihydropyridine ring system behaves as both a diene and dienophile ⟨80JOC1657⟩. The aspidosperma and iboga analogs (**255**) and (**256**) were obtained in a 2.3 : 1 ratio when the indolyl acrylate (**254**) was treated with *N*-methyldihydropyridine (equation 61). In this example the *N*-methyl-1,2-dihydropyridine behaved as both a diene and dienophile with respect to the acrylate (**254**), which in turn acted as dienophile and diene respectively.



Intramolecular Diels–Alder reactions of dihydropyridines are rare. Although these reactions could be useful for the synthesis of polycyclic nitrogen heterocycles, there is only one report of this being a successful reaction ⟨74HCA1204⟩. Heating the dihydropyridine dimer (**257**) in toluene generated the monomeric dihydropyridine which was observed to undergo the intramolecular Diels–Alder reaction. Although the adduct (**258**) was produced in moderate yield, attempts to prepare analogous compounds were less successful.

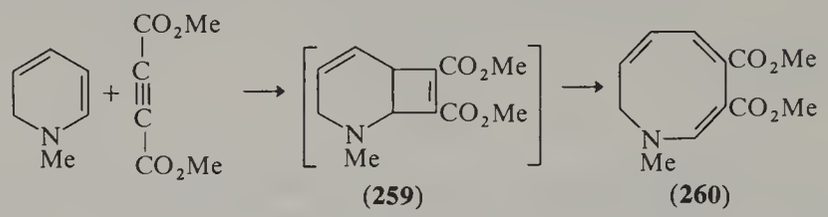


The 1,2-dihydropyridines are also known to undergo [2+2] cycloadditions of the enamine double bond with alkynes ⟨74JCS(P1)2496⟩. The products of these reactions are azocine derivatives such as (**259**), which, after removal of the *N*-protecting group, have been used as intermediates in pyrrolizine synthesis (Scheme 47) ⟨77JOC2903⟩.



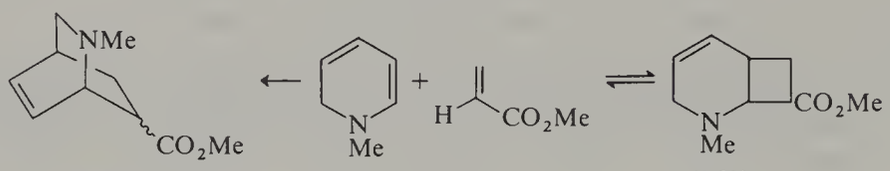
Scheme 47

It is interesting that the same dihydropyridines that undergo [2+2] cycloadditions with alkynes (Scheme 48) are reported to give [2+4] cycloadditions with alkenes. In both cases the primary product has been shown to be a [2+2] cycloadduct. With alkenes the cyclobutane (**262**) is unstable at high temperatures, reverting to the dihydropyridine and alkene (Scheme 49). This process allows the slower [2+4] cycloaddition to proceed, giving the thermodynamically stable isoquinuclidine (**261**) ⟨80JOC1657⟩. Therefore, if a dihydropyridine is treated with an alkene at high temperature only the [2+4] cycloadduct is observed.



(259) (260)

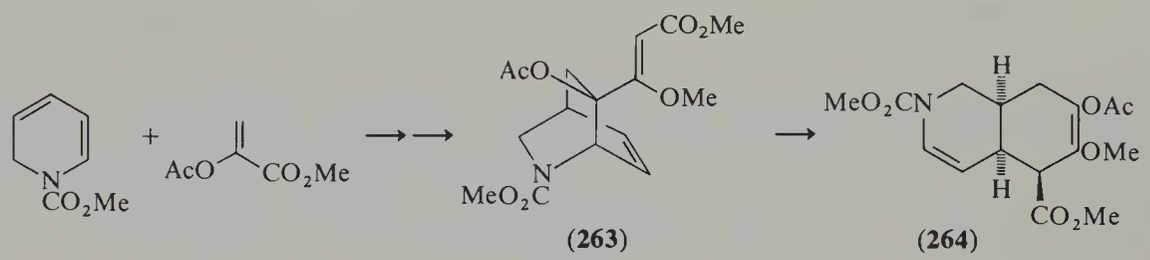
Scheme 48



(261) (262)

Scheme 49

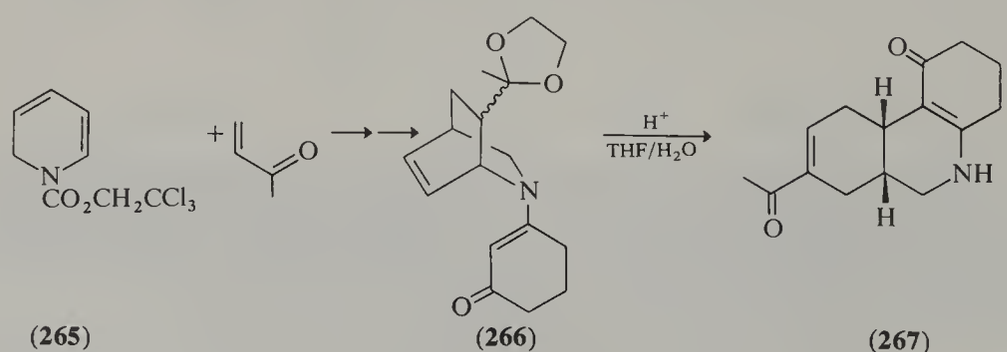
Dihydropyridines have also been starting points for stereospecific syntheses of hydrophenanthridines and isoquinolines. Interest exists in these compounds because of the occurrence of this structural feature in alkaloids. For example, isoquinuclidine (**263**), derived from *N*-alkoxycarbonyl-1,2-dihydropyridine, undergoes a Cope rearrangement to give the isoquinoline derivative (**264**) ⟨80JA6157⟩. Further chemical transformations of (**264**) provided a formal total synthesis of reserpine (Scheme 50).



(263) (264)

Scheme 50

A similar approach using *N*-vinylisoquinuclidines has led to stereospecific syntheses of reduced isoquinolines and phenanthridines (*e.g.* Scheme 51) ⟨79JOC124, 81JOC4643⟩.

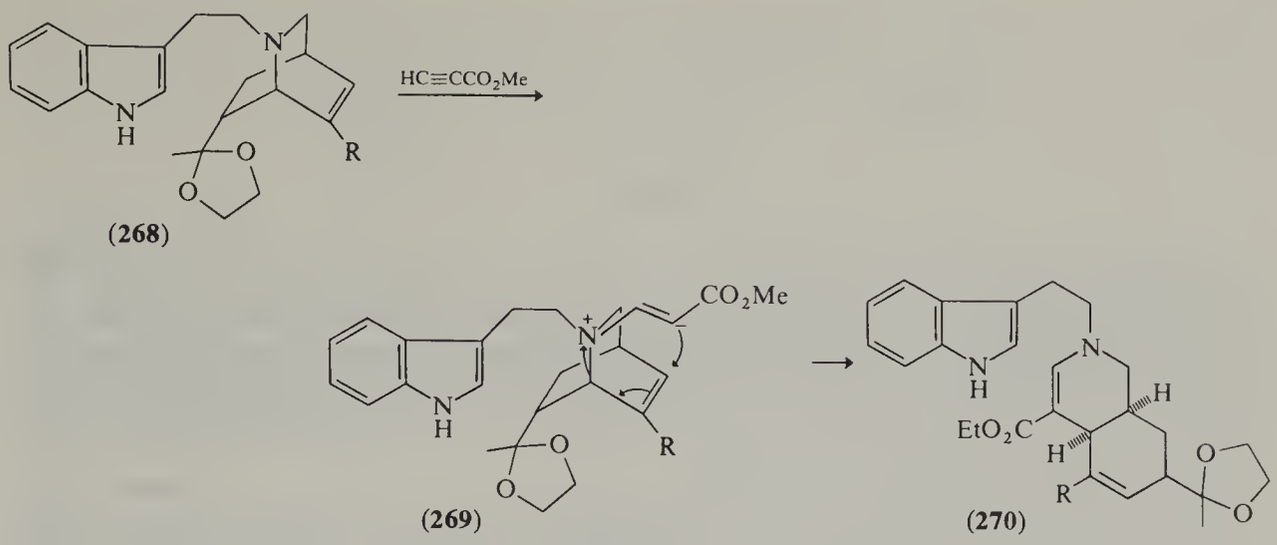


(265) (266) (267)

Scheme 51

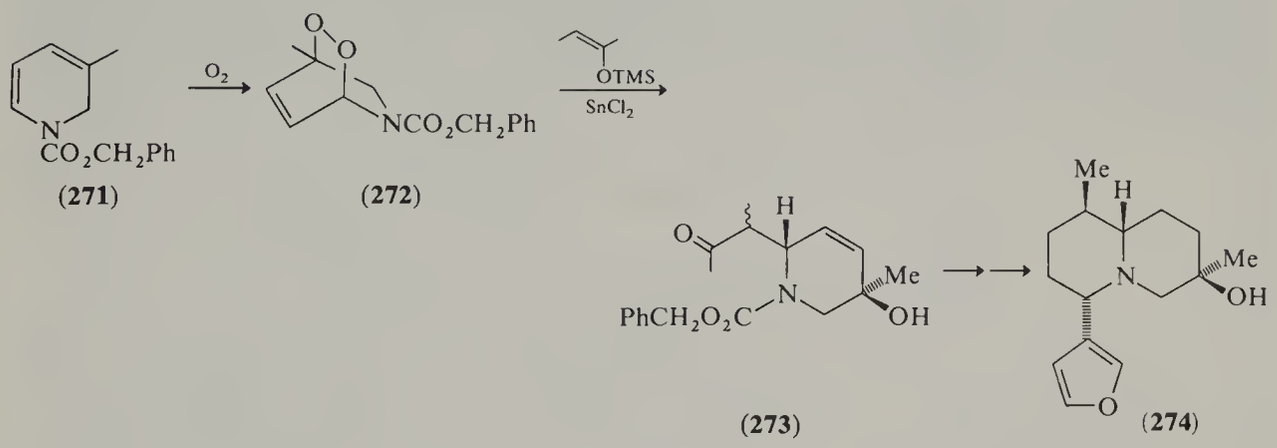
A potentially useful route to reserpine alkaloids has been suggested by the application of the amino-Claisen reaction (Scheme 52) to the indolyl-substituted isoquinuclidine (**268**). Treatment of (**268**) with methyl propiolate gave the intermediate zwitterion (**269**) which rapidly rearranged to (**270**). This latter compound has all the necessary functionality for further elaboration into the reserpine ring system ⟨B-82MI20700⟩.

It has recently been shown that 1,2-dihydropyridines react with singlet oxygen to give *endo*-peroxides ⟨75CPB2567, 80TL839, 81H(16)973⟩. These compounds react with nucleophiles



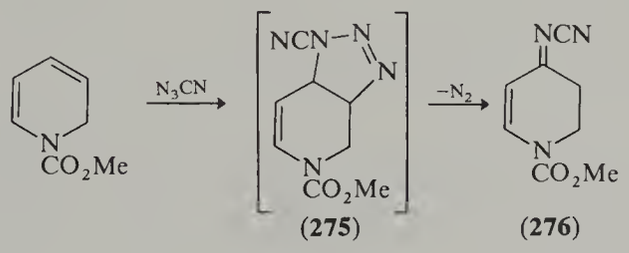
Scheme 52

in the presence of $SnCl_2$ and have proven to be particularly valuable in the total synthesis of a number of alkaloids. For example, the singlet oxygen adduct of dihydropyridine (**271**) reacts with 2-trimethylsilyloxybut-2-ene to give predominantly (**273**). This compound was then transformed into nupharolutine in a series of straightforward steps (Scheme 53) ⟨81H(15)237⟩.



Scheme 53

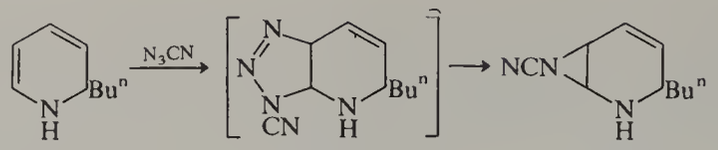
Dihydropyridines react with cyanogen azide but the product is dependent upon the structure of the reactant. *N*-Methoxycarbonyl-1,2-dihydropyridine with cyanogen azide at 25 °C for 20 h gave a 52% yield of the cyanamide (**276**; Scheme 54) and its *anti* isomer ⟨78CJC1026, 79JHC409⟩. The mechanism postulated for this reaction is dipolar addition to the 3,4-double bond of the dihydropyridine followed by hydrogen shift and loss of nitrogen. If the 1,2-dihydropyridine was not substituted on nitrogen then cyanogen azide reacted with the enamine double bond to give ultimately the bicyclic aziridine (**278**; Scheme 55) in quantitative yield.



Scheme 54

Diels–Alder reactions of 1,2-dihydropyridines with reactive dienophiles such as azo compounds and maleimides are also known ⟨76JHC481⟩.

In summary, the cycloaddition reactions of 1,2-dihydropyridines have proven to be very useful in the total synthesis of natural products. The primary reasons for their utility are that they have electron-rich reactive π-systems, they contain a heterocyclic nitrogen atom for alkaloid synthesis, and the stereochemistry is controlled in their cycloaddition reactions.



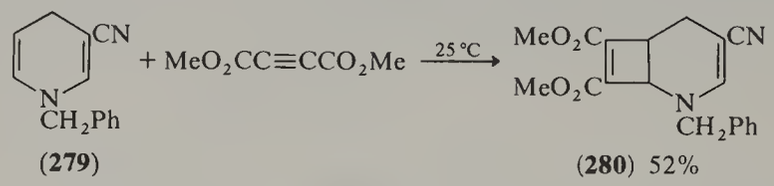
(277) (278)

Scheme 55

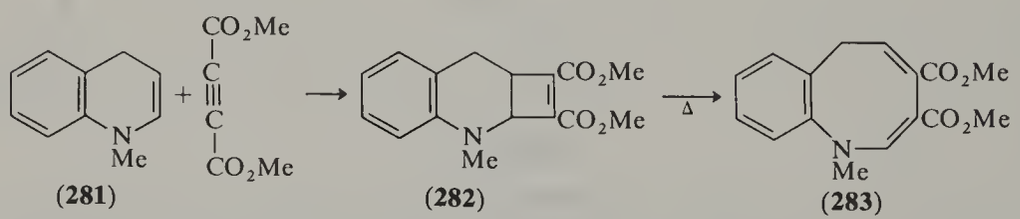
It is apparent from the above discussion that there are two kinds of dihydropyridines: those that contain electron-withdrawing groups on the ring, particularly nitrogen, and those that do not have these substituents. The electron-withdrawing groups stabilize the dihydropyridine ring system with respect to oxidation and polymerization. They also deactivate the π-system with respect to cycloadditions, causing the 1,2-dihydropyridine to behave more as a diene. The 1,2-dihydropyridines without these stabilizing substituents are more reactive but behave as enamines.

The cycloaddition reactions of 1,4-dihydropyridines have not been as extensively studied as those of their 1,2-dihydro isomers. Possibly this is on account of an early report on the attempted reactions of *N*-trimethylsilyl-1,4-dihydropyridine ⟨69JOC3672⟩. Also, until recently, simple 1,4-dihydropyridines were not as synthetically accessible ⟨75CC480, 80TL2105⟩.

Some 1,4-dihydropyridines containing electron-withdrawing groups on the ring have been reported to react with dimethyl acetylenedicarboxylate to give cyclobutane derivatives (equation 62) ⟨72JCS(P1)2918⟩. The 1,4-dihydroquinolines behave in a similar fashion (Scheme 56). The stability of these cyclobutenes with respect to the ring-opened diene is probably due to the presence of the electron-withdrawing group in conjugation with the nitrogen. It has been reported (Scheme 56) ⟨72TL4863⟩ that a simpler 1,4-dihydroisoquinoline gave the cyclobutene (**282**), which ring-opened in refluxing benzene to the benzazocine (**283**).



(279) (280) 52% (62)

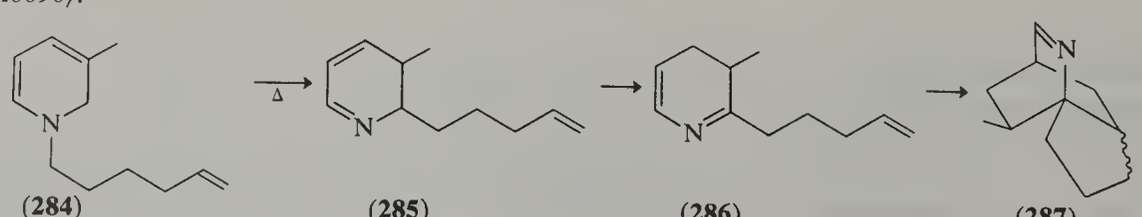


(281) (282) (283)

Scheme 56

The other dihydropyridines containing electron-deficient π-systems should also be capable of undergoing cycloaddition reactions. However, the instability of these compounds and lack of general methods for their preparation have precluded their study. In principle both the 2,3- and 3,4-dihydropyridines could behave as heterodienes in the Diels–Alder reaction. Although these reactions are known for the 2-azadienes, lack of information in the literature on 1-azadienes suggests that they will be reluctant to participate in cycloadditions ⟨B-67MI20700⟩. The double bonds present in the 2,5-dihydropyridine are isolated and would only be expected to behave as two-electron partners in cycloaddition reactions.

There are isolated reports where these dihydropyridines are involved in cycloaddition reactions. For example, the thermal rearrangement of 1,2-dihydropyridines gives 2,3-dihydropyridines. It has been postulated that the formation of (**287**) from the 1,2-dihydropyridine (**284**) occurs by rearrangement to (**286**) *via* the 2,3-dihydropyridine (**285**). An intramolecular cycloaddition reaction of (**286**) gives the observed product (Scheme 57) ⟨78JA6696⟩.



(284) (285) (286) (287)

Scheme 57

2.08

Pyridines and their Benzo Derivatives: (v) Synthesis

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2.08.1 INTRODUCTION

In view of the enormous number of preparative procedures available for pyridine, its derivatives and its benzologues, it is fortunate that there are some very substantial and comparatively recent reviews available for reference. There are two for pyridine itself

⟨60HC(14-1)99, 74HC(14-15)224⟩, one for quinoline ⟨77HC(32-1)93⟩ and one for isoquinoline ⟨81HC(38-1)139⟩. Among the polycycles, acridines have been the subject of two books ⟨B-66MI20800, 73HC(9)141⟩, the latter a revision of an earlier treatment. Phenanthridines have been reviewed to 1950 in a book ⟨B-52MI20800⟩ and to a later date in a review ⟨71AHC(13)315⟩. The benzoquinolines have been less recently reviewed ⟨B-52MI20801⟩, although there is a general review on 'azachrysenes' ⟨81JHC207⟩.

These reviews often contain tables of compounds together with the routes used to prepare them and in many cases reference in the present work will be directly to the appropriate chapter. Nevertheless, there are in most cases direct references to all the principal routes of synthesis; in such a restricted format a completely comprehensive account is impossible. The section on synthesis from other ring systems is weighted towards the work of the last 20 years.

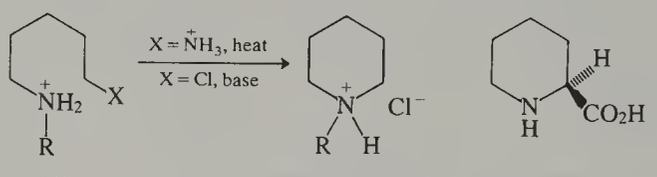
2.08.2 RING SYNTHESIS FROM NON-HETEROCYCLIC COMPOUNDS

2.08.2.1 Formation of One Bond

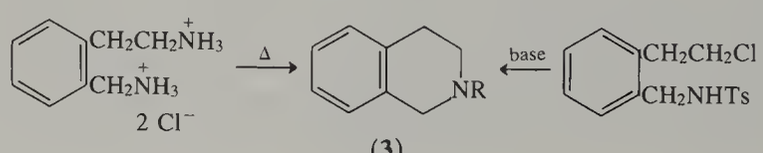
2.08.2.1.1 Bond formation adjacent to nitrogen

In general, the syntheses described in this section start with those suitable for saturated six-membered heterocyclic rings and proceed through increasing degrees of unsaturation to the fully aromatic pyridines.

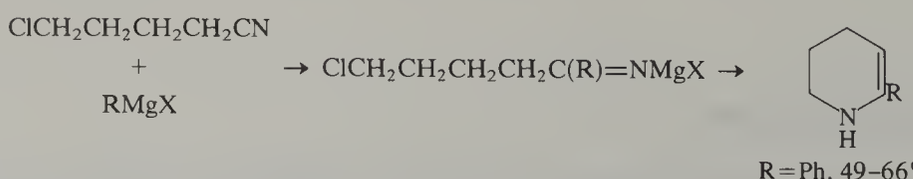
The simplest approach to piperidines is from a derivative of 1-pentanamine, with a leaving group on carbon 5. In the original Ladenburg synthesis ⟨1885CB3101⟩, distillation of 1,5-diaminopentane dihydrochloride (**1**; R = H, X = $\overset{+}{N}H_3$) gave piperidine hydrochloride, and 1,2,3,4-tetrahydroisoquinoline (**3**; R = H) has been similarly prepared ⟨23HCA785⟩. A recent modification uses disodium nitrosylpentacyanoferrate(II) to convert L-lysine into L-pipecolic acid (**2**) ⟨82SI63⟩. A 5-halogenopentanamine possesses a better leaving group, and such compounds are generally stable only as salts, basification of the salt (**1**; R = Pr^i, X = Cl) giving the piperidine ⟨46JA1530⟩. Tetrahydroisoquinoline (**3**; R = H) can be made by heating the salt of 2-(aminomethyl)phenethylamine ⟨23HCA785⟩, or by treating 2-(*N*-tosylaminomethyl)phenethyl chloride with base ⟨72CPB1592⟩ and hydrolyzing the *N*-tosyl derivative (**3**; R = Ts) thus obtained. From 2-aminophenylpropyl chloride, 1,2,3,4-tetrahydroquinoline is formed ⟨05CB850⟩. The lack of reactivity of aryl halides toward nucleophiles makes this route unsuitable for the preparation of tetrahydroquinolines from 2-halogenophenylpropanamines, although benzyne routes are available to polycycles (Section 2.08.2.1.3). Tetrahydropyridines have been obtained from 4-chloro-1-cyanobutane by reaction with Grignard reagents, followed by cyclization of the chloroimines (equation 1) ⟨37JA984⟩. A similar cyclization has been achieved using a lithium imine ⟨74BSF1710⟩.



(**1**) (**2**)



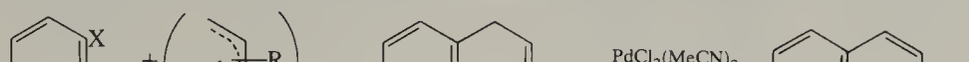
(**3**)



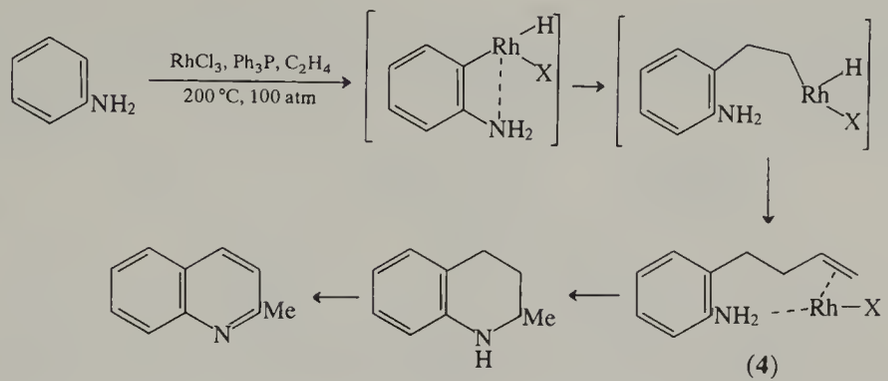
(1)

Unactivated double bonds remote from a primary amino group can be used in cyclizations mediated by transition metal catalysts. Equation (2) shows a palladium(II)-catalyzed prepar-

ation of quinoline (indolines are also formed) ⟨78JA5800⟩, and equation (3) shows a synthesis of quinaldine or tetrahydroquinaldine from aniline and ethylene; the intermediate (**4**) has been isolated ⟨79JA490⟩.



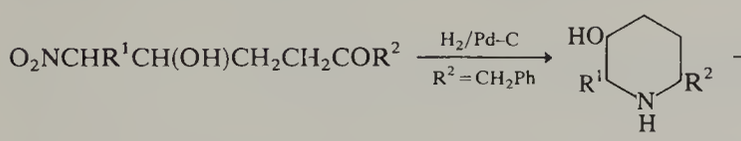
(2)



(3)

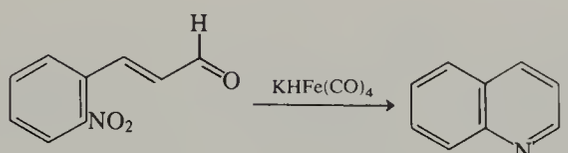
(**4**)

Piperidines have often been prepared by condensation between suitably placed primary amino and carbonyl groups. The simplest cases would be 5-aminopentanals or the corresponding ketones, and the common approach to these is from the nitro compounds by reduction. Syntheses of 3-hydroxypiperidines follow this route (equation 4) ⟨74BSF1001⟩. A number of quinoline syntheses involve the reduction of an *o*-nitrocinnamyl derivative; the simplest uses *o*-nitrocinnamaldehyde. Potassium tetracarbonylhydridoferrate reduces (**5**) to quinoline in quantitative yield. If more vigorous reduction is required the aldehyde



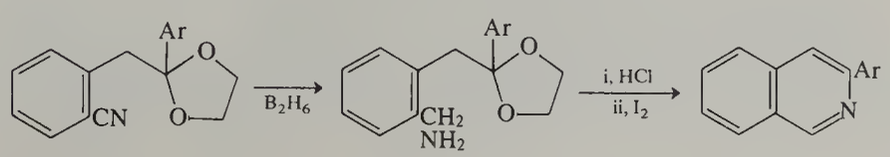
R^1	H	Me	Et
%	97	100	90

(4)

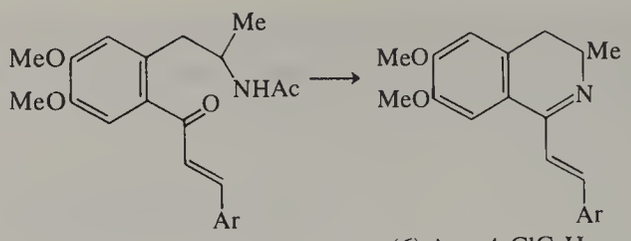


(**5**)

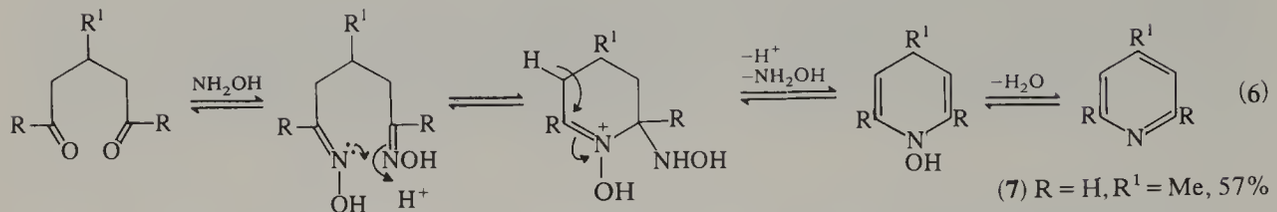
or ketone must be protected, as shown in the synthesis of 3-arylisoquinolines (equation 5) ⟨78JOC3817⟩. The *o*-cyanobenzyl ketones are readily prepared from *o*-cyanotoluene, an aromatic ester, and a strong base. Again, the amine can be protected (for example by acetylation) while the rest of the molecule is assembled, then released by acid, as in the synthesis of the dihydroisoquinoline (**6**) ⟨72MI20800⟩. Derivatives of the ketone or aldehyde (oximes or anils) can be used; a simple synthesis of pyridines giving high yields involves reaction between a diketone, or a keto aldehyde, and hydroxylamine. The intermediate is a mono- or di-oxime and these can be used, although more commonly the dicarbonyl compound is boiled with alcoholic hydroxylamine hydrochloride. A number of examples are given in a review ⟨60HC(14-1)307⟩ where a mechanism is suggested (equation 6) which accounts for the necessary change in oxidation state to provide the fully unsaturated pyridines. Glutaric dialdehydes are difficult to obtain but, if available, give pyridines (**7**) without substituents at positions 2 and 6 ⟨55BRP734381⟩. There is no advantage in the use of the oxime rather than the dicarbonyl compound, unless there is an alkyl group which can take part in an intramolecular aldol condensation to give a cyclohexenone; this side reaction is suppressed by using the oxime. The pyrrolidine enamine of cyclohexanone can be converted into 1,5-diketones such as (**8**), which give 5,6,7,8-tetrahydroquinolines when boiled with hydroxylamine hydrochloride in alcohol ⟨70MI20800⟩.



(5)

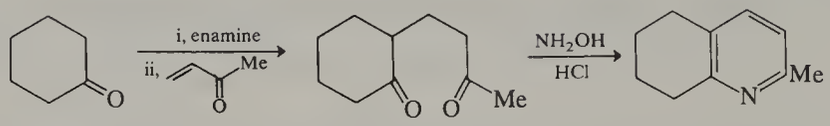


(**6**) Ar = 4-ClC_6H_4



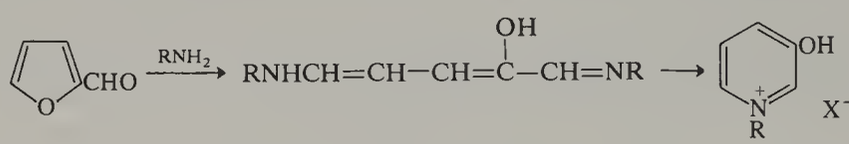
(6)

(**7**) R = H, R^1 = Me, 57%

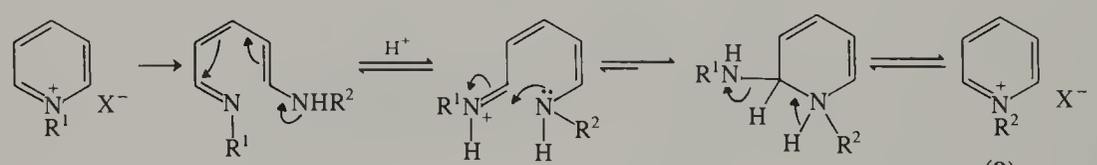


(**8**)

Other carbonyl derivatives used in cyclization are mono- or di-anils; pyridines are obtained, although dihydropyridines might have been expected. Dianils are generally made from pyridinium salts (see Section 2.08.3.4.4) but can be obtained from furfural (equation 7) ⟨05CB3824⟩. The products from dianils are *N*-arylpyridinium salts (equation 7 and compound **9**). The latter example shows the full sequence for conversion of one pyridinium salt to another, included here because the intermediate dianil can be isolated ⟨05LA(341)365⟩.



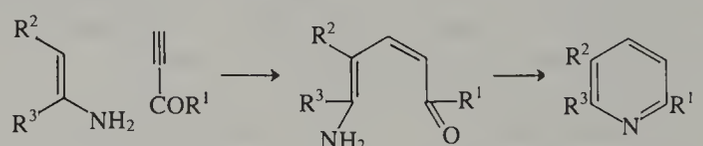
(7)



(**9**)

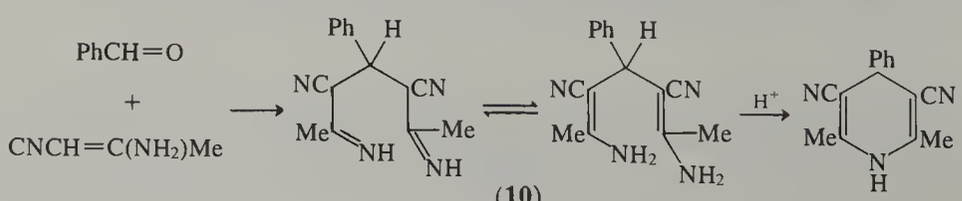
e.g. R^1 = 2,4-$(O_2N)_2C_6H_3$, R^2 = Ph

The interconversion can be achieved without isolating the dianil if the added amine is a stronger base than the leaving group ⟨05LA(341)365⟩. Aminopentadienones can be obtained from β-aminocrotonates and ethynyl ketones, and will cyclize when heated under vacuum to give trisubstituted pyridines (equation 8) ⟨57CB2265⟩. Diimines (**10**) are obtained from aldehydes and β-aminocrotononitrile and are cyclized in boiling acetic anhydride or boiling hydrochloric acid ⟨1897JPR(56)124⟩. Another route to diimines starts from the anion (**11**) and a nitrile. Cyclization of the diimine gives a 2,5-dihydropyridine, and elimination of *t*-butylamine completes the aromatization ⟨75TL4375⟩. Cyclization of unsaturated monoximes can be achieved with phenoxide ion and a palladium complex (equation 9) ⟨76TL383⟩ or, with a higher degree of unsaturation, can be electrocyclic (equation 10) ⟨74HCA1676⟩. The electrocyclic route has been used to obtain 5,6,7,8-tetrahydroisoquinolines (equation 11).

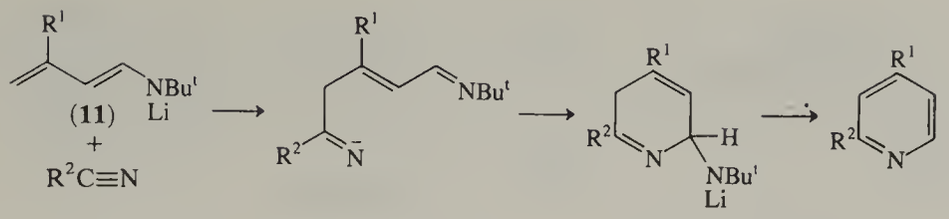


(8)

R^1 = Me, Ph, aryl; R^2 = CN, COMe, CO_2Et; R^3 = H, alkyl, Ph

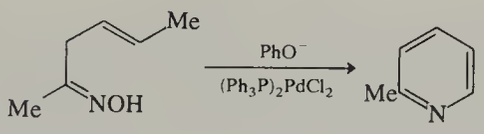


(**10**)

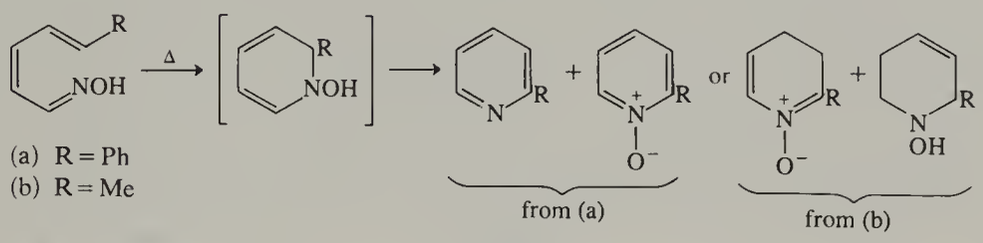


R^1 = H, Me; R^2 = alkyl, aryl

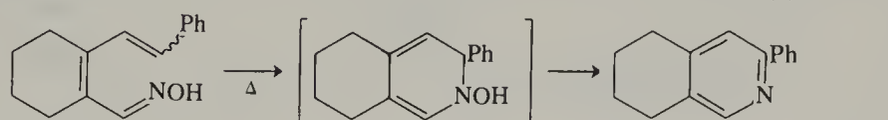
The yields of pyridines are generally low, but precursors for equation (10) are easily prepared by condensation of cinnamaldehydes with acetophenones. Sulfonyl- and acyl-hydrazones of *o*-ethynylbenzaldehyde can be cyclized by base to give isoquinolinium ylides (equation 12) ⟨80JCS(P1)1331⟩.



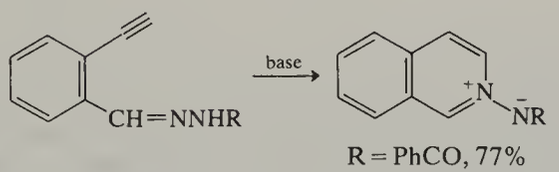
(9)



(10)

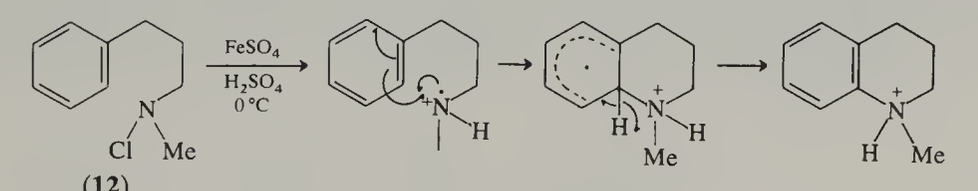


(11)

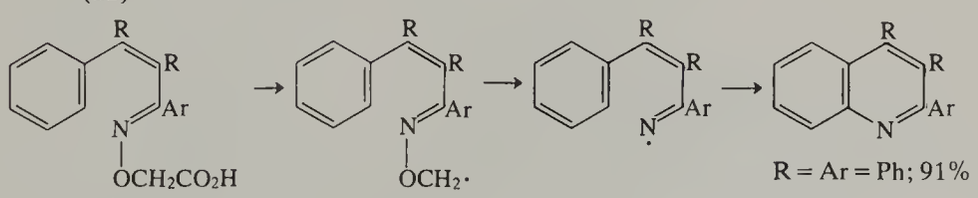


(12)

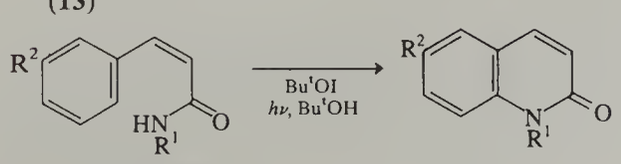
A number of syntheses of quinolines or tetrahydroquinolines, and of polycycles, involve the attack by a reactive nitrogen atom on a benzene ring. A free radical attack causes the cyclization in the formation of *N*-methyl-1,2,3,4-tetrahydroquinoline from the chloroamine (**12**) ⟨66TL2531⟩ in the persulfate oxidation of oxime (**13**) ⟨76CC677⟩, and in the photochemical cyclization of the unsaturated amide (**14**) ⟨77JCS(P1)1348⟩. A similar radical cyclization of derivatives of *o*-benzoylstilbenes (equation 13) can give isoquinolines or isoindoles ⟨81JCS(P1)1721⟩, while biphenyls give phenanthridines ⟨75CC291⟩. Radical cyclization of the biphenylcarboxamides probably proceeds through a spirodiene intermediate (**15**) ⟨73JCS(P1)1647⟩. A radical intermediate is suggested for the photochemical cyclization of the 2-bromophenylpropanamine (**16**); an equal amount of a benzazocine is obtained ⟨79JOC1236⟩.



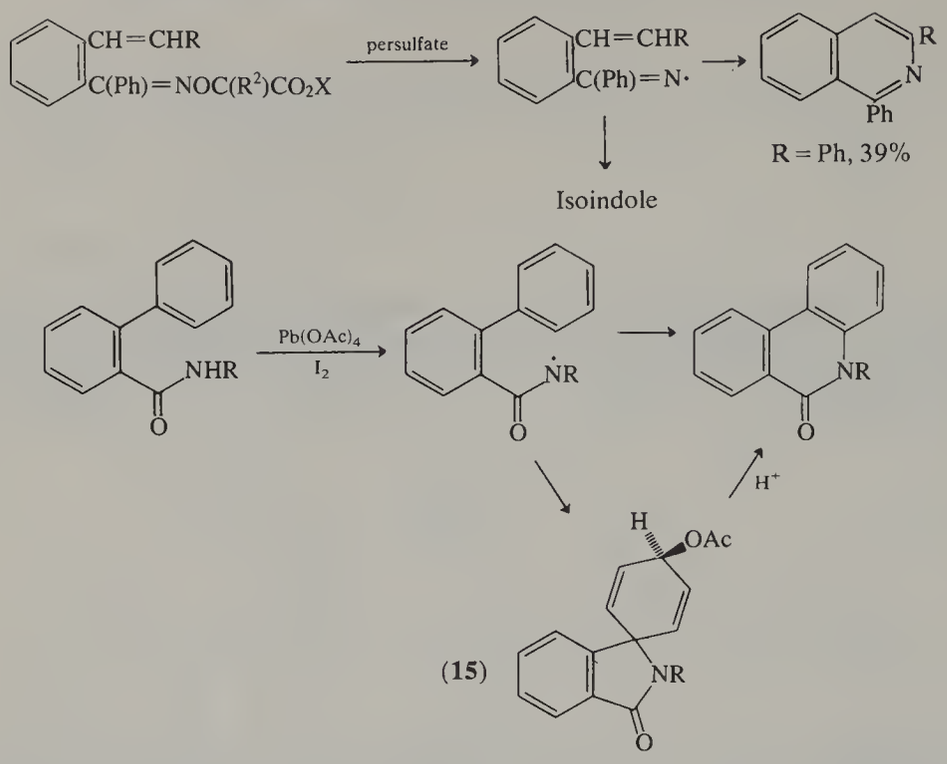
(**12**)



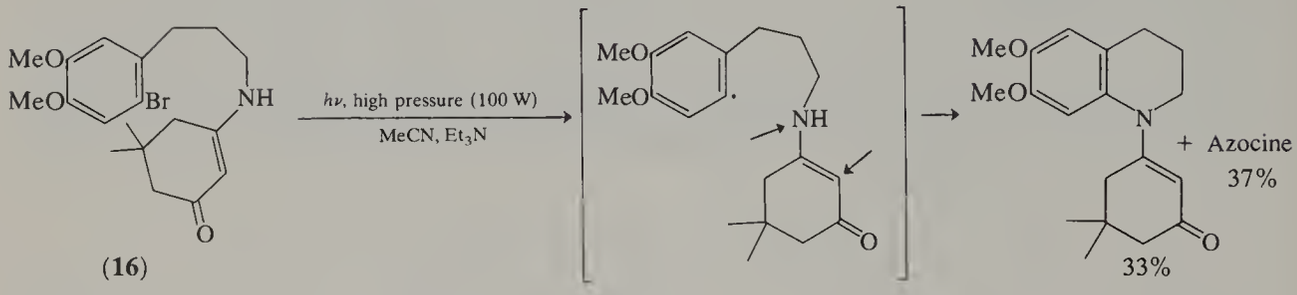
(**13**)



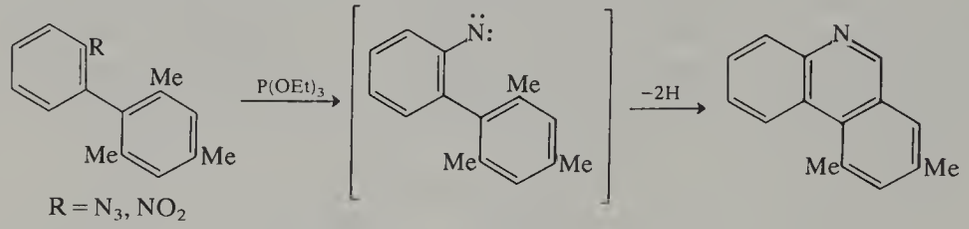
(**14**)



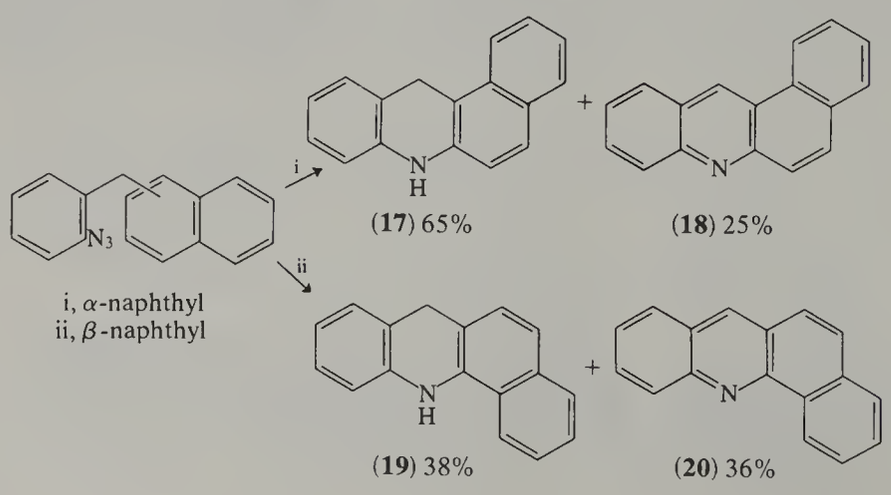
(13)

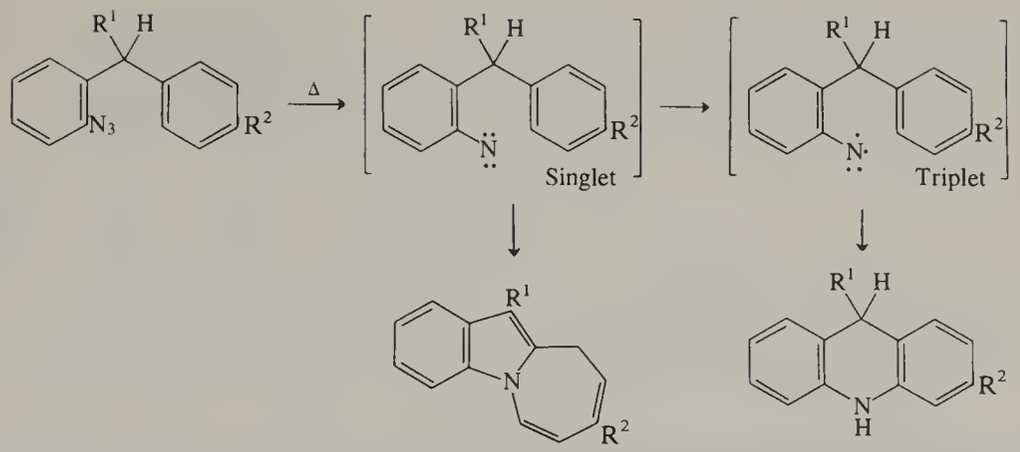


Nitrenes can insert into the C—H bonds of adjacent methyl groups; 2,4-dimethylphenanthridine has been obtained from the azido- or the nitro-biphenyl (equation 14) ⟨60JA4717, 67CC178⟩. Insertion can occur also into aromatic π-systems, so that *o*-nitreno-di- or -triphenylmethanes can give acridans as well as the more normal azepinoindoles, as in equation (15). It has been suggested that the acridans arise from the triplet nitrene, and thus the cyclization is due to a nitrogen radical species ⟨78JCS(P1)1211⟩. Insertion into adjacent naphthalenes gives exclusively acridans (or acridines); thus high yields of benz[*a*]-acridan (**17**) and -acridine (**18**) and of benz[*c*]-acridan (**19**) and -acridine (**20**) are obtained from the appropriate *o*-azidobenzylnaphthalenes ⟨74JCS(P1)2066⟩.



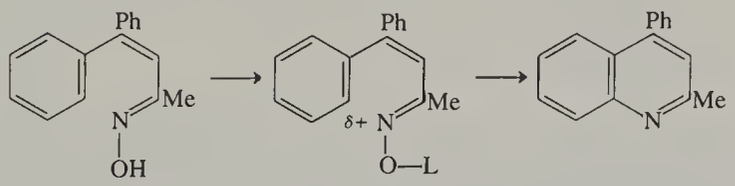
(14)





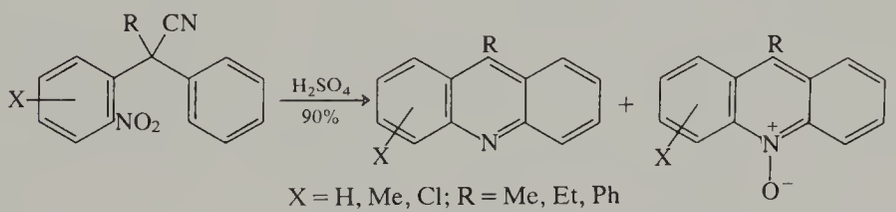
(15)

Attack on a benzene ring is more commonly associated with formation of an electrophilic site, a route which can also give monocyclic pyridines. Electrophilic cyclization of cinnamaldoximes to give quinolines has been reported using phosphorus pentoxide or alumina. When acetic anhydride was used as the cyclization solvent it was discovered that oxime esters can be cyclized without Lewis acids, if they have the correct stereochemistry about the double bond (in some cases irradiation was used to cause *E–Z* isomerization). The reaction is summarized for the most favorable case in equation (16) ⟨72ZOR2586⟩; the competing Beckmann rearrangement can lead to isoquinolines. An unusual use of a nitro group as an electrophile gives 9-substituted acridines and their *N*-oxides (equation 17) ⟨73CC794⟩. The cyclization of cyanides by electrophilic reagents is dealt with later.



(16)

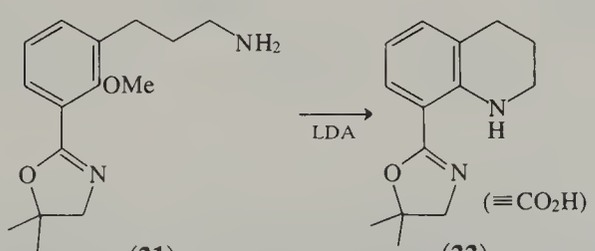
L = Lewis acid, *e.g.* BF_3, $SnCl_4$; Al_2O_3, P_2O_5 give isoquinolines



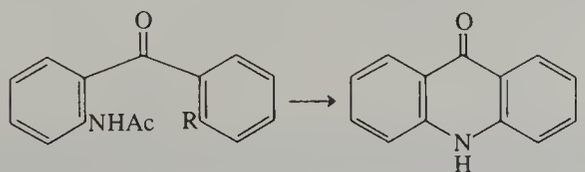
(17)

X = H, Me, Cl; R = Me, Et, Ph

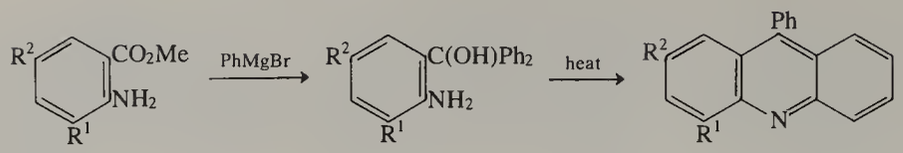
In its more normal role as a nucleophile, or as an amide ion, a suitably placed nitrogen atom can displace a methoxy or tosyloxy group. In the synthesis of the tetrahydroisoquinoline (**22**) from the amine (**21**), the substituent oxazoline (a masked carboxylic acid) is known to aid displacement of the adjacent methoxy group ⟨81JOC783⟩, while in the synthesis of the acridone (**23**) the adjacent carbonyl group aids nucleophilic substitution ⟨76JCS(P1)2089⟩. In a synthesis of acridines a triarylmethanol or its acetate is heated (equation 18); it seems that a carbenium ion intermediate is formed, but a dehydrogenation stage is also necessary ⟨04CB3191, 57ZOB1558⟩. An apparent replacement of an hydroxyl group occurs when the hydroquinone (**24**) is oxidized by ferricyanide to give 6-hydroxyquinoline ⟨64JOC2860⟩.



(**21**) (**22**)

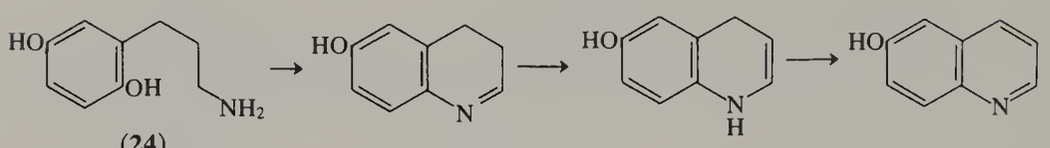


(**23**) R = OTs, 100%; R = OMe, 68%



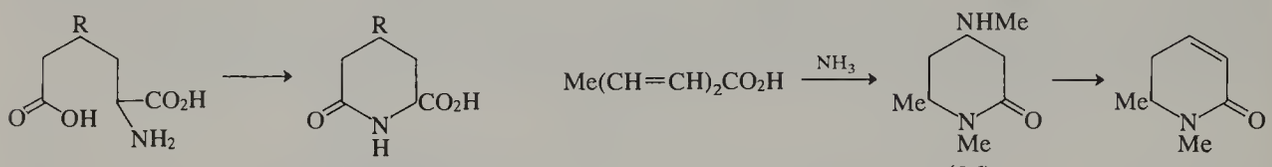
(18)

R^1	Br	Cl	Cl	Br
R^2	Cl	Br	Cl	Br
%	61	55–66	53–61	63–67



(24)

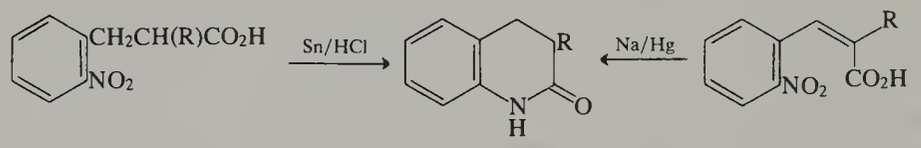
In a very large group of syntheses of pyridines and their benzologues, cyclization occurs by condensation between an amine and a carboxylic acid or derivative. The formation of the six-membered ring is so easy that attempts to prepare 5-aminopentanoic acids often yield only the cyclic lactam. Simple examples of this are the thermal cyclizations of α-aminoadipic acids to give the piperidones (**25**) ⟨05CB1654⟩. Addition of methylamine to sorbic acid gives the methylaminopiperid-2-one (**26**) which on heating gives a dihydropyrid-2-one ⟨54CJC683⟩.



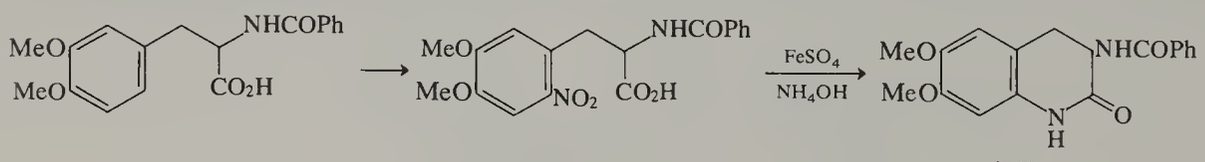
(25) R = H, Me

(26)

One of the earliest and most versatile routes to 3,4-dihydroquinol-2-ones (**27**) was by reduction of *o*-nitrophenylpropanoic acids ⟨1880CB115⟩ or *o*-nitrocinnamic acids ⟨1890G396⟩. Appropriately substituted phenylpropanoic acids can give derivatives of 3-amino- or 3-carboxy-dihydroquinol-2-one (**28**) ⟨36JIC260⟩ or (**29**) ⟨1896CB665⟩. The synthesis of compound (**28**) highlights a weakness of this route. Unless a powerful directing group is present in the benzene ring, nitration of the phenylpropanoic acid will give mixtures of *o*- and (unwanted) *p*-nitro derivatives. However, a considerable variety of *o*-nitrophenylcinnamic acids is available from the condensation of *o*-nitrobenzaldehyde with active methylene compounds. These possibilities are summarized in Scheme 1 and have been reviewed in detail ⟨77HC(32-1)207⟩. Of the groups shown in Scheme 1, almost any can take precedence in the cyclization if the correct reducing agent is used, but it is not clear if this is due to a preferred stereochemistry in the condensation stage or because of varied activity in the cyclization stage.



(27)



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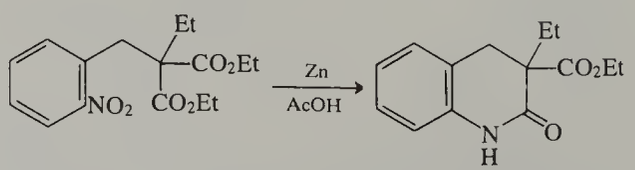
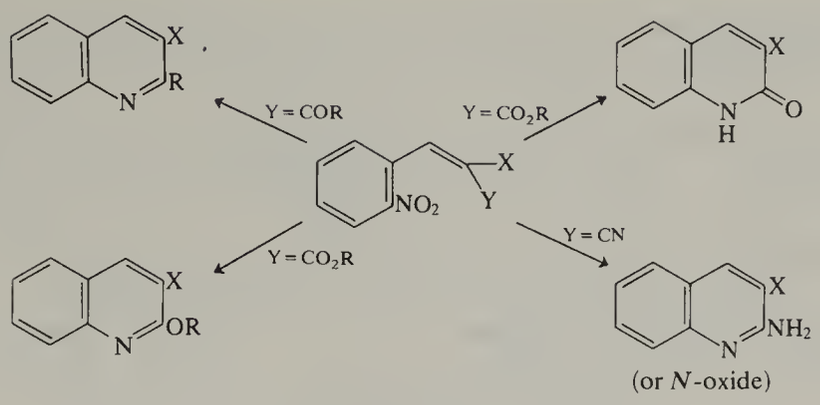


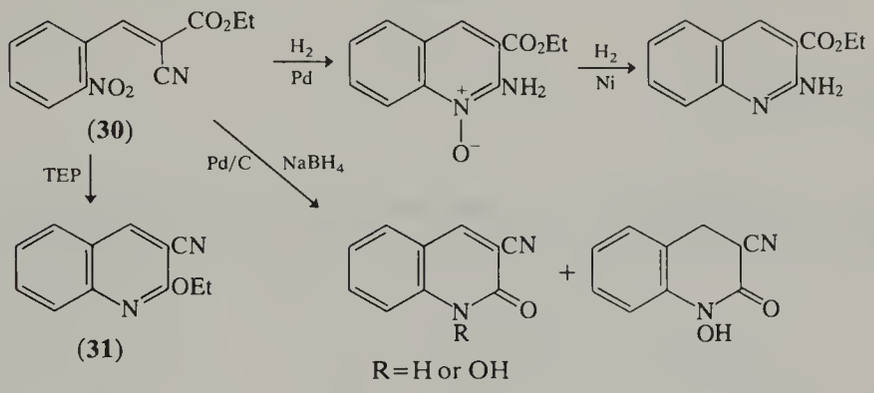
(29)

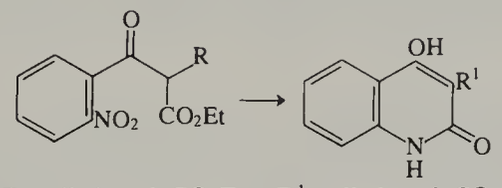
The *o*-nitrobenzylidenecyanoacetate (**30**) will serve to illustrate the possibilities; it is catalytically reduced to the 2-aminoquinoline *N*-oxide or to the 2-aminoquinoline



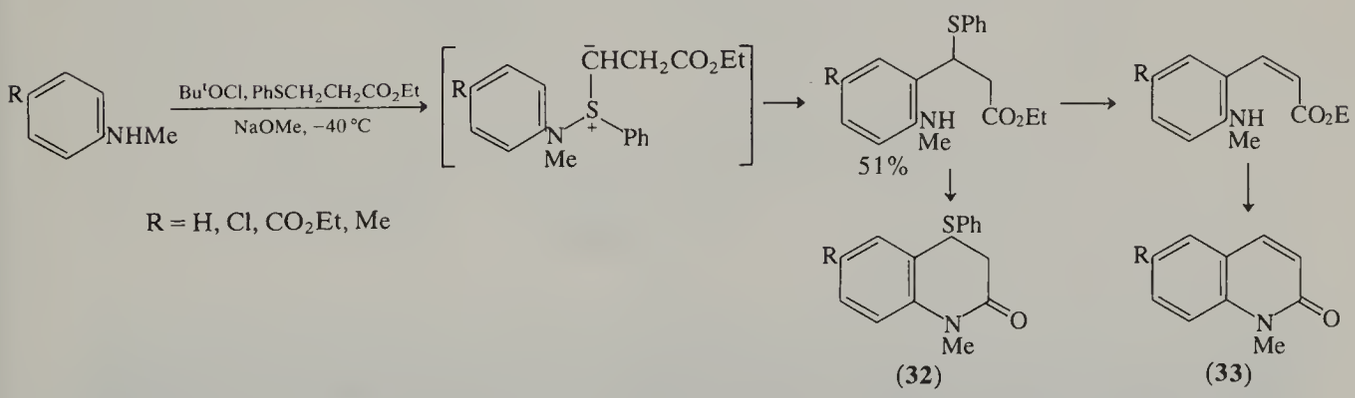
Scheme 1

⟨26HCA980, 38CB2226⟩, but is reduced by sodium borohydride and palladium–charcoal to the 3-cyanoquinol-2-one or its *N*-hydroxy derivative ⟨69JCS(C)713⟩. The borohydride reduction products vary with solvent and temperature, and can include the 1-hydroxydihydroquinol-2-one. Deoxygenation of the cyanoacetate (**30**) by triethyl phosphite also gave a product (**31**) from cyclization with the ester group ⟨71CPB1321⟩. The reduction of *o*-nitrobenzoyl-acetates or -malonates gives derivatives of 4-hydroxyquinol-2-one as in equation (19) ⟨21CB1079⟩. One route which avoids the nitration stage with its attendant disadvantages starts from an *N*-methylaniline and uses a 2,3-sigmatropic shift to introduce the side chain. The products can be a 3,4-dihydroquinol-2-one (**32**) or a quinol-2-one (**33**) ⟨77CC694⟩.



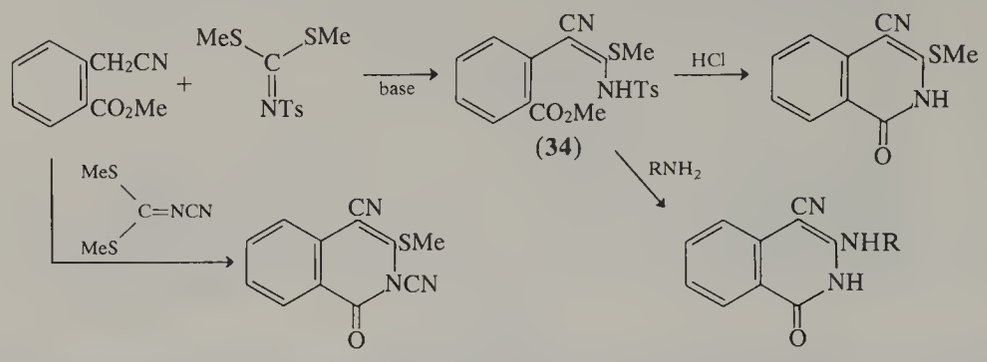


(19)



Isoquinolin-1-ones and isoquinolin-3-ones can be made by condensation of appropriate amino esters. The sequence shown in equation (20) gives a 3-methylthioisoquinolin-1-one ⟨80YZ456⟩. Modification of the starting material produces an *N*-cyanoisoquinolin-1-one, while treatment of the intermediate (**34**) with ammonia or an amine gives a 3-aminoisoquinolin-1-one. Removal of the *N*-acetyl group from compound (**35**) allows the formation of the dihydroisoquinolin-3-one ⟨75JMC395⟩. Phenanthridinones and benzophenanthridinones can be obtained by intramolecular lactamization; in the former case the precursor is a 2,2′-disubstituted biphenyl. The 2-nitrobiphenyl-2′-carboxylic acids (**36**) and

(**37**) can be reduced (*e.g.* with tin and hydrochloric acid) and the amino acids cyclize readily ⟨1891LA(266)138, 78JOU830⟩.



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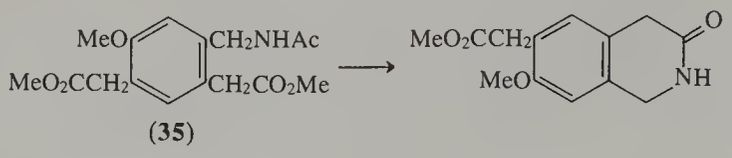
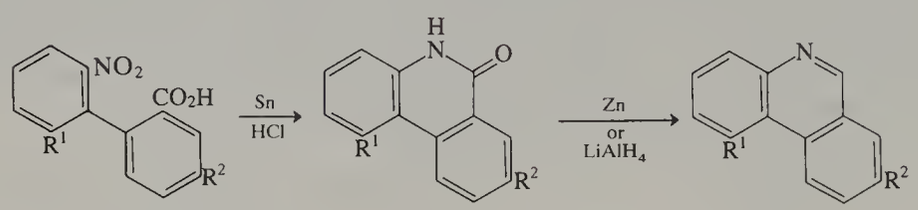
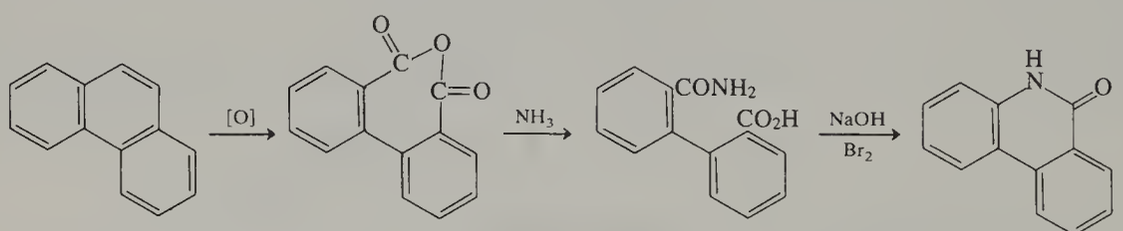




(**36**) $R^1 = R^2 = H$
(**37**) $R^1 = CO_2H$; $R^2 = NO_2$

Oxidation of a phenanthrene gives a diphenic anhydride, the monoamide of which is converted by the Hofmann procedure to the amino acid and cyclization gives phenanthridinone (equation 21) ⟨1893LA(276)245⟩. The benzophenanthridinone (**38**) is made by a similar route ⟨04LA(335)122⟩. Surprisingly, the phenanthridinone is also obtained by a Curtius–Schmidt reaction on 2-carboxy-2′-formylbiphenyl ⟨78JGU1526⟩. Phenanthridinones can be converted into phenanthridines by zinc dust distillation or *via* the chlorides; lithium aluminum hydride reduction is said to give good yields of phenanthridines ⟨50MI20800⟩.



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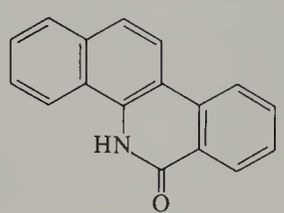
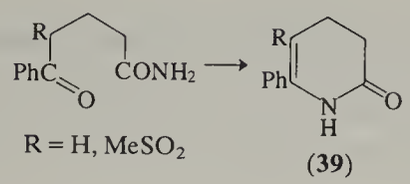
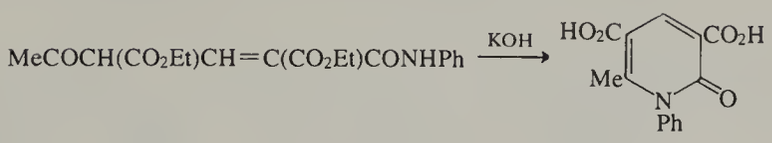


(**38**)

An alternative route to pyridones or piperidones is by reaction between an amide or nitrile (which provide the nitrogen atom) and a carbonyl group (ketone or ester). When a 5-ketobutanamide is cyclized (for example by acetyl chloride, or by anhydrous acids) a dihydropyrid-2-one (**39**) results, the double bond taking up the 5,6-position ⟨37JA686, 72JOC2147⟩. If additional unsaturation is available in the starting material, as in equation (22) ⟨08JCS1022⟩, the pyridone is produced. The unsaturation can also be introduced if a leaving group is present in the starting material (equation 23) ⟨57CB711⟩ or is introduced by the reagent as in equation (24) ⟨22JA2903⟩. The sequence shown in equation (23) has been used to prepare 5,6,7,8-tetrahydroquinolin-2-one.



R = H, $MeSO_2$ (39)



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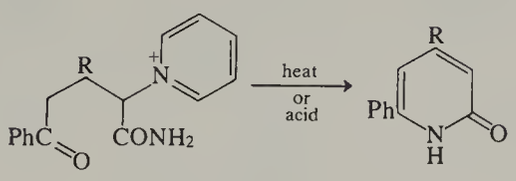
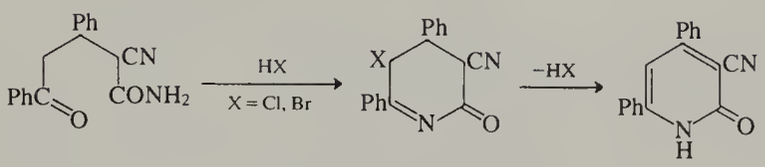


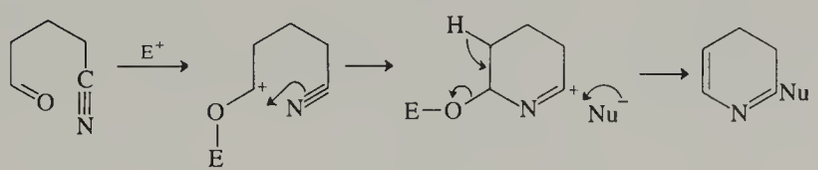
R = H, Ph R = H, 43%

(23)



(24)

Cyclization of δ-ketonitriles may proceed through the amide, but more commonly is initiated by electrophilic attack on the carbonyl group, thence on the nitrogen atom, and completed by entry of a nucleophile (often a halide) at position 2; the sequence is shown in equation (25). Two modes of cyclization are demonstrated for ketonitrile (**41**) ⟨27JA1112⟩. Anhydrous hydrogen bromide in acetic acid gives the dihydropyridone (**40**), while bromine gives the 2-bromopyridine (**42**). Alumina has been used to synthesize the dihydropyridone (**43**) ⟨64MI20800⟩; dehydrogenative procedures using palladium and alumina ⟨59USP3007931⟩ or nickel under a hydrogen atmosphere ⟨53CB25⟩ give the pyridines (**44**) and (**45**).



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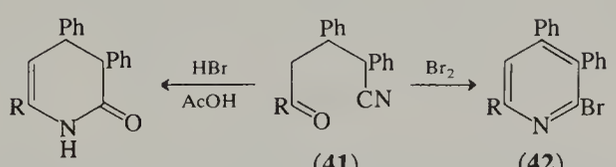
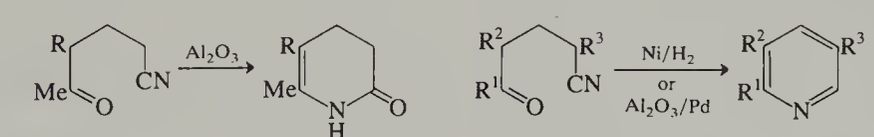


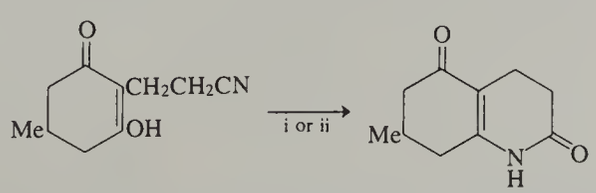
(**40**) 91% (**41**) R = 4-$MeOC_6H_4$ (**42**)



R = $AcOCH_2CH_2$ (**43**) 40%

(**44**) R^1 = Me, R^2 = Et, R^3 = H, 10%
(**45**) R^1 = Me, R^2 = Aryl, R^3 = CO_2Et

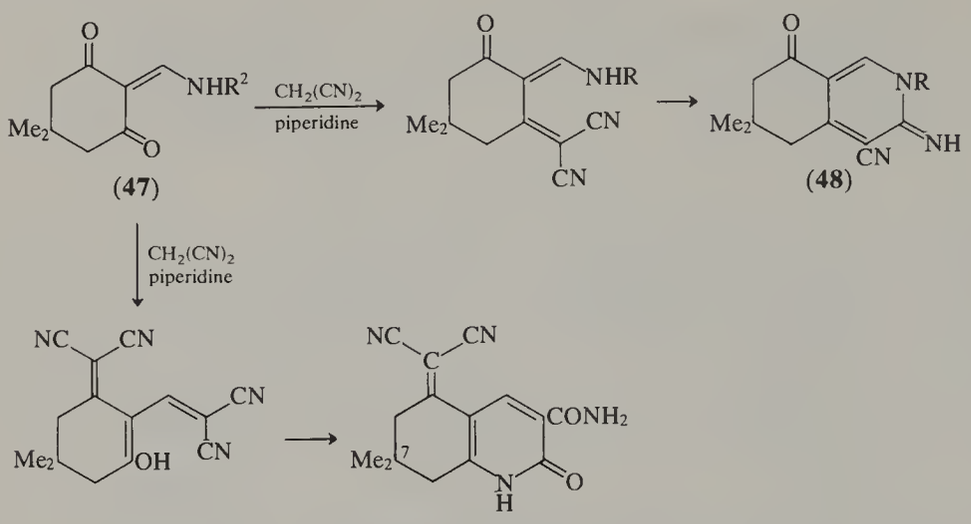
The tetrahydroquinoline-2,5-dione (**46**) is obtained when the 2-cyanoethylcyclohexane-1,3-dione is treated with acetyl chloride in chloroform, or phosphorus tribromide in pyridine ⟨76JOC636⟩. In contrast, the cyclohexane-1,3-dione (**47**) can be converted into an isoquinolin-



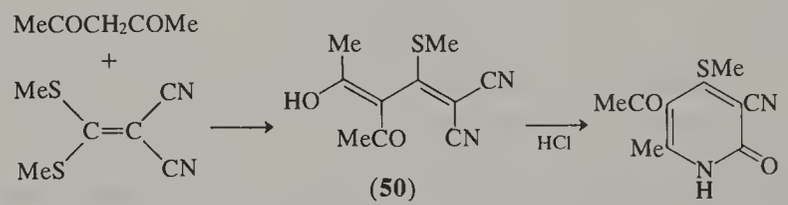
(**46**)

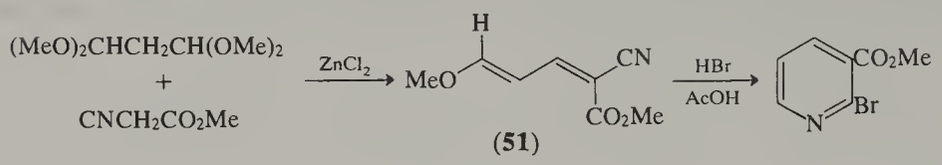
i, AcCl, $CHCl_3$, 29–39%; ii, PBr_3/C_5H_5N, 20%

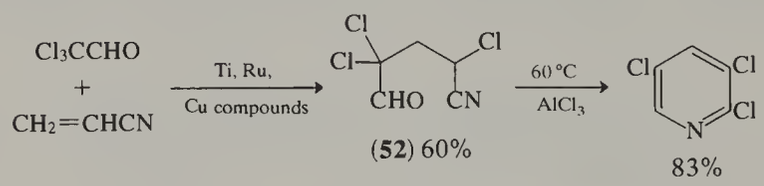
3-imine (**48**) or into a quinol-2-one (**49**) ⟨74M1283⟩. The formation of the isoquinolinimine shows an alternative mode of cyclization of nitriles, dealt with later, involving attack by nucleophilic nitrogen on the nitrile carbon. For the preparation of fully unsaturated pyridines or pyrid-2-ones, the additional double bond can again be in the starting material as in the enol (**50**) ⟨75YZ623⟩ or the enol ether (**51**) ⟨74JOC3436⟩, or latent, as in the chloro derivative (**52**) ⟨80EUP12117⟩.



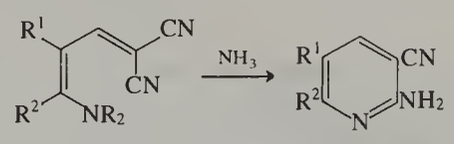
(**49**) 42%; 7,7-dihydro, 70%



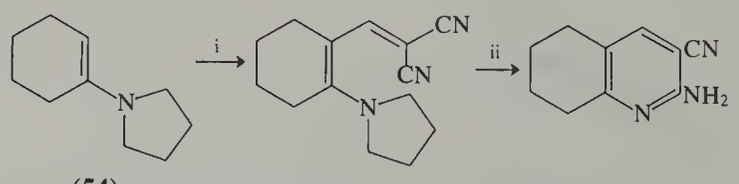




Enamines or imines can form pyridines by cyclization to a nitrile group, as shown in the production of compound (**48**). Alternatively, the nitrogen atom of the nitrile can be made more nucleophilic by attack on the carbon atom by an external nucleophile. Ammonia causes cyclization of the dienamines (**53**) ⟨77JHC1077⟩ and (**54**) ⟨78JAP(K)7868781⟩; in both cases, elimination of the amine introduces the extra double bond. Dimethylamine or piperidine cause cyclization of 1-cyano-2,5,5-trimethylhex-1-en-3-yne to the *t*-butylpyridine (**55**). There are a few other examples of the synthesis of bicyclic compounds from

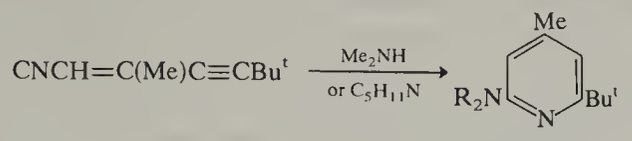


R^1 = alkyl; R^2 = H or alkyl; 37–91%

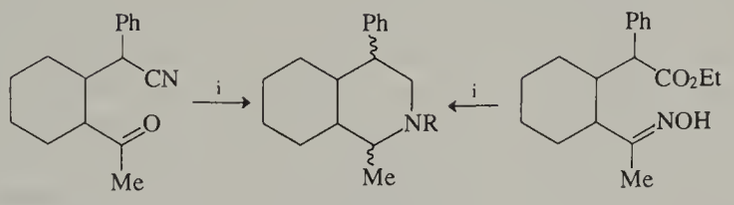


i, $MeOCH{=}C(CN)_2$; ii, NH_4OH; *N.B.* HCl or HBr give 2-Cl or 2-Br

amides or nitriles. The decahydroisoquinolines (**56**) (mixture of stereoisomers) have been obtained by reductive cyclization ⟨51JCS1392⟩ and the dihydroisoquinolone (**57**) by carbenium ion attack on the amide nitrogen atom ⟨70JOC3704⟩.

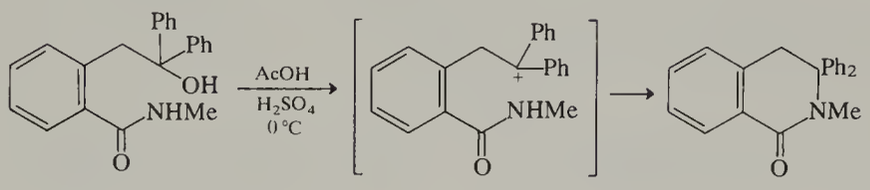


(**55**) R = Me or $R_2 = (CH_2)_5$



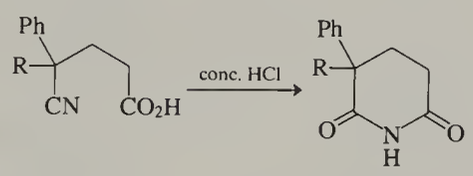
(**56**) R = Me, Et

i, H_2, copper chromite, ROH

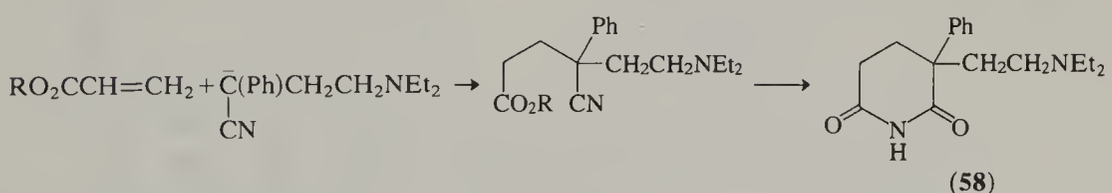


(**57**)

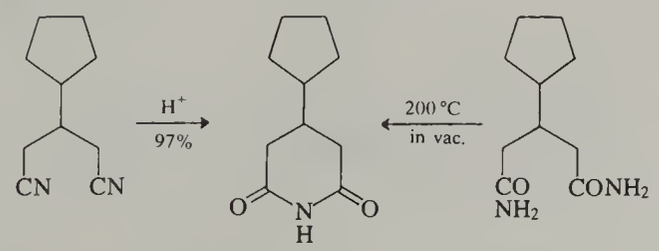
When the cyclization occurs between a nitrile or carboxamide and another carboxylic acid or derivative, the products are glutarimides (2,6-dioxopiperidines). Such compounds can often be better prepared directly from the glutaric acids (5 + 1 cyclization) or from glutaric anhydrides and ammonia or amines (ring transformation). Cyclization of the monoamide of a glutaric acid can be brought about by acid chlorides, anhydrides or, in the example shown in equation (26), by concentrated mineral acid ⟨53BSF70⟩. Diamides can be cyclized by heat (equation 27) ⟨44JA1550⟩ but in neither case is there any advantage over the direct use of the glutaric acid. On the other hand, glutaric acid mononitriles can be prepared by Michael addition of phenylacetonitriles to acrylates, and then cyclized by concentrated sulfuric acid to give 3-aryl-2,6-dioxopiperidines (**58**) ⟨53USP2664424⟩. Glutaric acid dinitriles can be obtained from 1,3-dihalopropanes and are cyclized by acid as in equation (27) ⟨54JA5548⟩ or by Grignard reagents as in equation (28) ⟨26MI20800⟩.



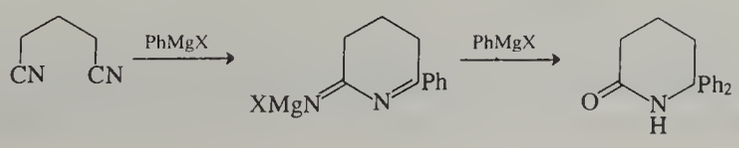
(26)



(**58**)

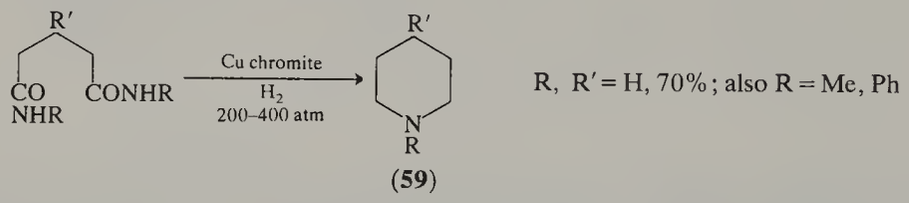


(27)



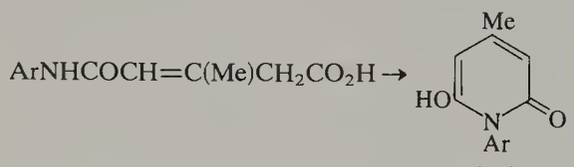
(28)

Reductive cyclization of glutaronitriles can give good yields of piperidines, and reductive cyclization of glutaramides has been used to prepare a number of substituted piperidines (**59**) ⟨36JA2487⟩. Additional unsaturation (to give 6-hydroxypyrid-2-ones) can be introduced in the precursor if glutaconic acid derivatives are used, or during the cyclization if β-hydroxyglutaric acids are used (for example citric acid). The yields are lower with glutaconic acids, as shown by the synthesis of the *N*-aryl-6-hydroxypyrid-2-ones (**60**) ⟨56JA4683⟩. Citric acid triamide is cyclized by acids or by bases to give the pyridone-4-carboxamide (**61**) in high yield ⟨55BRP741712⟩. Cyclization of 3-ketoglutaramides gives 4,6-dihydroxypyrid-2-ones (**62**) ⟨57JCS356⟩, while a 3-iminoglutaronitrile gives a 4-aminopyrid-2-one (**63**) ⟨04JCS1726⟩. Similar routes to bicyclic systems are available. The *o*-cyanophenylacetyl chlorides (**64**) are cyclized by hydrogen halides to give 1-halo-3-hydroxyisoquinolines; the reaction is illustrated for the 1-chloro derivatives ⟨74LA1802⟩. The cyclohexene (**65**) gives a 5,6,7,8-tetrahydroisoquinoline-1,3-dione ⟨71JCS(C)3620⟩. In the Meisenheimer adduct (**66**) the electrophilic amidinium group cyclizes with the nitrile to produce an isoquinoline-1,3-diamine ⟨78JOC3600⟩. Lithium chloropalladite cyclizes the pentadienocarboxamides (**67**) and the *o*-carbamoylstilbenes (**68**) to give pyridones ⟨75CI(L)745⟩ and isoquinol-1-ones ⟨80CI(L)666⟩ respectively. A link with the next type of cyclization is provided by the conversion by reduction of the *o*-nitrophenylethyl cyanides (**69**) into 3,4-dihydroquinoline *N*-oxides and the deoxygenated compounds ⟨77S56⟩.



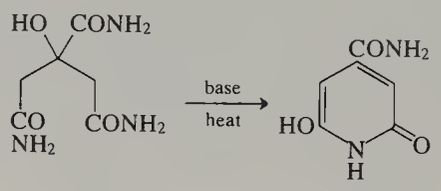
R, R′ = H, 70%; also R = Me, Ph

(**59**)

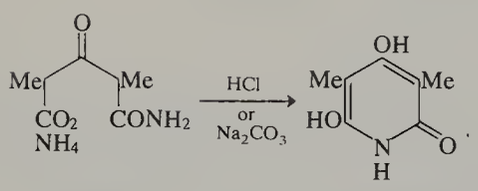


Ar	Ph	*p*-MeC$_6$H$_4$	*p*-ClC$_6$H$_4$
%	35	30	45

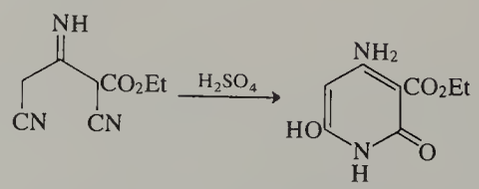
(**60**)



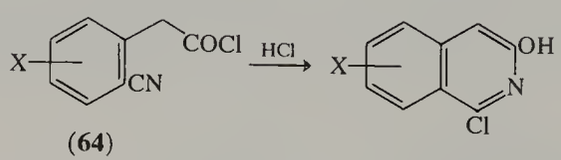
(**61**) 81%



(**62**) 86%



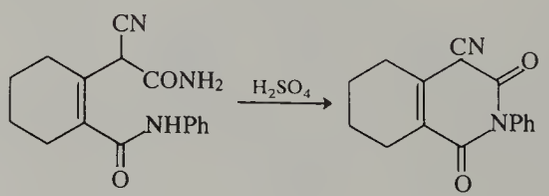
(**63**)



(**64**)

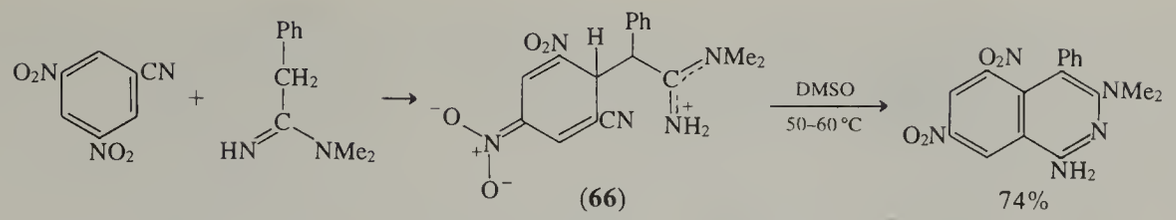
X	H	6-Me	7-Me	6-Cl
%	79	84	94	80

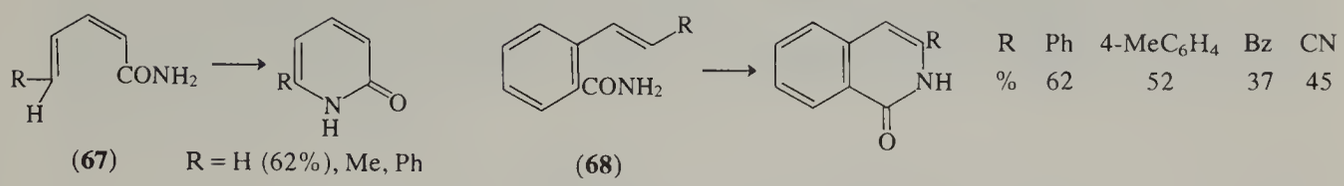
X	6-Br	6-OMe	7-OMe
%	70	72	70

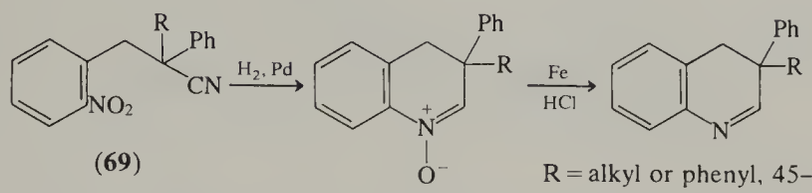


(**65**)

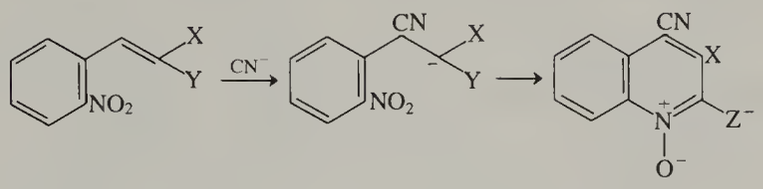
Nitro compounds can be cyclized to give quinolines in two non-reductive processes. In the first, an *o*-nitro-cinnamate or -cinnamonitrile is cyclized by treatment with cyanide ions, *via* the cyanide addition product as generalized in equation (29). The reaction has been







reviewed ⟨64QR389, 72CRV627⟩, and two examples of typical products are given. From a cinnamonitrile a 2-aminoquinoline *N*-oxide (**70**) is obtained, while a benzylidene malonate gives an *N*-hydroxyquinol-2-one (**71**). By-products (which can become main products under appropriate conditions) are *N*-hydroxyindoles. Acid-catalyzed cyclization of *o*-nitrostyrene oxides, and the closely related reaction between *o*-nitrobenzaldehyde and active methylene compounds, have also been reviewed ⟨72CRV627, 77HC(32-1)220⟩. The latter process is summarized in equation (30), and the mechanism proposed for the cyclization of *o*-nitrostyrene oxides is illustrated by the conversion of compound (**72**) into the 1-hydroxyquinol-4-one (**73**). Points to note are the introduction of a chlorine atom in the 6- or 8-position of the quinoline if hydrogen chloride is used, and the observation that no chlorine is introduced if quinol is present. Hydrogen bromide gives halogen-free products with or without quinol. In the condensation of *o*-nitrobenzaldehyde, ethyl acetoacetate, acetylacetone and acetonedicarboxylates have been used; the reaction failed with deoxybenzoin and with benzoylacetate. Intramolecular condensation between a nitro group and an active methylene takes place in the synthesis of the quinoline *N*-oxide (**74**) ⟨66BCJ195⟩ and of the phenanthridine *N*-oxide (**75**) ⟨60JOC736⟩; further examples are given in the review ⟨72CRV627⟩. A Smiles rearrangement is involved in the base-catalyzed conversion of *o*-nitrobenzoyl-1,3-diketones (**76**) into quinolines ⟨75CC782⟩.



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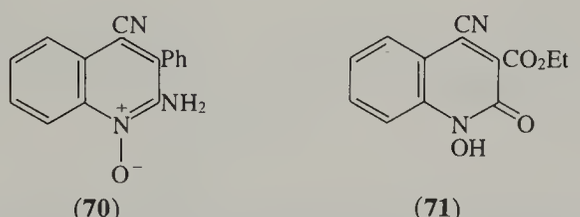

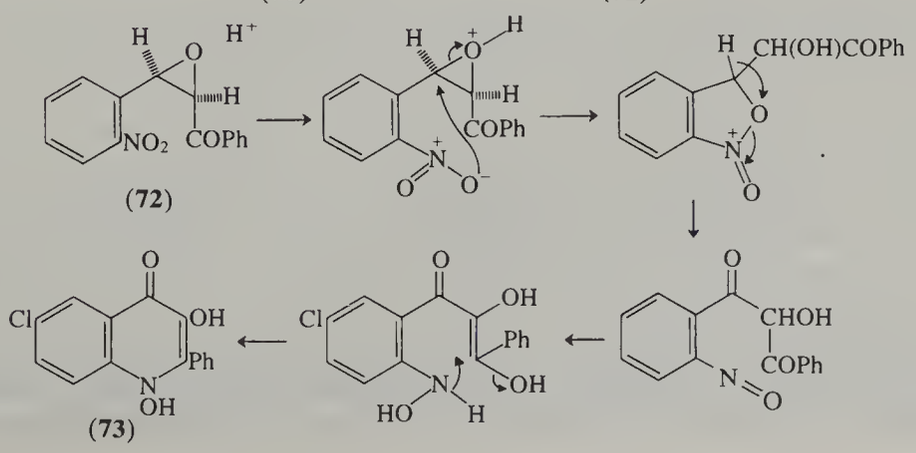

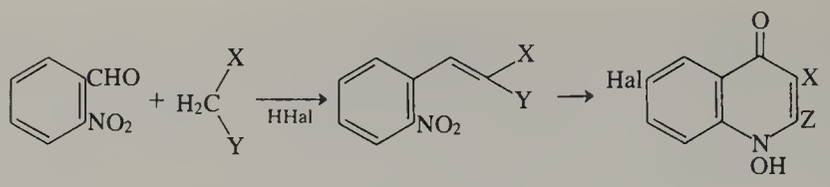

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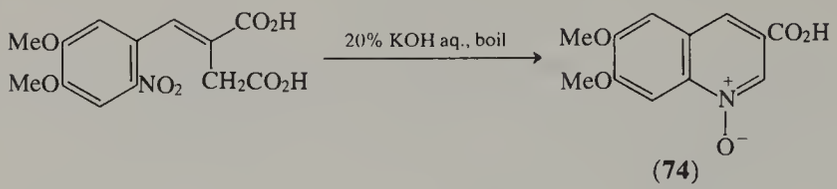

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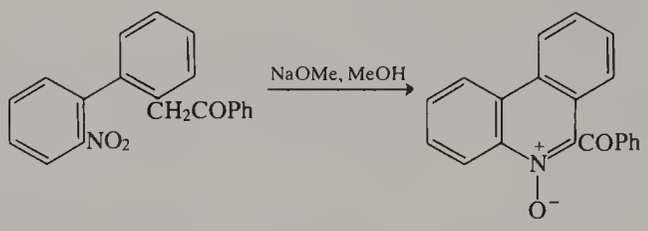
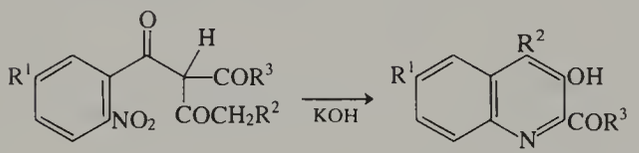


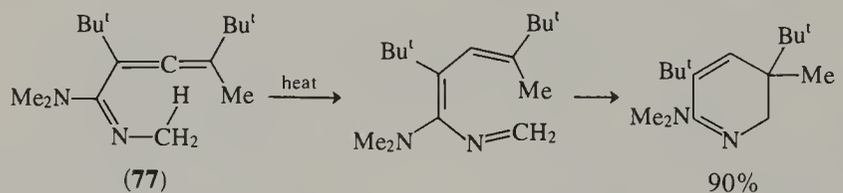
(75) 88%



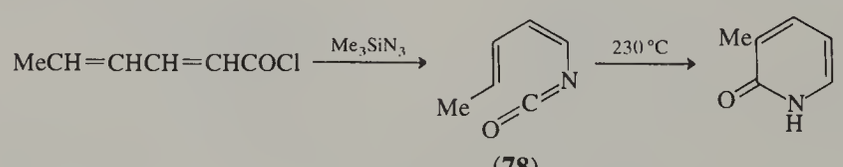
(76) R^1 = H, Me, Cl; R^2 = H, Me; R^3 = Me, Et, Ph

2.08.2.1.2 Bond formation between α- and β-carbons

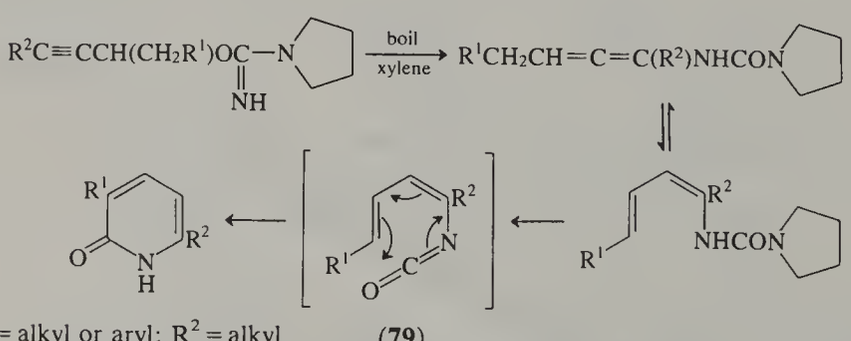
Cyclization of acyclic molecules to give pyridines, in which the bond formed is that between α- and β-carbon atoms, are not important, although one of the methods is distantly related to the well known Bischler–Napieralski isoquinoline synthesis. There are three reports which postulate an intermediate capable of an electrocyclic reaction. In one of these an allene (**77**) undergoes a 1,5-sigmatropic shift to produce a 6π-system which cyclizes ⟨76BSB147⟩. In the others the crucial intermediates are unsaturated isocyanates (**78**) and (**79**) which cyclize to give pyrid-2-ones ⟨70JHC1191, 77JA2813⟩.



(77) 90%



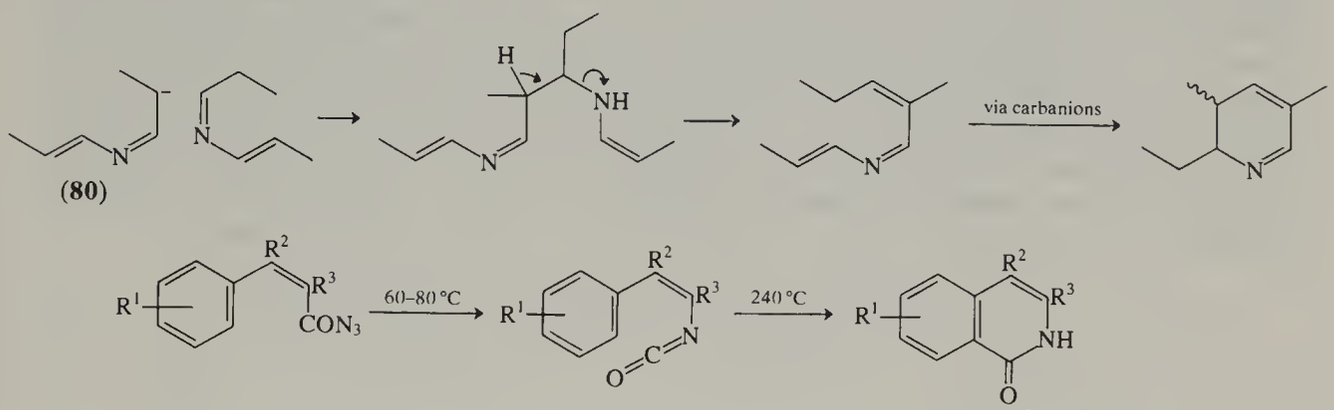
(78)



R^1 = alkyl or aryl; R^2 = alkyl (79)

The azabutadiene (**80**), on treatment with strong base, gives 2-ethyl-3,5-dimethyltetrahydropyridine; the proposed mechanism involves dimerization and cleavage, followed by

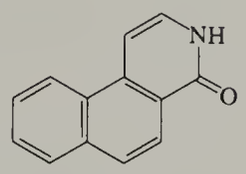
cyclization *via* a carbanion ⟨72T1055⟩. Isocyanates are formed by rearrangement from the corresponding acyl azides and can be cyclized to give isoquinolin-1-ones (**81**) ⟨69HCA1755⟩; a similar reaction from the 1-naphthyl derivative gives a benz[*f*]isoquinolinone (**82**) ⟨70JHC1191⟩. Isocyanates can also be cyclized by Friedel–Crafts catalysts, as in the synthesis of phenanthridinone (**83**) ⟨49JA2578⟩. Aryl isocyanides can also be ring-closed to a suitably placed aromatic ring, either thermally as in the synthesis of benzo[*c*]phenanthridine (**84**) ⟨77CC855⟩ or photochemically as in the synthesis of phenanthridine (**85**) ⟨71CC961⟩. In the latter case it was established that solvent interaction was required and the methoxyimine (**86**) also gave phenanthridine on irradiation. By-products from the isocyanide cyclizations are non-alternant azaazulenes.



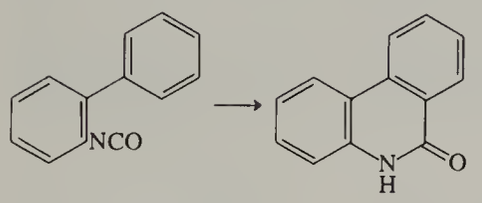
(**80**)

(**81**) $R^2 = R^3 = H$;

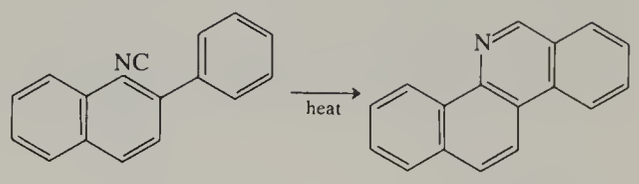
R^1	H	7-Cl	6,7-$(MeO)_2$
%	64	69	77



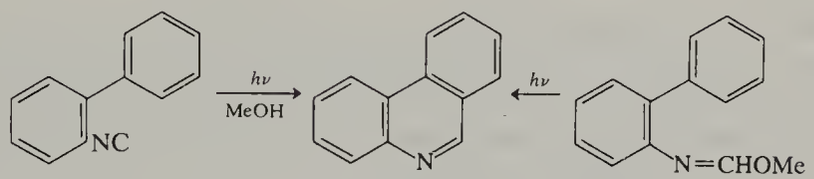
(**82**)



(**83**)



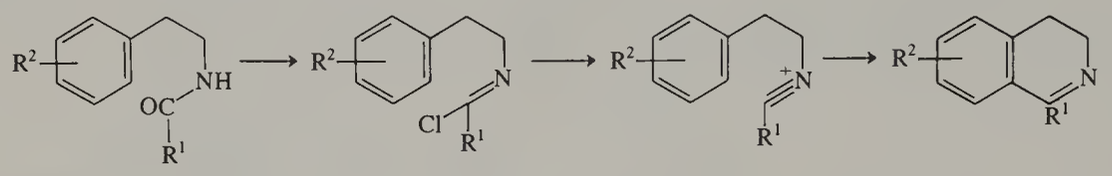
(**84**)



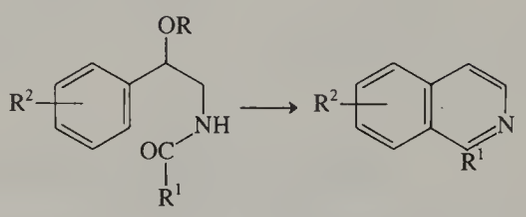
(**85**) (**86**)

Unquestionably the major synthesis of this type is the Bischler–Napieralski synthesis of dihydroisoquinolines, and the Pictet–Gams modification leading to isoquinolines. The Pictet–Spengler synthesis is dealt with in Section 2.08.2.2.1(ii). The Bischler–Napieralski synthesis involves the electrophilic cyclization of the carbon atom of an amide on to an adjoining aromatic ring as in equation (31), and reviews are available ⟨51OR(6)74, 81HC(38-1)142⟩. The dihydroisoquinolines are easily dehydrogenated to isoquinolines or reduced to tetrahydroisoquinolines. The isoquinolines may also be obtained directly by the Pictet–Gams modification, in which β-hydroxy-β-phenylethylamides are cyclized and dehydrated (equation 32). Bischler and Napieralski used phosphorus pentoxide or zinc chloride at high temperature as their reagent ⟨1893CB1903⟩. Probably the most common modification is the use of phosphoryl chloride in toluene or xylene. Phosphorus pentachloride, polyphosphoric acid and polyphosphates have been used as cyclizing agents and chloroform, benzene, nitrobenzene and tetralin as solvents. Acetonitrile has been reported to give good yields

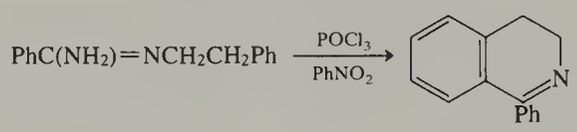
under mild conditions ⟨68JHC825⟩. The mechanism of the reaction when phosphoryl chloride is used has been accepted as proceeding through the chloroimine and the nitrilium ion (isolated in one case ⟨72AG(E)919⟩ as its hexafluoroantimonate), as shown in equation (31). Electron-releasing substituents *meta* to the side chain make for easier reaction, but in the *para* position they can inhibit cyclization. Electron-withdrawing substituents are in general disadvantageous, and in this context it must be remembered that the cyclizing side chain is itself a substituent. Hence a β-keto-β-phenylethanamide will not cyclize unless the ketone is converted into a ketal. The amide can be aliphatic or aromatic, giving an alkyl or an aryl group at position 1 in the final isoquinoline. Substituents at the α-position of the phenylethanamide usually inhibit reaction. The use of a *meta*-substituted phenylethanamide could give a 6- or an 8-substituted isoquinoline but a 6-substituent is usually formed if a choice is available and 8-substituted isoquinolines require blocking groups in the starting material. Some simple modifications of the reaction involve the use of carbamates to give dihydroisoquinolin-1-ones ⟨64HCA2089⟩ and of amidines (equation 33) ⟨50BRP642286⟩. Examples of the preparation of polycycles by the Bischler–Napieralski synthesis come from the cyclization of the isomeric phenanthrylethylamides to give naphtho[1,2-*h*]- (**87**) and naphtho[2,1-*f*]-isoquinoline (**88**) ⟨54JOC661⟩. Both can easily be dehydrogenated.



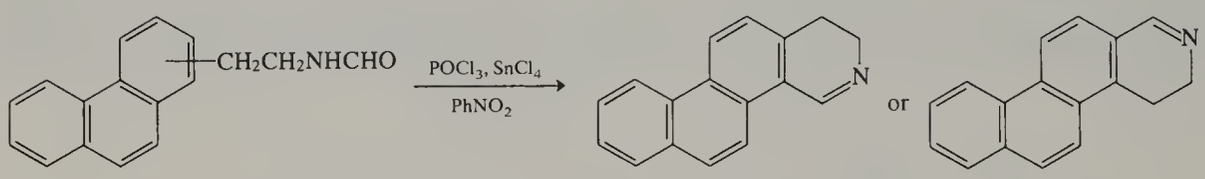
(31)



(32)

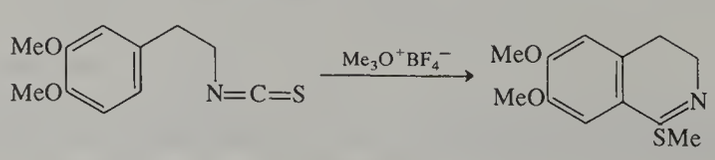


(33)

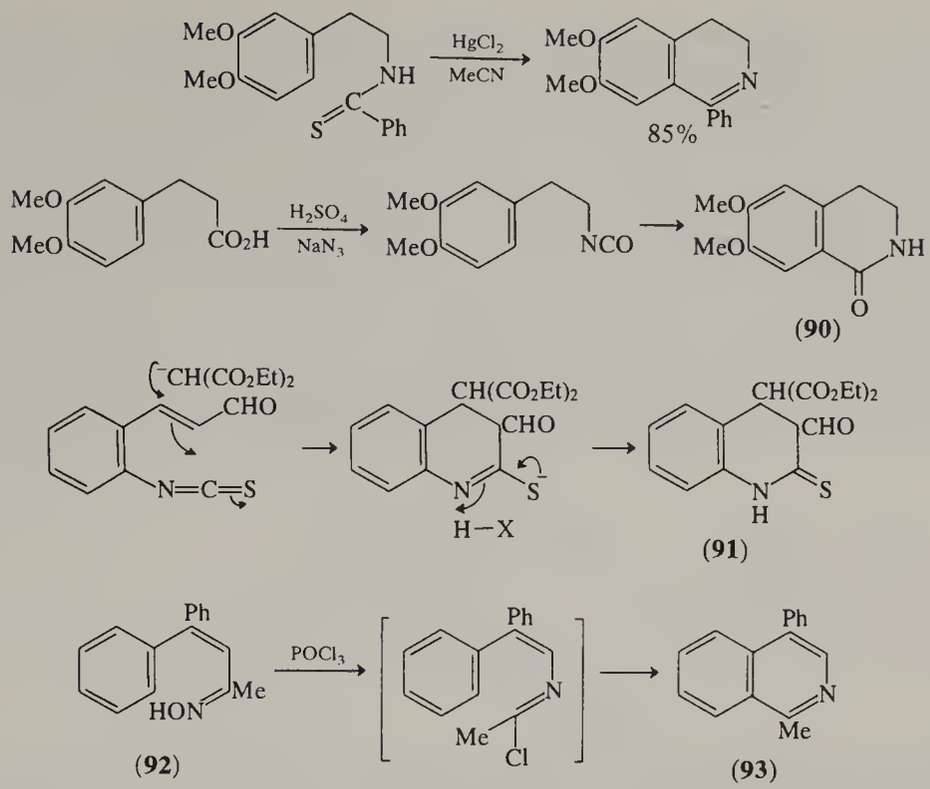


(87) (88)

Isothiocyanates can be cyclized by PPA, aluminum chloride or trimethyloxonium fluoroborate, in the last case to give a 1-methylthio-3,4-dihydroisoquinoline (**89**) ⟨76JCS(P1)33⟩; thioamides can be cyclized by mercury(II) chloride as in equation (34) ⟨66CPB842⟩. The cyclization of isocyanates has been mentioned as a thermal reaction; acid-catalyzed electrophilic cyclization can give dihydroisoquinolin-1-ones such as compound (**90**) ⟨76H(5)157⟩. The isocyanates are made by Curtius rearrangement from the phenylpropanoic acids. Much improved yields of isoquinolin-1-ones from isocyanates have been reported when phosphoric acid and dichloromethane are used at room temperature; the mixture is much easier to stir than the conventional polyphosphoric acid solutions ⟨80CPB1003⟩. When the cyclization is between an isothiocyanate and a double bond the reaction can be base-initiated, as in the synthesis of quinoline-2-thiones (**91**) ⟨73JCS(P1)2911⟩. The amides for the Bischler–Napieralski synthesis can be obtained by Beckmann rearrangement. If the starting material is a cinnamaldoxime or the oxime of an α,β-unsaturated ketone (**92**), treatment with phosphoryl chloride gives the isoquinoline (**93**) ⟨72ZOR2585⟩; it is unnecessary to isolate the amide.

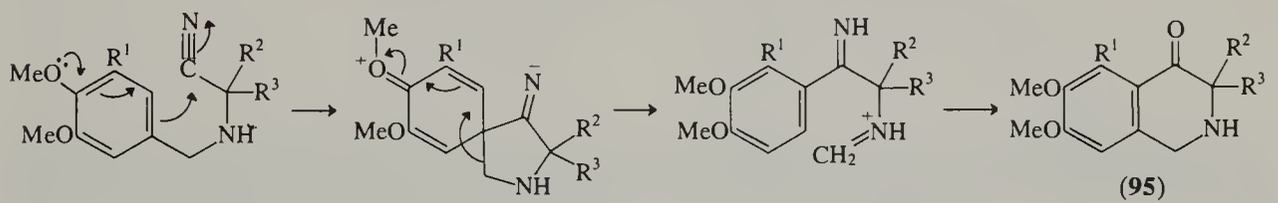


(89)

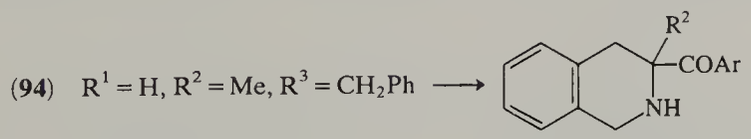


(34)

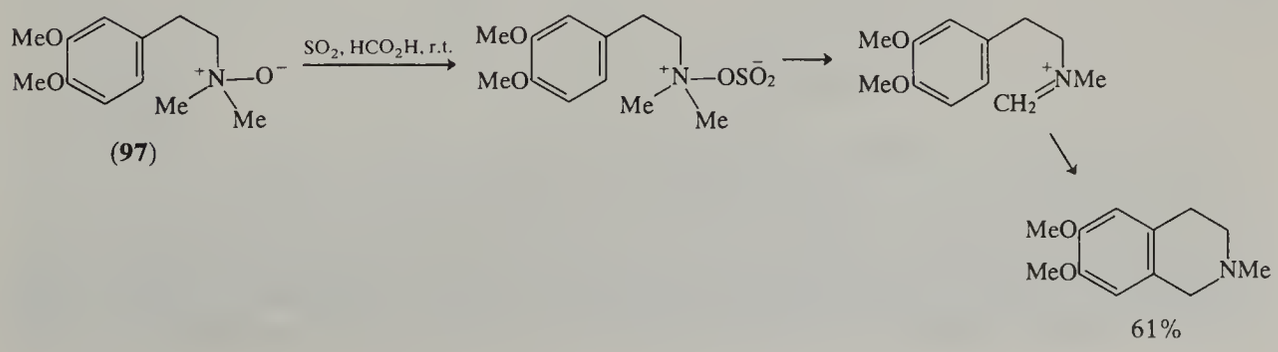
As mentioned in Section 2.08.2.1.1, direct electrophilic cyclization of oximes gives quinolines. The rearrangement can also be achieved with an alumina and phosphorus pentoxide mixture. An iminium intermediate has been assumed in the conversion of the cyanomethylphenylethylamines (**94**) into isoquinolin-4-ones (**95**) ⟨72CC643⟩, and in the cyclization of the *N*-oxide (**97**) to give a tetrahydroisoquinoline ⟨71JCS(C)3060⟩. In the former reaction, if the substituent R^2 is benzyl a 3-benzoyltetrahydroisoquinoline (**96**) is obtained. Another cyclization which probably involves an iminium species is that of the *N*-hydroxymethylamide (**98**). Pyrophosphoric acid is the preferred cyclizing agent. A striking difference was observed between the *N*-methyl derivative (**98**) and the unmethylated (**99**). Whereas the former gave a good yield of the dihydroisoquinolin-3-one (**100**), the latter gave a dimer (**101**), which formed the isoquinolin-3-one on pyrolysis ⟨81H(16)609⟩. The cyclization of the cyclohexene derivative (**102**) has an obvious analogy with the Bischler–Napieralski synthesis ⟨72JHC1441⟩.

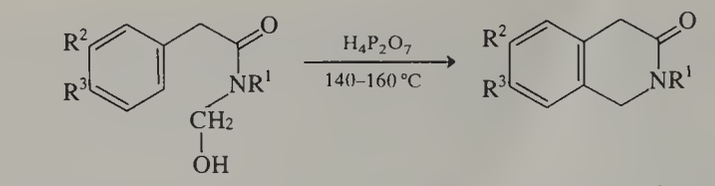


(**94**) $R^1 = OMe$; R^2, $R^3 = (CH_2)_5$



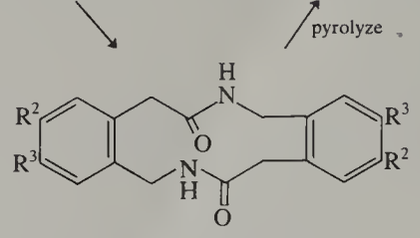
(**96**) $R^2 = Me$; $Ar = 3,4(MeO)_2C_6H_3$



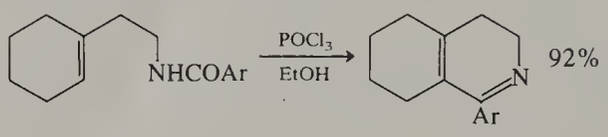


(**98**) R^1 = Me, R^2 = R^3 = H
(**99**) R^1 = H, R^2 = R^3 = OMe

(**100**) R^1 = Me, R^2 = R^3 = H, 76%
R^1 = H, R^2 = R^3 = OMe, 80%

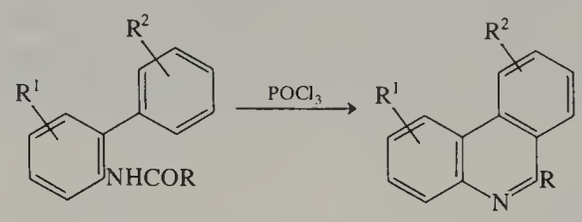


(**101**) R^2 = R^3 = OMe, 93%

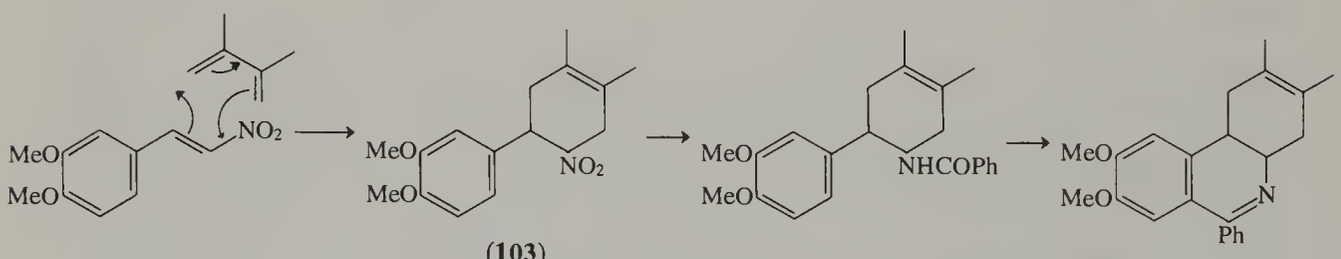


(**102**) Ar = 2-$MeOC_6H_4$

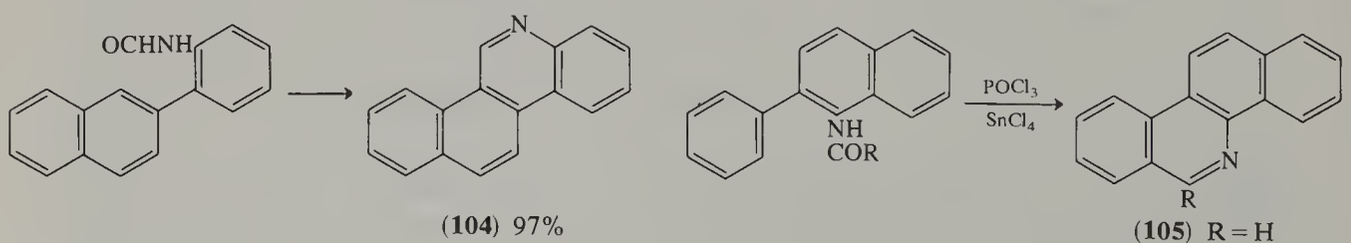
Phenanthridines can be obtained by cyclizing amides of 2-aminobiphenyl using phosphoryl chloride, although the yields are not good with formamides (equation 35). The reaction is well discussed in a review ⟨B-52MI20800⟩, and the discussion includes the effects of substituents in either ring of the biphenyl. Examples of the cyclization of amides are given by Morgan and Walb ⟨31JCS2447⟩ and of amidines by Cymerman and Short ⟨49JCS703⟩. An ingenious route to tetrahydrophenanthridines uses a Diels–Alder addition to produce the intermediate (**103**) ⟨39CB675⟩. A very high yield of benzo[*i*]phenanthridine (**104**) is provided by the cyclization of 2-(*o*-formamidophenyl)naphthalene ⟨78S205⟩. By contrast, the cyclization of 1-formamido-2-phenylnaphthalene gives only a 60% yield of the isomeric heterocycle (**105**) ⟨54JOC661⟩; the methyl derivative (**106**) has been similarly prepared ⟨45MI20800⟩.



(35)



(**103**)

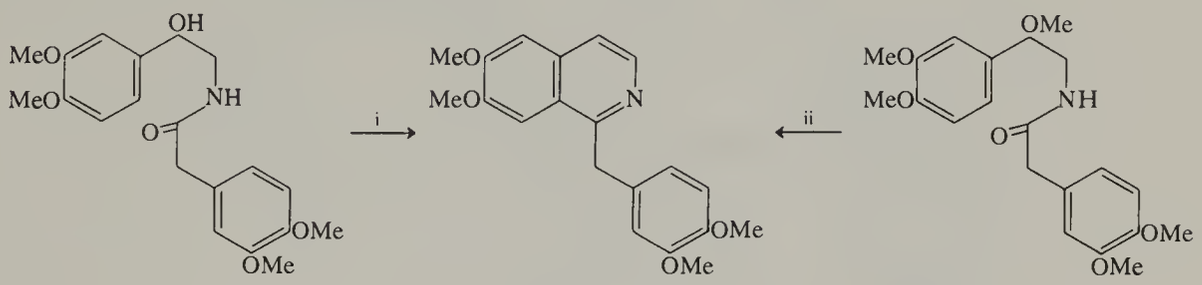


(**104**) 97%

(**105**) R = H
(**106**) R = Me

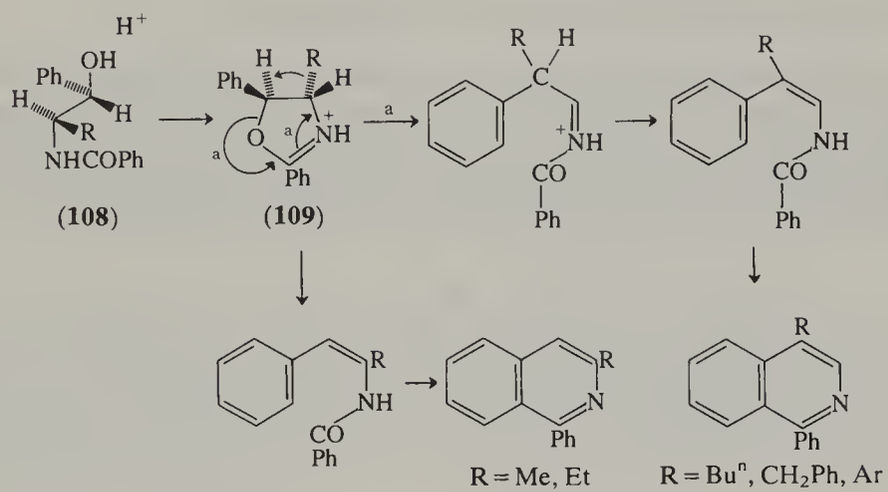
The Pictet–Gams modification of the Bischler–Napieralski synthesis has also been reviewed ⟨51OR(6)74, 81HC(38-1)161⟩. As shown in equation (32), the additional unsaturation is achieved by elimination of ROH before the cyclization. The commonest examples use β-hydroxy or β-methoxy substituents on the phenethylamide. Papaverine (**107**) is an example of an isoquinoline obtained from both precursors ⟨09CB2943, 27AP(265)1⟩. The precursors can be made from 5-aryloxazolines by reaction with an acid chloride and

subsequent treatment with triethylamine ⟨81JOC3742⟩. It has been shown that isoquinolines can be obtained directly from a carboxylic acid and a β-aryl-β-methoxyphenethylamine in about 50% yield if the two are heated together in toluene with phosphoryl chloride ⟨52YZ252⟩. Among the problems associated with the Pictet–Gams modification is the migration of groups from the α-position of the phenethylamide to the carbenium ion at the β-position. Thus, groups which should appear at the 3-position of the isoquinoline are found at position 4. The migration was first observed during an attempt to synthesize 1-methyl-3-phenylisoquinoline ⟨71JIC873⟩. A study of the rearrangement by several groups has implicated oxazolines as intermediates. When amide (**108**) is cyclized, the rearrangement occurs when the α-substituent is a butyl, benzyl, or aromatic group, but not when the substituent is a methyl or ethyl group ⟨77TL4107⟩. The intermediate oxazoline (**109**) was isolated from the *erythro* form of the amide (**108**) and shown to give the isoquinoline when treated with phosphorus pentoxide in boiling decalin ⟨73JOC1245⟩.



(**107**)

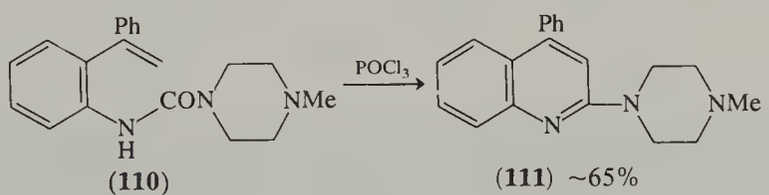
i, P_2O_5, xylene, boil, 30%; ii, $POCl_3$, P_2O_5, 40%



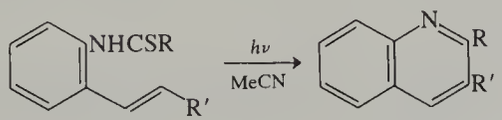
(**108**) (**109**)

R = Me, Et R = Bu^n, CH_2Ph, Ar

The quinoline (**111**) is obtained when the *o*-aminostyrene derivative (**110**) is cyclized by phosphoryl chloride ⟨77HCA1644⟩. Other syntheses involving α,β-bond formation are the photochemical cyclization of the *o*-thiocarboxamidostyrene (**112**) ⟨79CC499⟩ and the acid-



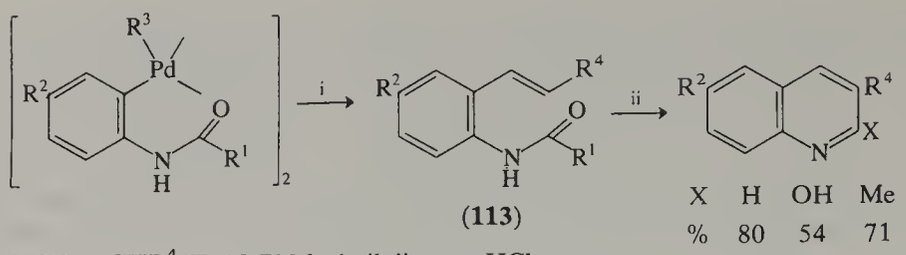
(**110**) (**111**) ~65%



(**112**)

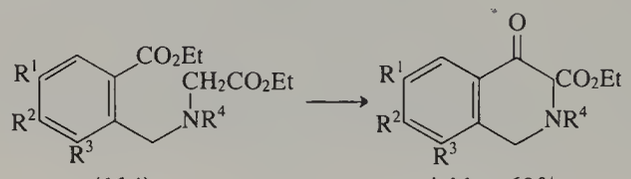
R = Me, R′ = Me, Ph, CN
R = Ph, R′ = Me

catalyzed cyclization of the *o*-aminostyrene derivatives (**113**) ⟨79TL2403⟩, the Dieckmann cyclization of a number of diesters of general formula (**114**) ⟨68JOC494⟩, and the acid-catalyzed cyclization of the aminobiphenyl–acetylenedicarboxylate adduct (**115**) ⟨73IJC112⟩.

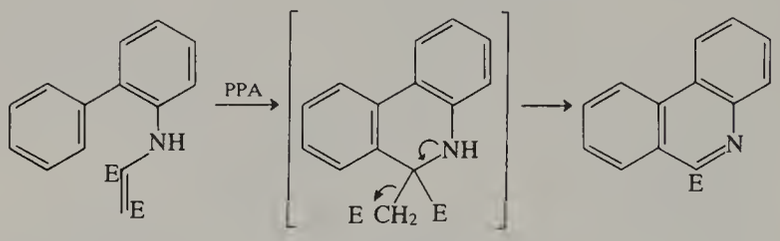


(113)

i, CH_2=CHR^4, Et_3N, PhMe, boil; ii, conc. HCl



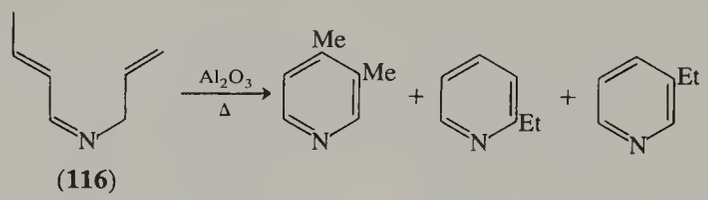
(114) yields ~60%



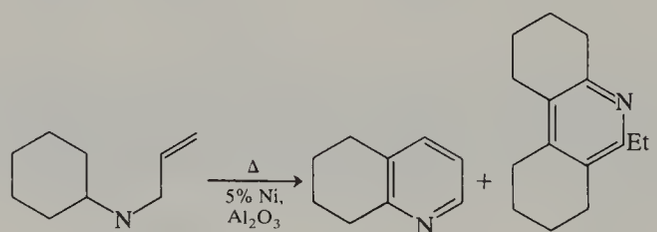
(115) E = CO_2Me

2.08.2.1.3 Bond formation between β- and γ-carbon atoms

A few pyrolytic methods of synthesis are known, leading directly to the formation of pyridine rings by formation of the β,γ-bond. Alkylpyridines are obtained when unsaturated imines (**116**) or (**117**) are passed over heated zeolites ⟨80IZV655⟩ or alumina ⟨72IZV2263⟩. More dehydrogenation is achieved by the use of nickel or alumina, as in the synthesis of tetrahydroquinolines (**118**) or octahydrophenanthridine (**119**) ⟨78IZV1446⟩.



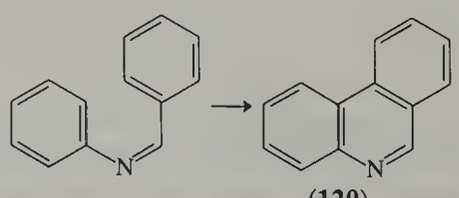
(116)



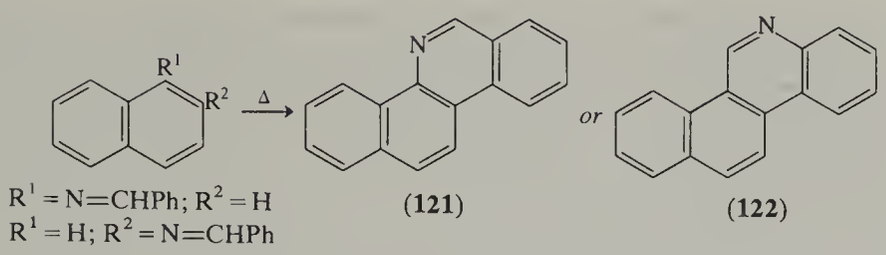
(117) (118) (119)

Pyrolysis of anils has long been known to give polycycles, as shown by the synthesis of phenanthridine (**120**) ⟨1889CB3340⟩ and of the two benzophenanthridines (**121**) and (**122**) ⟨1891LA(266)155⟩. More recently, quinoline has been obtained by flash vacuum pyrolysis of the dianil (**123**) ⟨80JCS(P1)2200⟩.

The synthesis of benzo[*h*]quinolines (**124**) and (**125**) from the propargylaminonaphthalenes involves a remarkable number of concerted rearrangements and a cyclization

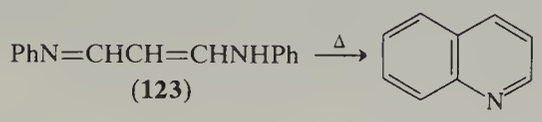


(120)

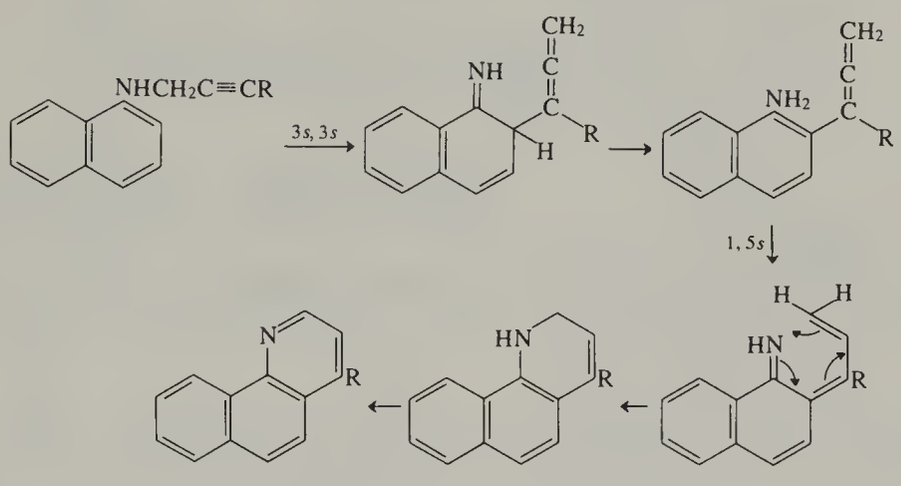


$R^1 = N{=}CHPh$; $R^2 = H$
$R^1 = H$; $R^2 = N{=}CHPh$

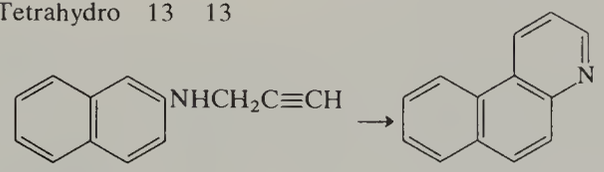
(**121**) (**122**)



(**123**)

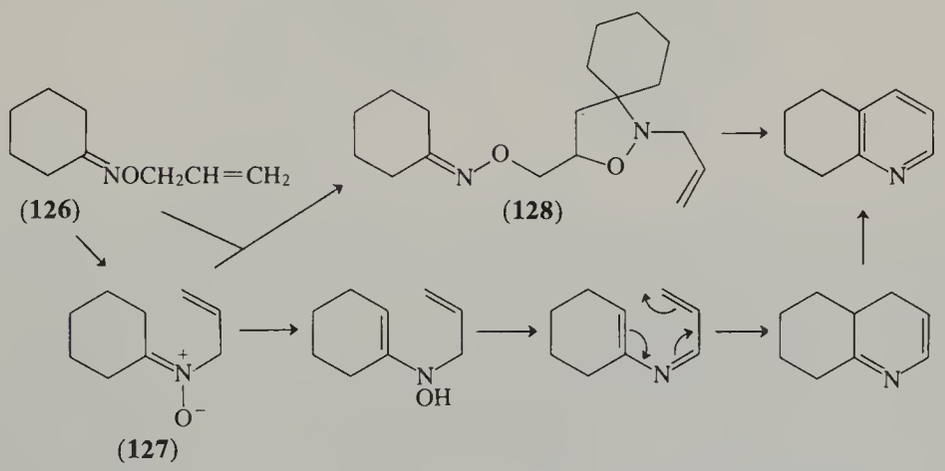


(**124**) R	H	Me
%	57	52
% Tetrahydro	13	13



(**125**) + Tetrahydro (16%)

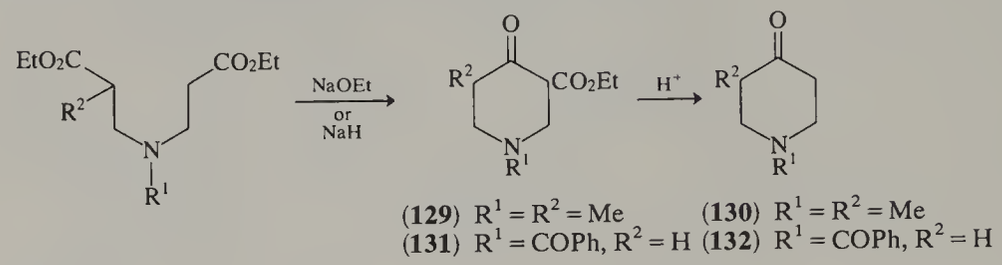
⟨73HCA478⟩. A similar route to quinolines *via* 1,2-dihydroquinolines starts from *N*-propargylanilines and is copper catalyzed ⟨62JOC4713⟩. The allyl ether of cyclohexanone oxime (**126**) heated in benzene at 200 °C gives 5,6,7,8-tetrahydroquinoline ⟨79S221⟩; the proposed mechanism is reinforced by the isolation of a compound (**128**) formed from the ether (**126**) and a suggested intermediate (**127**).



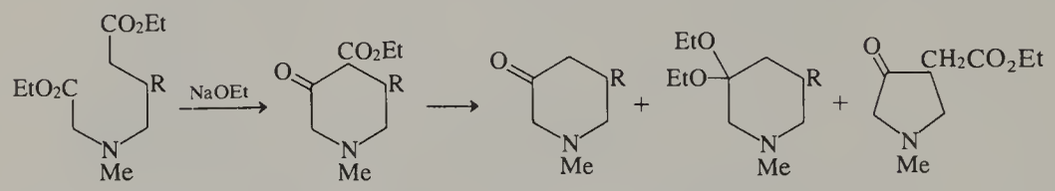
(**127**)

A very popular route to piperid-4-ones is by a Dieckmann or Thorpe cyclization of appropriate diesters or dinitriles. In most cases the nitrogen atom is tertiary, to avoid the formation of amides as by-products. A simple example is provided by the synthesis of the piperidone ester (**129**) which, after hydrolysis and decarboxylation, gives the piperid-4-one (**130**) ⟨45JOC277⟩. The diesters are available by addition of amines to acrylates and so the two ester fragments can be different. For the production of *N*-benzoylpiperid-4-one (**132**) the whole operation from benzamide and ethyl acrylate to the ester (**131**) can be achieved

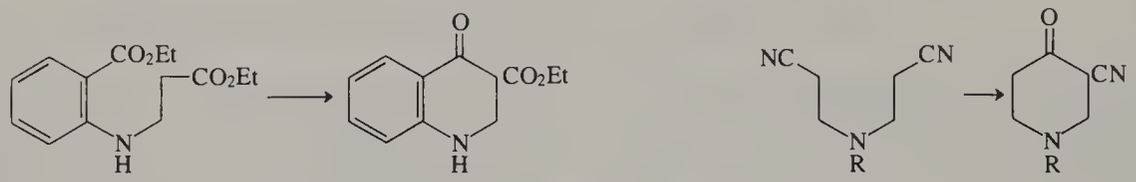
in good yield in a one-pot reaction ⟨67JCS2645⟩. If substituted glycinates are used, piperid-3-ones such as compound (**133**) can be obtained ⟨33JA1233⟩, but it has been reported that with the triester (**134**) the major product is the ketal (**135**) which is difficult to hydrolyze ⟨73JHC339⟩. A substantial amount of pyrrolidone (**136**) was also obtained. The normally poor yields from secondary amines have been mentioned; it has been reported, however, that good yields of the quinolone ester (**137**) can be obtained ⟨72JCS(P1)1803⟩. The synthesis of 3-cyanopiperid-4-ones (**138**) provides a simple example of the use of dinitriles ⟨45JCS399⟩. Related reactions are the aldol condensation used to prepare the piperidin-4-ol (**139**) in a reaction said to be regio-and stereo-specific ⟨74ZOR1265⟩, and the cyclization of the dicarboxylic acids (**140**) to give dihydroquinol-4-ones ⟨75KGS1118⟩.



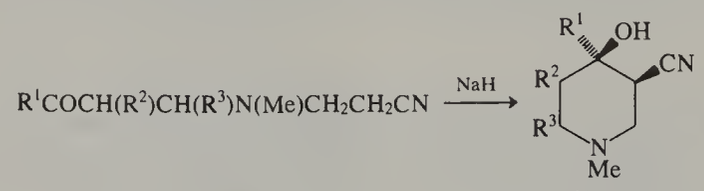
(**129**) $R^1 = R^2 = Me$ (**130**) $R^1 = R^2 = Me$
(**131**) $R^1 = COPh$, $R^2 = H$ (**132**) $R^1 = COPh$, $R^2 = H$



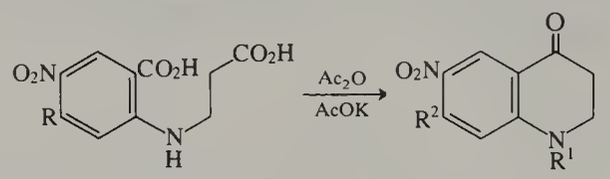
(**134**) $R = CO_2Et$ $R = H$, 85% (**133**) $R = H$ (**135**) $R = CO_2Et$ (**136**)



(**137**) (**138**)



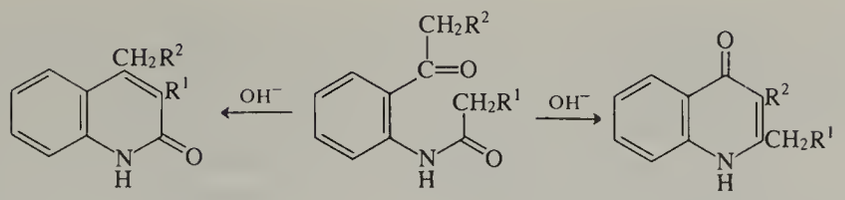
(**139**)



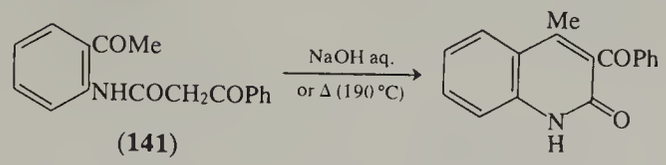
(**140**)

R^1	Ac	Ac
R^2	H	Cl
%	93	69

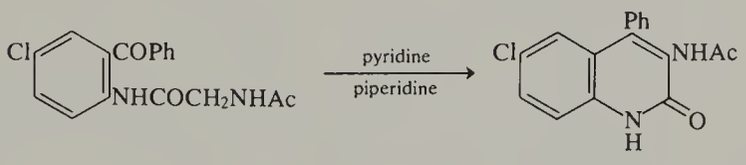
Quinoline derivatives are obtained by an intramolecular aldol condensation in the Camps synthesis, shown in equation (36). The synthesis is reviewed, so an outline will suffice. The synthesis is least useful if cyclization can give either a quinol-2-one or a quinol-4-one as in Camps' original report ⟨1899CB3228⟩. The synthesis becomes unambiguous if the amine has a formyl or aroyl substituent (H or aryl instead of R^1CH_2), or if the *o*-carbonyl component is an aldehyde, an aryl ketone or a carboxylic acid derivative (H, aryl or OR instead of R^2CH_2). Another case where one direction of cyclization predominates is provided by amide (**141**), presumably because of the enhanced acidity of the methylene group ⟨02AP(240)135⟩. In this case the quinol-2-one carries a substituent in position 3; other examples are the synthesis of 3-acetamidoquinol-2-ones (**142**) ⟨65USP3202661⟩, and the dihydroquinol-2-one (**143**) ⟨73JOC449⟩. In the last two cases the bases used are non-aqueous, which is mandatory if an *o*-amido ester is to be cyclized to give a 4-hydroxyquinol-2-one (**144**) ⟨71AP81⟩. Suitable bases are sodium, potassium or calcium hydroxides, sodium ethoxide or triphenylmethylsodium, piperidine and triethylamine.



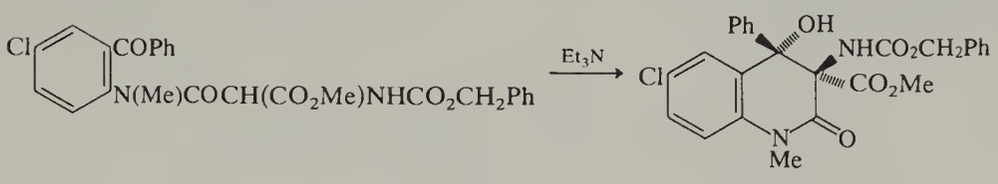
(36)



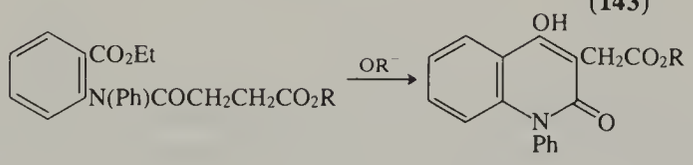
(141)



(142)

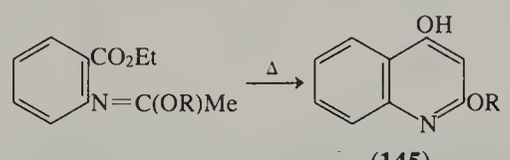


(143)

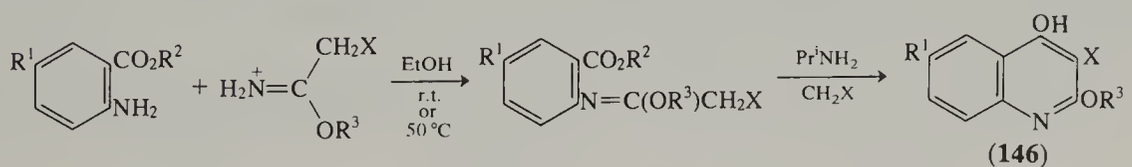


(144) R = Me, 64%

Extensions of the Camps synthesis include the use of acetimidates to give substituted quinol-2-ones or their derivatives. Cyclization can be achieved by heat, as in the preparation of 2-alkoxy-4-hydroxyquinolines (**145**) ⟨78S826⟩, or by isopropylamine as in the synthesis of the 3-substituted derivatives (**146**) ⟨78S698⟩. Treatment of the acetimidate (**147**) with aminoacetal and *p*-toluenesulfonic acid in boiling toluene gives the 2-aminoquinoline (**148**) ⟨78JOC4865⟩. Cyclization of a series of *N*-acetylanthranilates by HMPT at 235 °C gave 2,4-bis(dimethylamino)quinolines (**149**) ⟨77T217⟩. A reaction bearing some resemblance to the Camps synthesis uses an intramolecular Wittig reaction to close the ring as in equation (37) ⟨77JOC200⟩ and, in a rather more tenuous comparison, the vinylamidine (**150**) cyclizes to a pyrid-4-one ⟨76KGS805⟩.

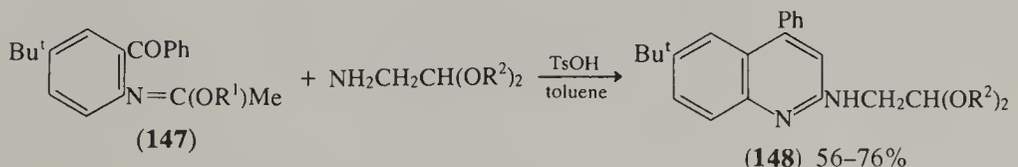


(145)



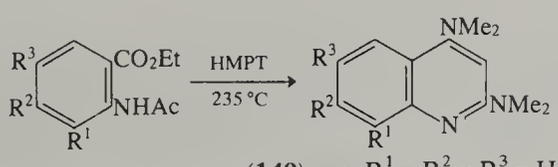
(146)

e.g. R^1 = H, R^2 = Me, R^3 = Et, X = CO_2Et, 80–95%

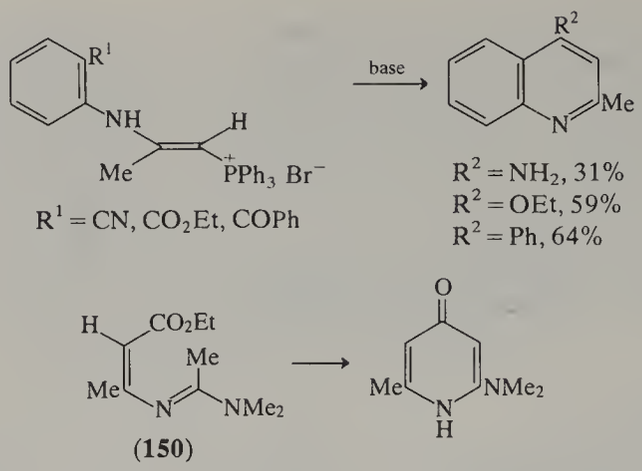


(147)

(148) 56–76%



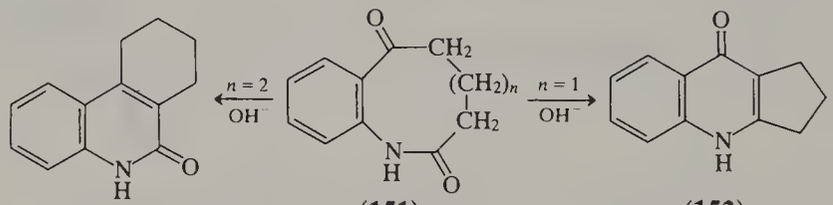
(149) *e.g.* R^1 = R^2 = R^3 = H, 70%



(37)

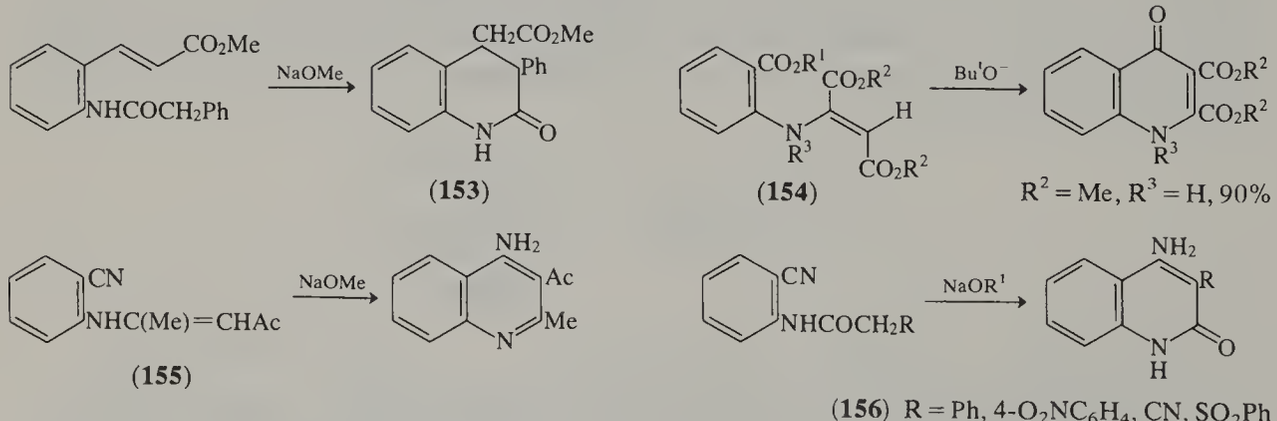
(150)

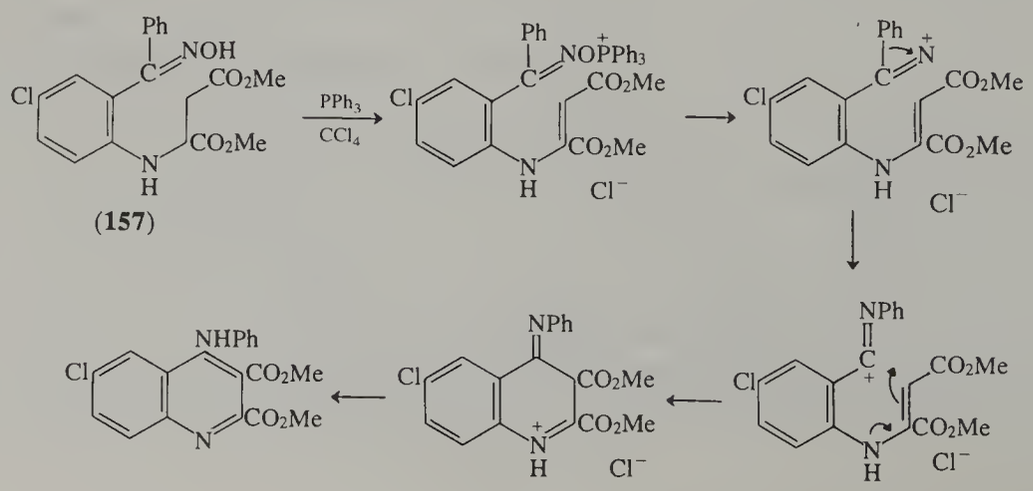
The Camps synthesis is not easily adapted to produce polycycles but an intramolecular aldol condensation in the medium-ring compound (**151**) gives a tetrahydrophenanthridinone; a change in the medium-ring size alters the pathway, producing a cyclopentaquinolone (**152**) ⟨51JA2641⟩.



(151) (152)

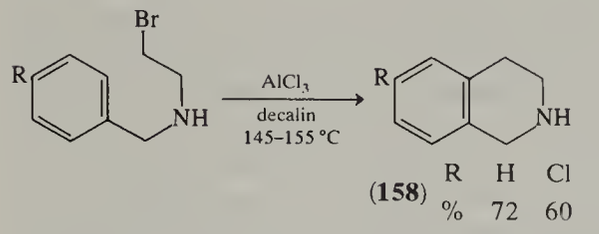
Related to the Camps synthesis are a number of cyclizations using the Michael addition. The most obviously related is the base-catalyzed cyclization of an *o*-amidocinnamate to give a 3,4-dihydroquinol-2-one (**153**) ⟨50JA2209⟩. Conversely, *N*-vinylanthranilates (**154**) give quinol-4-ones ⟨76LA1972⟩. The comparable nitrile (**155**) is converted by sodium methoxide into a 4-aminoquinoline ⟨79JPR695⟩; in the same paper it is reported that 4-aminoquinol-2-ones (**156**) can be made by a modified Camps synthesis. Cyclization of the anthranilonitrile (**155**) can also be achieved with aluminum chloride, although with loss of the acetyl group. Another synthesis of 4-amino(anilino)quinolines from the *o*-aminobenzophenone oxime (**157**) is suggested to involve an electrophilic centre ⟨74JOC2137⟩.





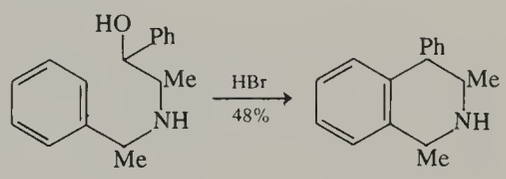
A very large group of syntheses in which the β,γ-bond is formed are those in which a side chain electrophile attacks the benzene ring. These include the Skraup and Doebner–von Miller syntheses (dealt with in Section 2.08.2.2.3(ii)), the Knorr, Conrad–Limpach and Combes syntheses of quinolines (dealt with here), the Pomerantz–Fritsch synthesis of isoquinolines, and many syntheses of phenanthridines and of acridines.

Among the simplest syntheses of this type are those of tetrahydro-quinolines or -isoquinolines based on Friedel–Crafts cyclizations. The use of side-chain halides is shown by the synthesis of 1,2,3,4-tetrahydroisoquinolines (**158**) ⟨71CC799⟩, and of 3,4-dihydroquinol-2-ones (**159**) ⟨27CB858⟩. Electrophilic carbon atoms can be developed from secondary or tertiary alcohols, or from alkenes or alkynes. In the synthesis of the tetrahydroisoquinoline (**160**) the expected product is obtained ⟨71JHC839⟩, but in the case of the tetrahydroquinolines (**161**) and (**162**) the major product is obtained *via* a Wagner–Meerwein rearrangement ⟨72IJC325⟩. Dihydroisoquinolin-3-ones are obtained in excellent yield when the protected glyoxylic amide (**163**) is cyclized by methanesulfonic acid ⟨80TL569⟩.

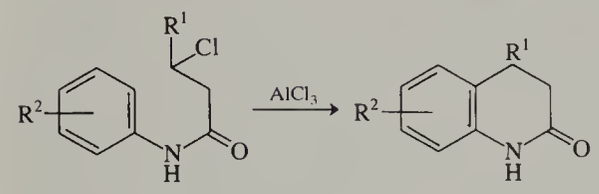


(**158**)

R	H	Cl
%	72	60

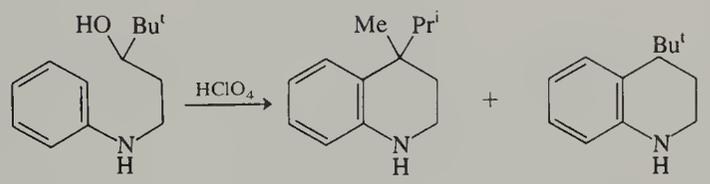


(**160**) 58%

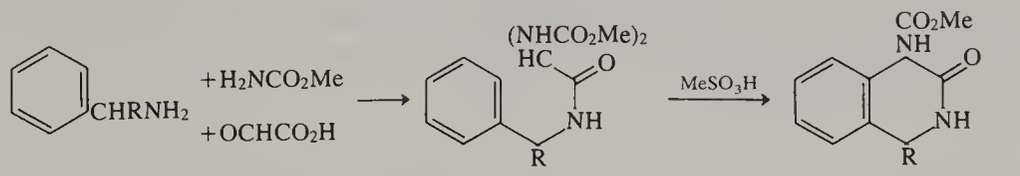


(**159**)

R^1	H	H	H	Me	Me	other examples
R^2	H	6-Me	8-Me	H	6-Cl	
%	95	100	90	55	92	



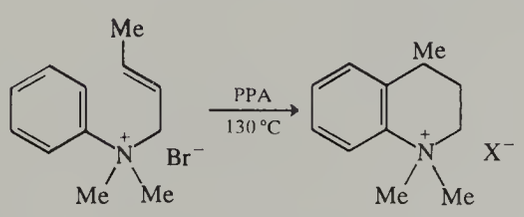
(**161**) Major product (**162**) Minor product



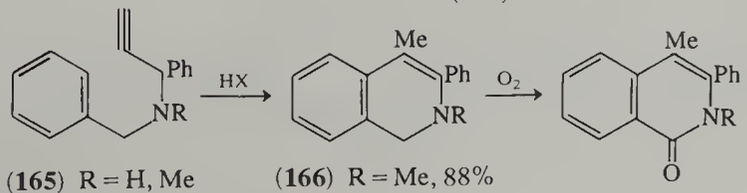
(**163**)

R	H	Me	CO_2Me
%	84	83	85

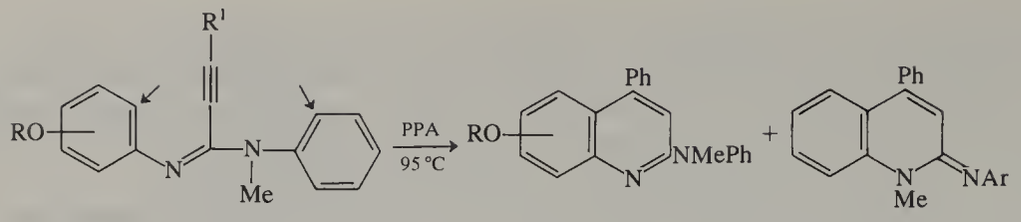
Protonation of an alkene has been used to give rather poor yields of tetrahydroquinolinium salts (**164**) ⟨77JOC2195⟩. Protonation of *N*-propargylphenethylamines (**165**) gives high yields of dihydroisoquinolines (**166**), but these are unstable in air, being readily oxidized to the isoquinolin-1-ones (**167**) ⟨73JCS(P1)2588⟩. The alkynylamidine (**167**) can cyclize to either aromatic ring; the major product is derived from cyclization to the more electron-rich ring ⟨76CB1643⟩. Acridans (**168**) can be obtained from *o*-arylaminostyrenes ⟨68MIP450415⟩.



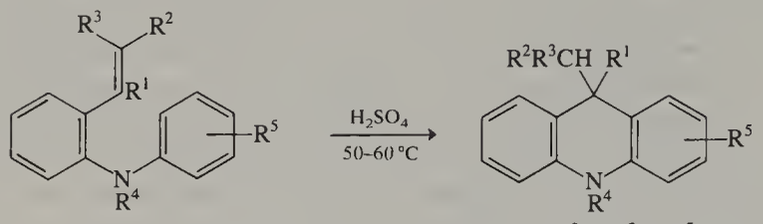
(**164**) 21%



(**165**) R = H, Me (**166**) R = Me, 88% R = H, Me

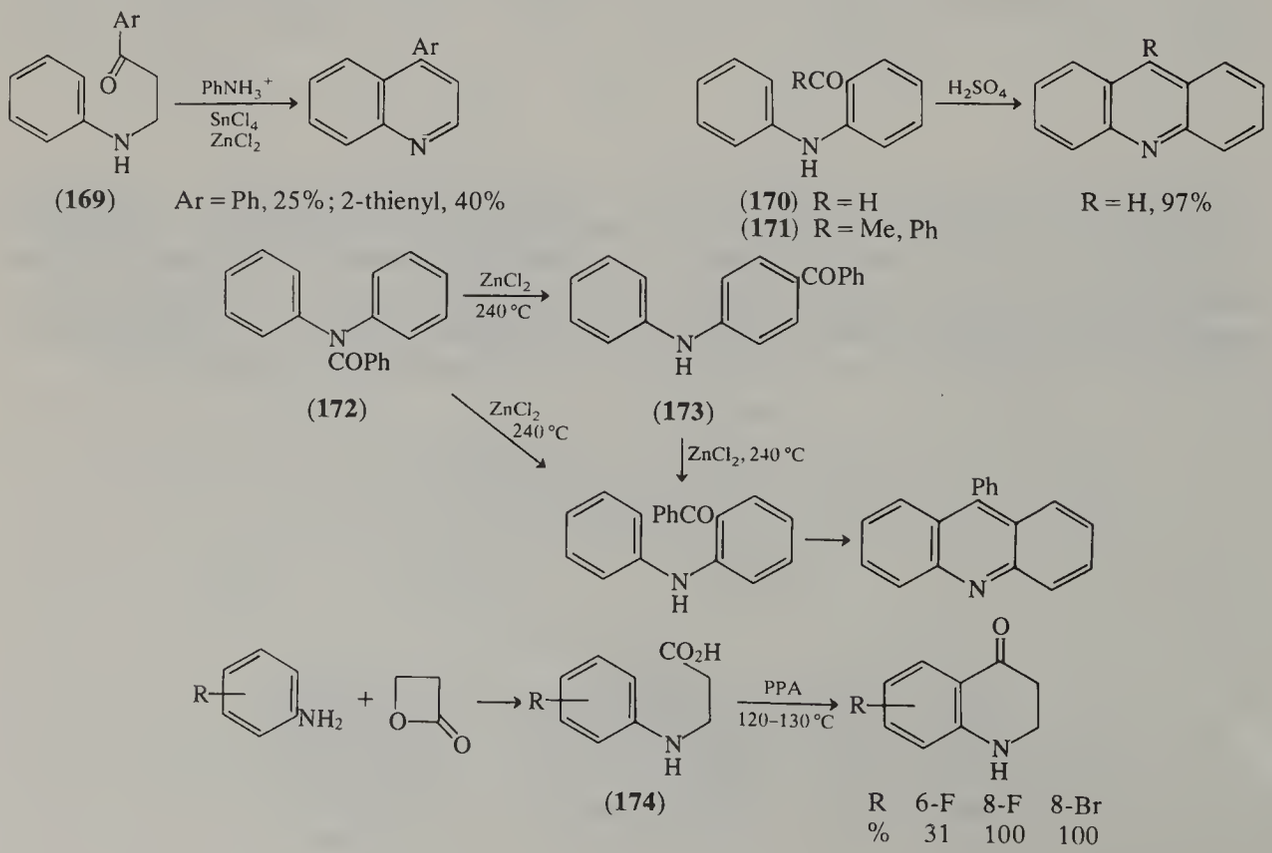


(**167**) 45–75% Ar = ROC_6H_4



(**168**) $R^2 = R^3 = R^5 = H$; $R^1 = Me$; $R^4 = (CH_2)_3NMe_2$

An important group of syntheses use a carbonyl group to generate the electrophilic centre; among these are the named syntheses due to Knorr, Conrad and Limpach, Combes, and Pomerantz and Fritsch. Cyclization of the *N*-substituted anilines (**169**) gives, surprisingly, the quinoline rather than the dihydroquinoline ⟨61MI20800⟩. Cyclization of *o*-formyldiphenylamine (**170**) ⟨48JCS1225⟩ or of the ketones (**171**) ⟨22CB2049⟩ gives acridines. At high temperature, with zinc chloride as Lewis acid, 9-phenylacridine is formed either from *N*-benzoyldiphenylamine (**172**) or 4-benzoyldiphenylamine (**173**), presumably *via* a common intermediate ⟨73JCS(P1)1259⟩. Many γ-arylaminopropanoic acids have been cyclized, with particularly good results when polyphosphoric acid is used. The acids (**174**) are made from an arylamine and butyrolactone and cyclized at 120–130 °C (the temperature is critical to ±5 °C) ⟨72JCS(P1)2019⟩; the 2-iodoaniline derivative failed to cyclize. Chirality is retained in the synthesis of (*R*)(+)-1,2-dihydro-2-methylquinolin-4-one (**175**) ⟨77JCS(P1)596⟩. Cyclization of *N*-phenylanthranilic acid by phosphoryl chloride gives 9-chloroacridine hydrochloride, which is easily hydrolyzed to acrid-9-one (**176**) ⟨42OS(22)5⟩; the acridone is obtained directly on cyclization with sulfuric acid ⟨39OS(19)6⟩. Friedel–Crafts cyclization of an acid chloride, using aluminum chloride and inverse addition, gives the dihydroquinol-4-one (**177**) ⟨49JA1901⟩. Cyclization of *N*-benzylglycinates provides a route to dihydroisoquinolin-4-ones (**178**) ⟨68JOC491, 70JHC91⟩, while *N*-phenylanthranilamides (**179**) give 9-alkylaminoacridines ⟨36JCS1546⟩. Quaternary 2,4-dichloroquinolinium salts are obtained from amides and carbonyl chloride; an acid chloride (**180**) was an intermediate ⟨75CB2300⟩. Cyclization of the benzylaminoacetonitrile (**181**) with sulfuric acid provides another route to dihydroisoquinolin-4-ones ⟨71JCS(C)967⟩.



(**169**) Ar = Ph, 25%; 2-thienyl, 40%

(**170**) R = H
(**171**) R = Me, Ph

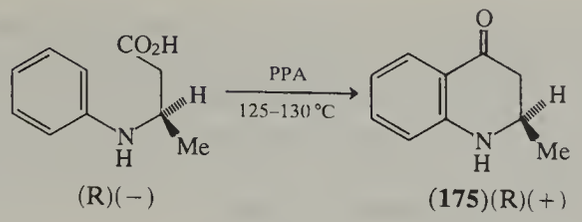
R = H, 97%

(**172**)

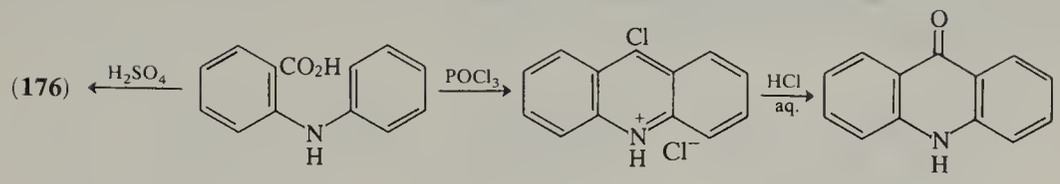
(**173**)

(**174**)

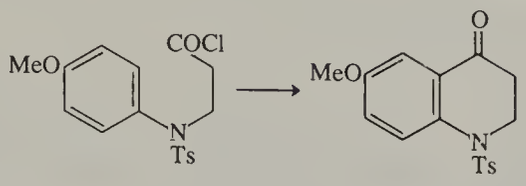
R	6-F	8-F	8-Br
%	31	100	100



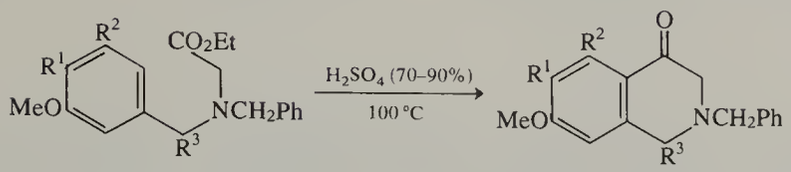
(R)(−) **(175)**(R)(+)



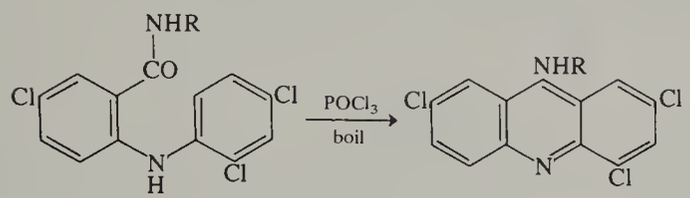
(176)



(177) 99%

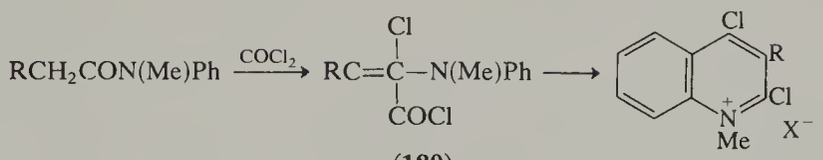


(178) *e.g.* $R^1 = R^2 = R^3 = H$, 50%; $R^1 = R^3 = H$, $R^2 = OMe$, 77%

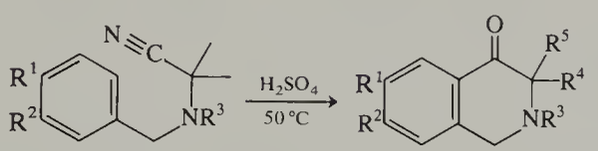


$R = (CH_2)_3NEt_2$ or $CH(Me)(CH_2)_3NEt_2$

(179)



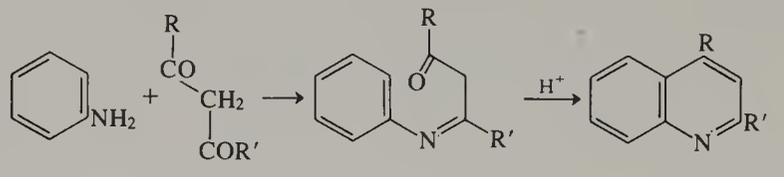
(180)



(181) $R^1 = OMe$, $R^2 = R^3 = R^4 = R^5 = H$, 30–80%

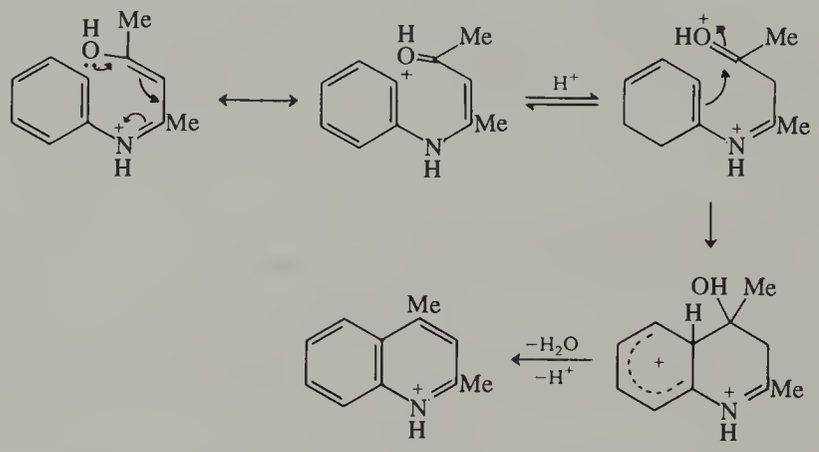
A group of related quinoline syntheses provide access to 2- and 4-quinolones, to 4-hydroxyquinol-2-ones and to 2,4-disubstituted quinolines; all involve cyclization between a carbonyl group and a benzene ring. The Combes synthesis uses the condensation between a β-diketone or β-ketoaldehyde to give an anil, which is cyclized by acid, as in equation (38) ⟨1888CR(106)142⟩. A better procedure for β-keto aldehydes is to use a mixture of aromatic amine hydrochloride and zinc chloride in addition to the amine and β-dicarbonyl compound ⟨42JCS693⟩. The mechanism for the normal Combes reaction is largely due to Bonner ⟨58JCS4181⟩ and is shown in equation (39); the amine hydrochloride version has a different mechanism, using a dianil as intermediate (equation 40) ⟨42JCS693⟩. The reaction is well summarized in a review ⟨77HC(32-1)119⟩, so only a few details will be given here. A dianil of 2-formylcyclohexanone (**182**) has been isolated and cyclized by hot acetic acid to give a tetrahydroacridine ⟨73TL2821⟩. Conversely, monoanils of 2-benzoylcyclohexanone gave tetrahydrophenanthridines (**183**) when cyclized by PPA ⟨75CPB1241⟩, and these two contrasting results highlight the differing results obtained when the Combes synthesis is applied to the production of polycycles. Cyclization of a β-naphthylamine derivative gives benzo[*f*]quinoline (**184**) when amine hydrochloride is used ⟨42JCS693⟩, but the linear benzo[*g*]quinoline (**185**) with hydrogen fluoride ⟨47JA566⟩. Unsymmetrical diketones often

produce mixtures; the delicate balance involved is illustrated by the synthesis of either a tetrahydrophenanthridine (**186**) or a tetrahydroacridine (**187**) from the same acetylcyclohexanone, by varying the temperature of the reaction ⟨10LA(377)10⟩. The benzo[*c*]acridine (**188**) can be obtained from a 2-formyl-1-tetralone derivative ⟨67BSF2373⟩, and a tetrahydrobenzo[*c*]acridine (**189**) is also obtained from a 2-formylcyclohexanone derivative ⟨68JCS(C)2237⟩. In the latter case a separation–recombination mechanism has been proposed for the rearrangement which must have taken place.

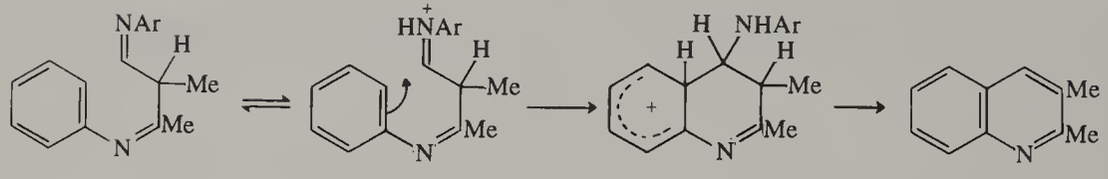


(38)

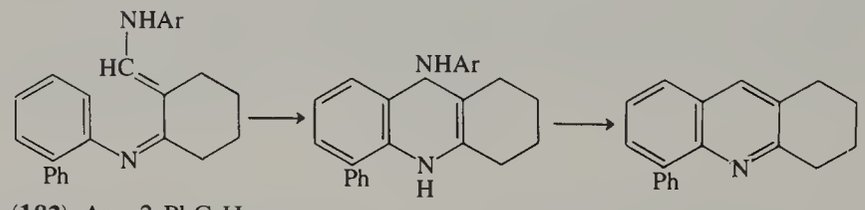
R = alkyl, aryl; R^1 = H, alkyl, aryl



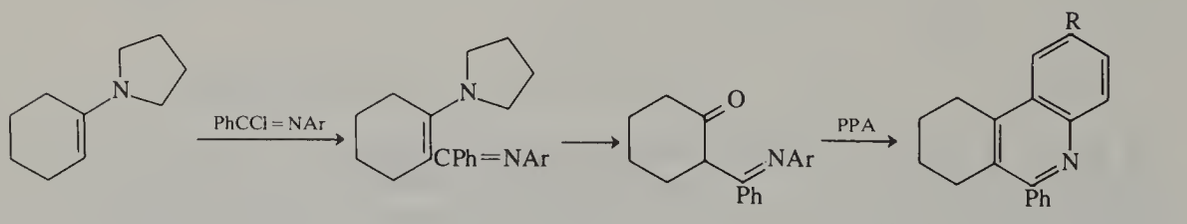
(39)



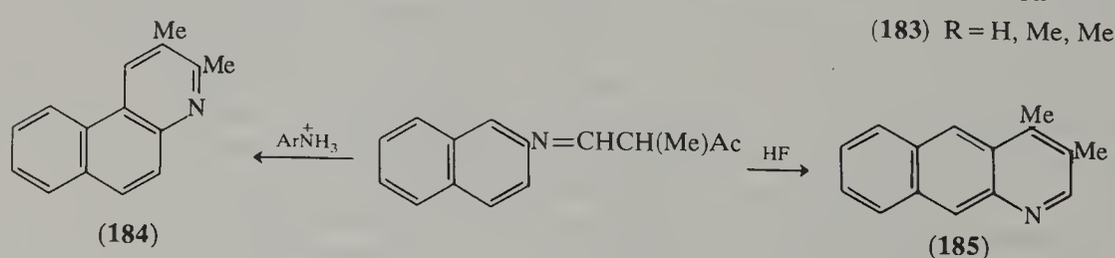
(40)



(**182**) Ar = 2-PhC_6H_4

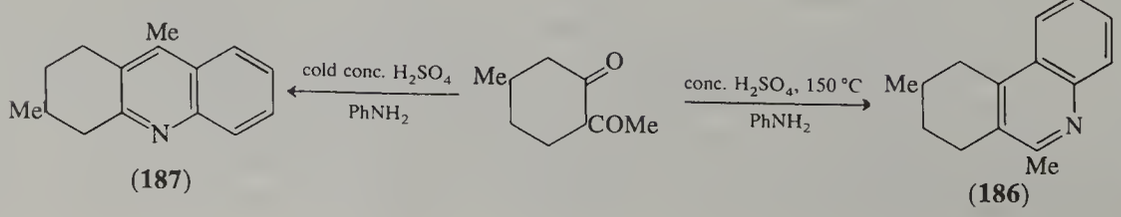


(**183**) R = H, Me, MeO, Cl



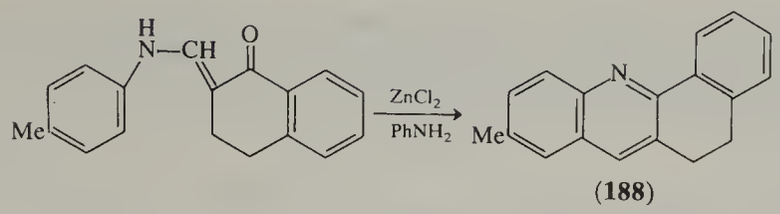
(**184**)

(**185**)

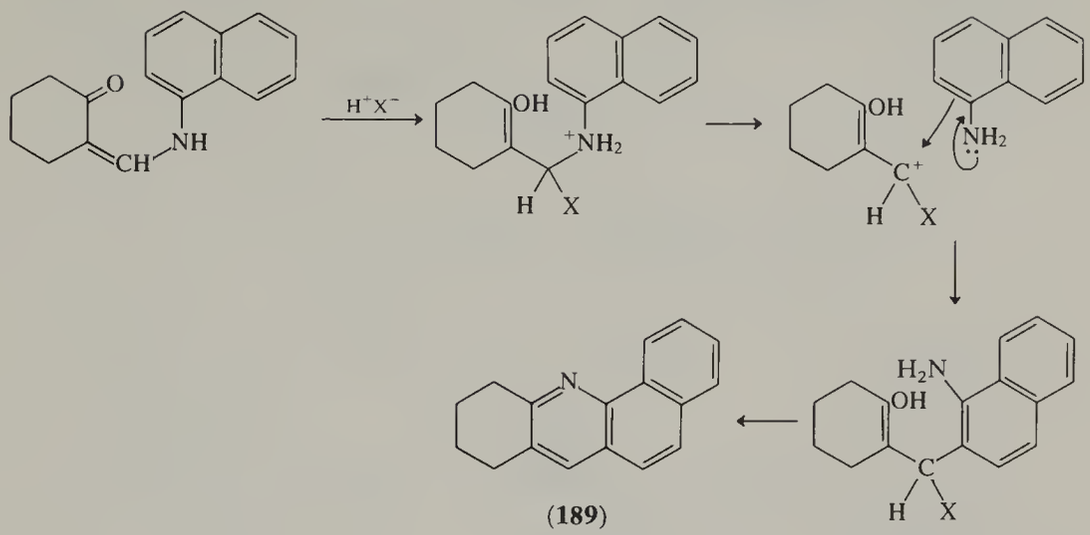


(**187**)

(**186**)

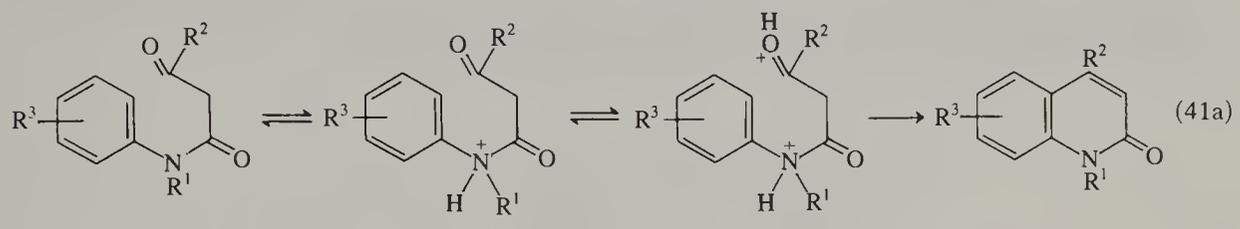


(**188**)

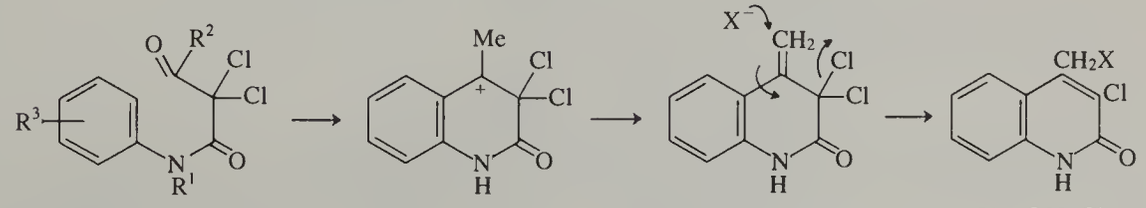


(**189**)

The condensation of arylamines with β-keto esters can be controlled to give either β-ketoanilides or arylaminoacrylates. By cyclization of the former, quinol-2-ones are obtained (Knorr synthesis) while the latter give quinol-4-ones (Conrad–Limpach synthesis). The processes are summarized in equations (41a) and (41b); both have been comprehensively reviewed ⟨77HC(32-1)137⟩. The high acid concentration necessary for the Knorr synthesis has led to the suggestion ⟨64JOC1153⟩ that a diprotonated species is involved as an intermediate (equation 40). The use of α,α-disubstituted acetoanilides has provided evidence for charged intermediates. When the α-substituents are alkyl or aryl groups, that which forms a carbonium ion most readily is lost during cyclization ⟨58JA3656⟩; when the dichloro derivative (**190**) was used, proton loss followed by nucleophilic attack gave the 4-hydroxymethyl- or 4-chloromethyl-quinol-2-ones ⟨69JOC1709⟩. A study of more hindered dichloro derivatives of type (**191**) has revealed that some cannot be cyclized because the preferred conformation places the carbonyl group away from the benzene ring ⟨80JOC2482⟩. A very wide range of substituents on the aryl ring can be tolerated during Knorr syntheses. On the pyridine ring it is possible to have alkyl or aryl groups on the nitrogen atom, and alkyl, aryl and alkoxycarbonyl groups in position 4 of the quinolone. If a 3-substituted quinol-2-one is required, the formylacetanilide is used and can be produced by formylating the acetanilide in some cases ⟨20LA(421)146⟩. The enol ethers (**192**) act as masked formyl groups and cyclize in a reaction reminiscent of the Pomerantz–Fritsch procedure described later in this section ⟨69CB3260⟩. Alkylation of β-ketoanilides to provide an α-alkyl group, followed by cyclization, gives 3,4-dialkylquinol-2-ones; increasing bulk in the potential 3-substituent can seriously inhibit the cyclization. The cyclizing medium is generally concentrated sulfuric acid, from 0 to 100 °C, but polyphosphoric acid has become more commonly used. Sulfonation can



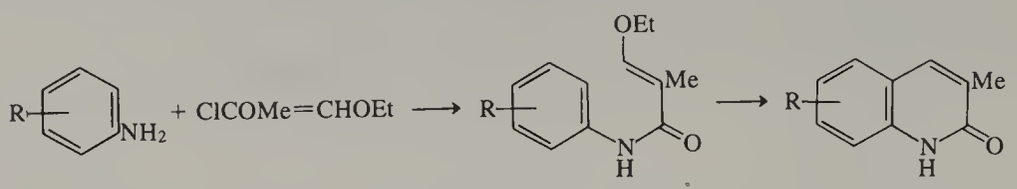
(41a)



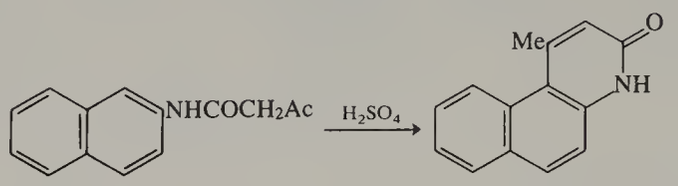
(**190**) $R^1 = R^3 = H$, $R^2 = Me$
(**191**) $R^1 = Et$, $R^2 = Ph$, $R^3 = 4\text{-Br-2-Cl-3,5-(Me)}_2$

X = OH, Cl

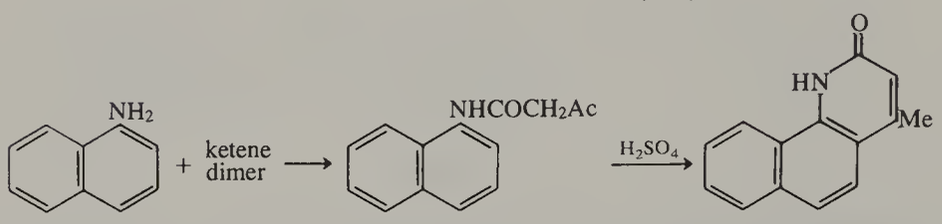
occur if the benzene ring contains electron-donating substituents. The use of the Knorr procedure to produce polycycles is exemplified by the synthesis of the benzo[*f*]quinolone (**193**) ⟨1884CB540⟩ and of the benzo[*h*]quinolone (**194**) ⟨46JA644⟩.



(**192**) R = H, *o*-Me

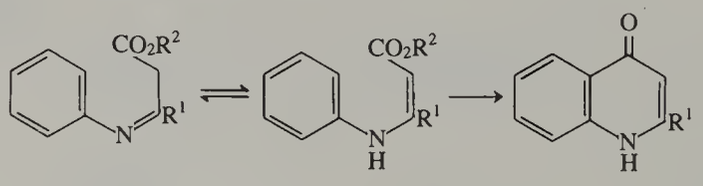


(**193**)

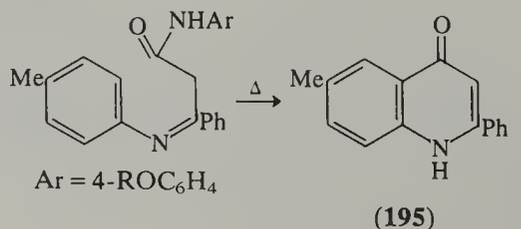


(**194**)

The cyclization of the arylaminoacrylates by heating in a solvent is due to Conrad and Limpach (equation 41b) ⟨1887CB944⟩. The cyclization medium is usually diphenyl ether or Dowtherm (diphenyl ether and biphenyl); the temperature should be high (260–280 °C) and contact time short. The full ramifications of the synthesis have been reviewed ⟨77HC(32-1)139⟩ and only the major points will be mentioned here. Most aromatic amines can be used, except nitroanilines, which are too weakly basic to form acrylates; a *meta*-substituted aniline gives mixtures of 5- and 7-substituted quinol-4-ones, with the latter usually predominating. Simple variation in the pyridine ring of the quinol-4-one can be achieved by varying the original β-keto ester; the synthesis of quinolone (**195**) shows that amides can be used ⟨68MI20800⟩. Neither the Knorr nor the Conrad–Limpach syntheses can be used to prepare phenanthridinones or acridones, but cyclic β-keto esters can be used to prepare tetrahydroacridones such as compound (**196**) ⟨39JCS784⟩. Benzoquinolones (**197**) and (**198**) can be obtained from α- and β-naphthylamines respectively ⟨31CB969⟩. To produce 3-substituted quinol-4-ones an α-substituted keto ester would be required; in practice it is simpler to alkylate the intermediate acrylates or crotonates ⟨46JA1279⟩. When an arylamine is condensed with oxaloacetates, and the aminofumarates (**199**) cyclized, a quinol-4-one-2-carboxylate (**200**) is obtained. In the general case, hydrolysis and decarboxylation give a quinol-4-one without a substituent at position 2 ⟨1889CB3348⟩; in the specific case shown a substituent is introduced to the 3-position by a 3,3-sigmatropic shift ⟨71CB2483⟩. A proposal for the mechanism of the cyclization is shown in equation (42) ⟨72AG(E)315⟩. Amino esters such as (**199**) can also be prepared by addition of arylamines to acetylenedicarboxylates, but if secondary amines are used the products are mixtures of malonates (which can be cyclized) and fumarates (which cannot).

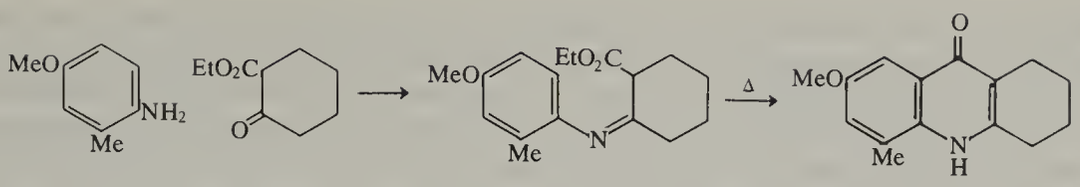


(41b)

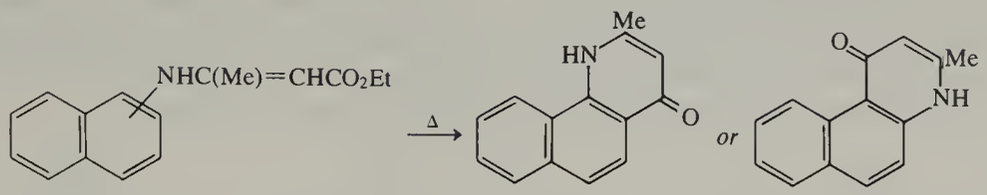


Ar = 4-ROC$_6$H$_4$

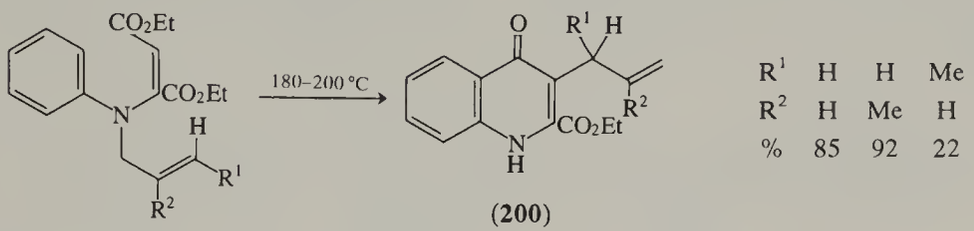
(**195**)



(196)

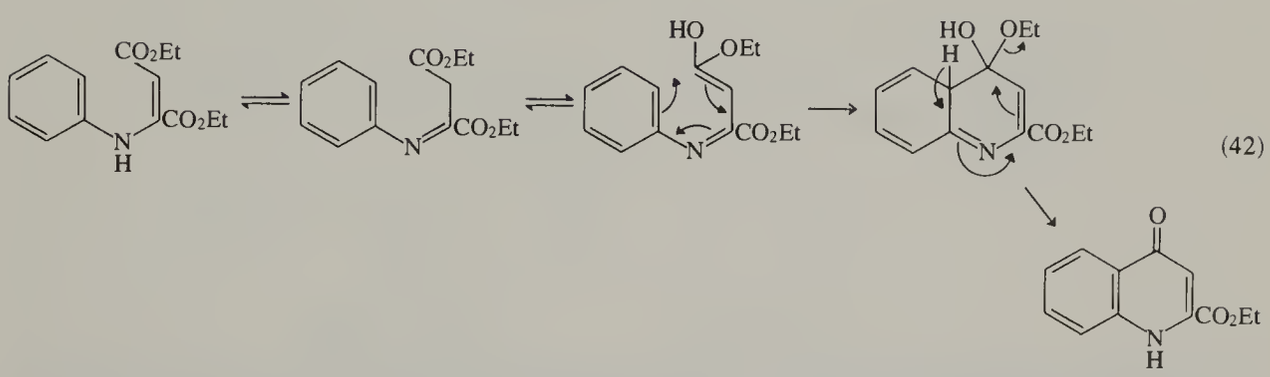


α- or β- (197) (198)



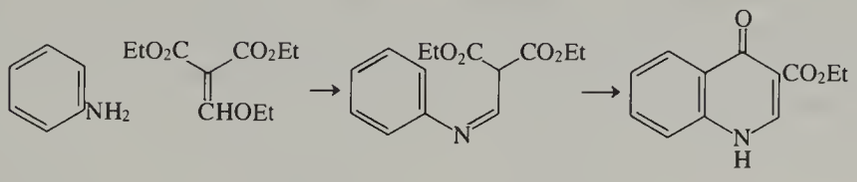
R^1	H	H	Me
R^2	H	Me	H
%	85	92	22

(199) (200)

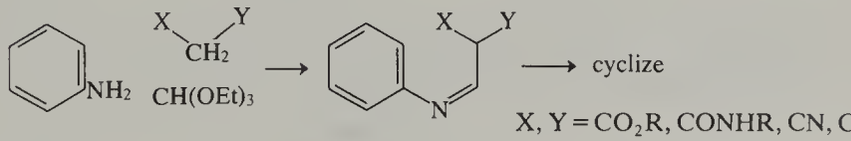


(42)

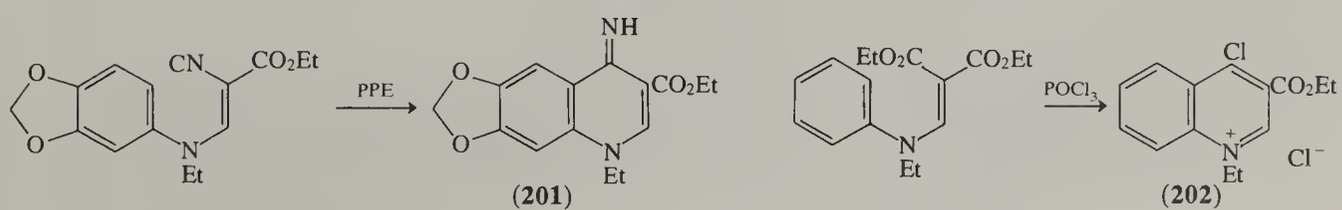
Reactions which are variations on the Conrad–Limpach synthesis, although the intermediates are not isolated, are those in which an arylamine reacts with ethoxymethylenemalonates ⟨39JA2890⟩ as in equation (43), or with ethyl orthoformate and an active methylene component ⟨46JA1253⟩ as in equation (44). Both routes provide quinol-4-ones substituted in position 3. The second route can give 4-iminoquinolines as shown by the preparation of compound (**201**), where the cyclization medium is ethyl polyphosphate ⟨71JAP7123386⟩. A large number of compounds of general formula ArNHC(R′)=C(X)CN have been cyclized by aluminum chloride; sometimes quinol-4-ones were obtained, sometimes 4-aminoquinolines ⟨78M527⟩. Cyclization of a tertiary aminomethylenemalonate by phosphoryl chloride gives a quaternary salt (**202**) ⟨73JAP733728⟩. On a large scale a very high yield of quinol-4-ones can be obtained from aminomethylenemalonates by using a climbing film apparatus with a screw rotor ⟨78MI20800⟩.



(43)

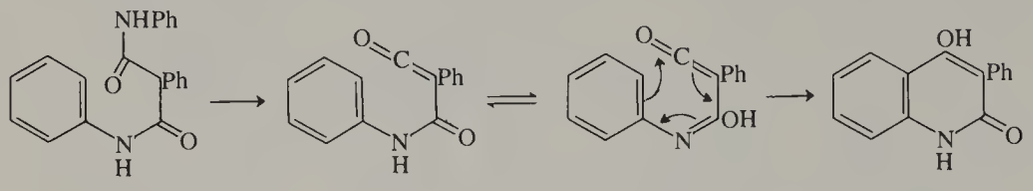


(44)

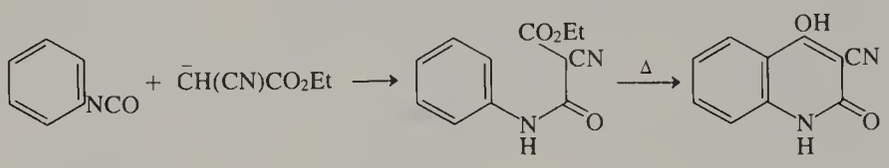


(201) (202)

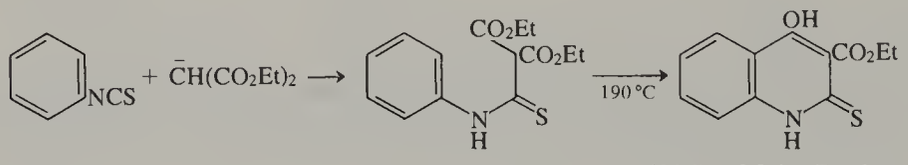
A further logical extension of the Conrad–Limpach synthesis uses malonic acid anilides or dianilides, giving 4-hydroxyquinol-2-ones ⟨77HC(32-1)158⟩. The mechanism proposed for the cyclization of one dianilide is shown in equation (45) ⟨70M762⟩. The amides can be prepared directly from diethyl malonate and an arylamine, or from phenyl isocyanate and the anion of an active methylene compound. The latter route is illustrated by the synthesis of 3-cyano-4-hydroxyquinol-2-one (**203**) ⟨74TL1781⟩. If an isothiocyanate is used, a thione (**204**) can be obtained ⟨70OPP161⟩. Carbon suboxide and aromatic amines give 4-hydroxyquinol-2-ones ⟨70BCJ1135⟩. Cyclizations can be thermal (often under vacuum), or may require phosphoryl chloride or polyphosphoric acid. As an example of a polycycle prepared by this route, the benzo[*h*]quinoline (**205**) is shown ⟨73JHC583⟩.



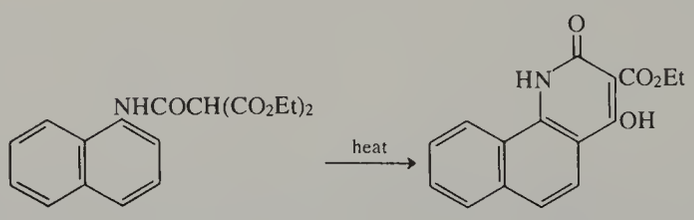
(45)



(**203**)

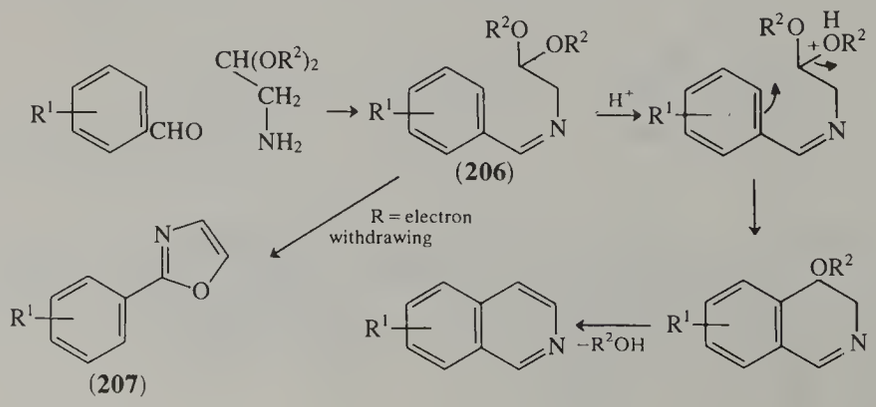


(**204**) Major Product



(**205**)

For the synthesis of isoquinolines, direct cyclization of a suitable benzyliminoacetaldehyde is seldom used, but the corresponding acetals form the basis of the synthesis first reported by Pomerantz ⟨1893M(14)116⟩ after Fritsch had failed to achieve the cyclization ⟨1893CB419⟩. The full sequence is shown in equation (46). The reaction has been reviewed ⟨51OR(6)191, 81HC(38-1)218⟩. In the general scheme (equation 46) the reaction proceeds best if R^1 is an electron-donating group so placed as to exert maximum influence at the position of cyclization. This implies a *meta*-substituent and mixtures can be obtained, but 6- or 6,7-substituted isoquinolines are normal products. The synthesis is particularly suited to the production of 8-substituted isoquinolines. The cyclizing medium has most often been sulfuric acid, but polyphosphoric acid can be used, and a mixture of boron trifluoride, acetic acid and trifluoroacetic anhydride ⟨71T1253⟩ is claimed to give good yields, for example of compounds (**208**). Attempts to extend the synthesis by the use of aromatic ketones (to

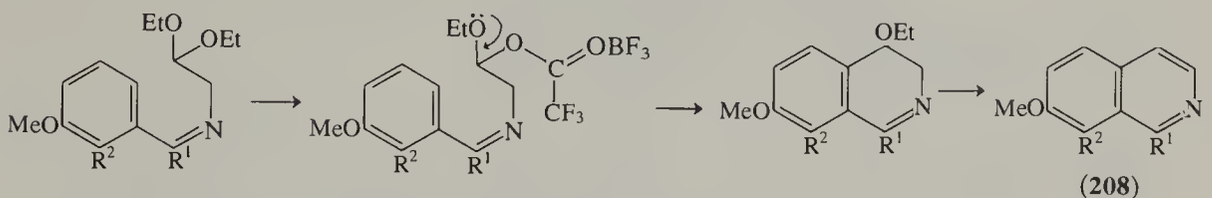


(**206**)

(**207**)

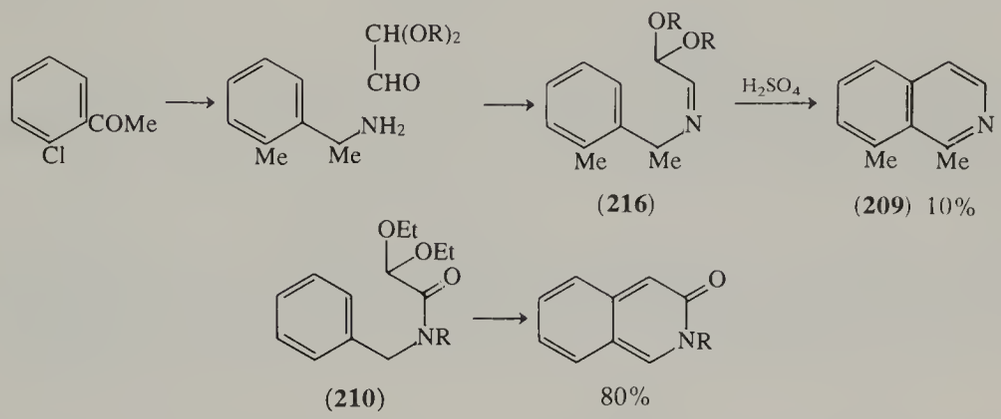
(46)

produce 1-substituted isoquinolines) have been largely unsuccessful. When the substituents on the benzene ring in intermediate (**206**) are electron withdrawing, an alternative cyclization to give oxazoles (**207**) becomes important; nitro groups are sufficiently deactivating so that only oxazoles are obtained ⟨77JOC3208⟩. A modification of the synthesis which allows the production of 1-substituted isoquinolines is due to Schlittler and Müller ⟨48HCA914⟩. A benzylamine (easily available, for example, by reduction of the oxime of an acetophenone) is condensed with glyoxal hemiacetal in high yield, and cyclized by hot concentrated sulfuric acid. Thus, even 1,8-dimethylisoquinoline (**209**) can be obtained ⟨60JCS1918⟩. Cyclization of the amidoacetal (**210**) gives isoquinolin-3-ones ⟨78H(9)1197⟩.



(**208**)

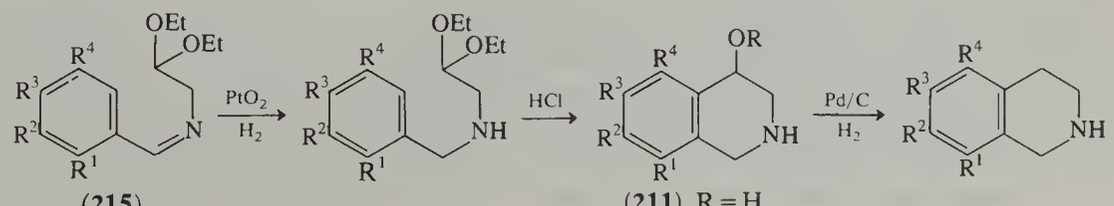
R^1	H	H	H	Me
R^2	OMe	OH	H	H
%	60–82	50–63	73	20



(**216**) (**209**) 10%

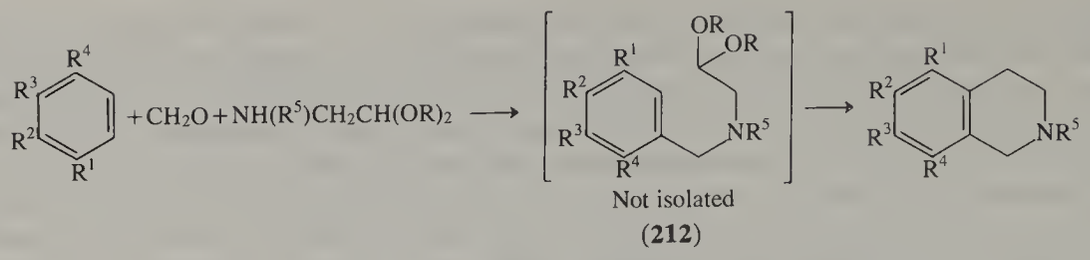
(**210**) 80%

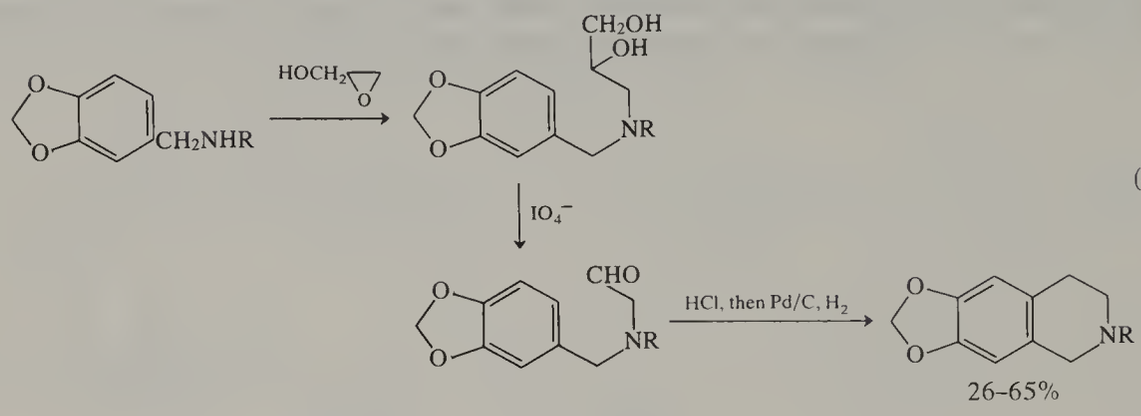
The importance of 1,2,3,4-tetrahydroisoquinolines in alkaloid chemistry has led to a number of improvements in the Pomerantz synthesis. Hydrogenation of the Schiff base (obtained by condensation of aromatic aldehyde and aminoacetal), followed by cyclization using hydrochloric acid, gives an intermediate 4-hydroxytetrahydroisoquinoline (**211**). Further reduction, without isolation of intermediate (**211**), gives the tetrahydroisoquinoline (equation 47) ⟨65JOC2247⟩. The Schiff base can be reductively alkylated before cyclization to give *N*-substituted tetrahydroisoquinolines. A further modification produces the benzylaminoacetals (**212**) directly by a Mannich reaction ⟨69JOC2001⟩ (the benzene ring must have at least one hydroxyl group and one other OR group). The free aldehyde can sometimes be obtained as shown in equation (48) and cyclized ⟨67JOC2225⟩. If the saturated intermediate (**213**) is treated with tosyl chloride, then cyclized, the intermediate dihydroisoquinoline (**214**) often eliminates toluenesulfonic acid to give the isoquinoline ⟨74JCS(P1)2185⟩. In one or two cases it was necessary to treat the intermediate (**214**) with a base to effect the elimination; the reaction can be run from the aromatic aldehyde in one pot. Another method for the introduction of a substituent into position 1 of the tetrahydroisoquinoline is to react the Schiff base (**215**; equation 47) with a Grignard reagent ⟨69JOC2478⟩. A similar reaction on the intermediate of type (**216**) from the Schlittler–Müller synthesis provides one of the few routes to 3-substituted tetrahydroisoquinolines ⟨60BSF617⟩. By adding an aromatic aldehyde during the cyclization stage a condensation with the dihydroisoquinoline intermediate (**217**) can introduce a benzyl group into position 4 of the tetrahydroisoquinoline ⟨65JOC2459⟩. All these electrophilic cyclizations demand some activation of the benzene ring, usually by at least one hydroxyl or alkoxyl group. The production of 4-oxytetrahydroisoquinolines has been reviewed ⟨73AHC(15)99⟩.



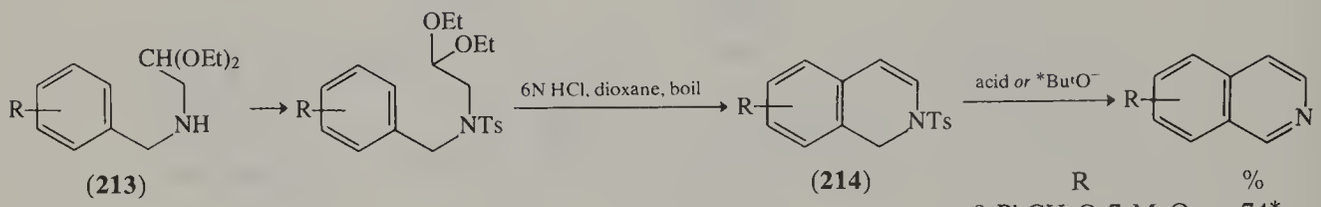
(47)

(**215**) (**211**) R = H

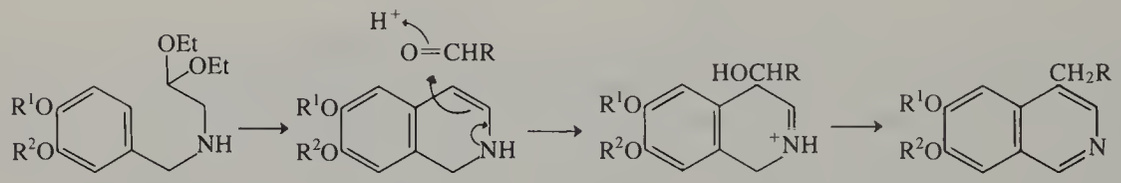




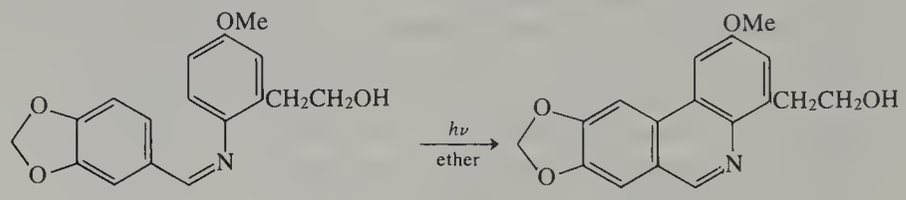
(48)



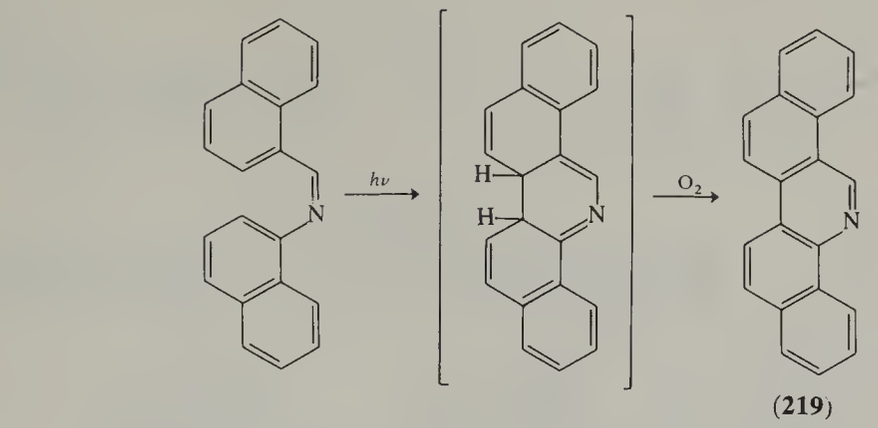
R	%
8-$PhCH_2O$-7-MeO	74*
6,7-$(MeO)_2$	90
7-MeO	70
6-MeO	88
7,8-$(MeO)_2$	75*



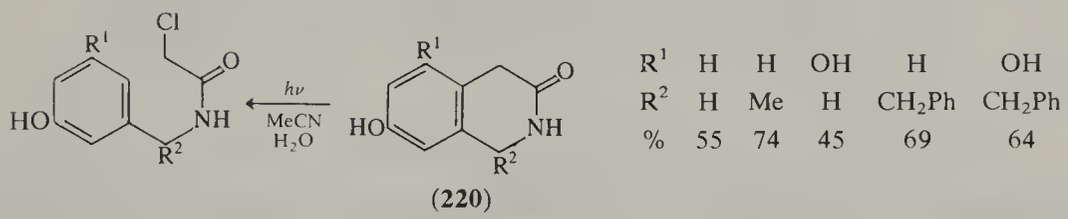
A number of syntheses are based on photochemical cyclization of diarylethylenes or of enamides. Most of the work has been centred on the production of polycyclic compounds, but there are a few examples of isoquinolines or quinolines prepared by photochemical routes. Phenanthridine can be prepared from benzaldehyde anil in concentrated sulfuric acid ⟨64TL3711⟩; some *N*-benzylaniline was isolated, presumably because some Schiff base acts as dehydrogenating agent. The more highly substituted phenanthridine (**218**) was obtained in 55% yield by irradiation in ether solution ⟨74TL1179⟩, and dibenzo[*c*,*i*]phenanthridine (**219**) in 40% yield ⟨64TL2109⟩; in the latter case, oxygen was the aromatization agent.



Much more work has been done on the cyclization of amides, mainly of enamides. There are examples of the use of *N*-chloroacetylbenzylamines to produce dihydroisoquinolin-4-ones (**220**) ⟨74TL1181⟩. Irradiation of enamides (**221**) can give either tetrahydrophenanthridinones ⟨71JOC3975⟩ or hexahydrophenanthridinones ⟨74JCS(P1)1747⟩. Without added iodine a mixture of *cis* and *trans* derivatives is obtained and the ratio varies with solvent; in non-polar solvents the *trans*:*cis* ratio can be 15.6:1. If iodine is added to the solution to be irradiated, the quinol-2-ones are obtained. The mechanism has been discussed and

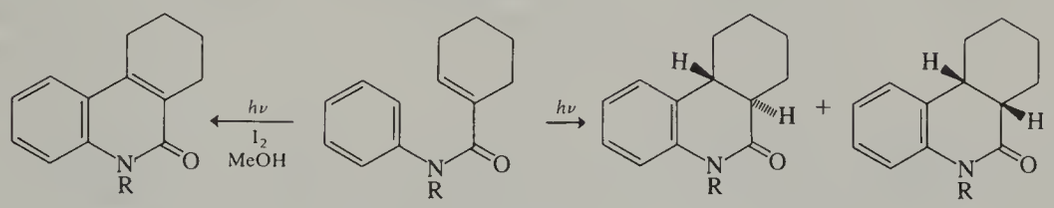


(**219**)



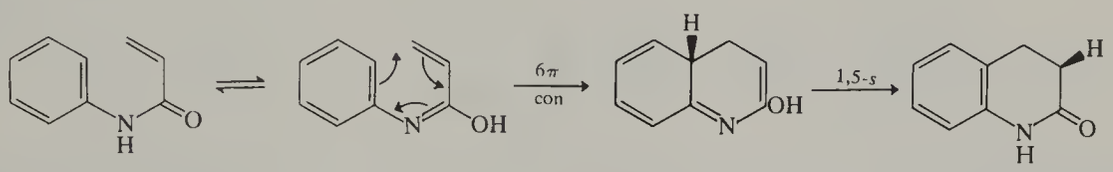
R^1	H	H	OH	H	OH
R^2	H	Me	H	CH_2Ph	CH_2Ph
%	55	74	45	69	64

(**220**)



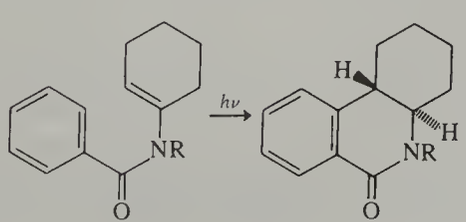
(**221**) R = Me, CH_2Ph

is shown in equation (49) ⟨78S489⟩; enolization is followed by conrotatory thermal 6π-electrocyclization, then a 1,5-suprafacial sigmatropic hydrogen shift. There is evidence of some incorporation of ^2H into the 3-position of the dihydroquinol-2-one if a [2,4,6-$^2H_3$]anilide is used ⟨67CC1064⟩.

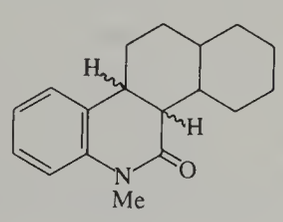


(49)

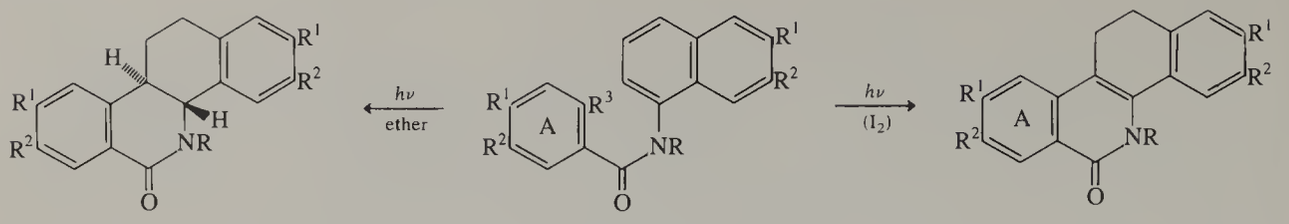
Much information is available on the cyclization of *N*-cyclohexenylbenzamides (**222**) and of *N*-phenylcyclohexenoic acid amides (**221**), which give hexahydro- or tetrahydro-phenanthridinones (the latter amides have been described above). The benzo[*i*]phenanthridinones (**223**) were similarly obtained. From the amides (**222**) only one isomer, with the *trans* ring fusion, was obtained ⟨70TL445⟩, as was the case also in the synthesis of the polycycle (**224**) ⟨73JCS(P1)1996⟩. The reaction is not regioselective unless an *ortho* substituent is present. Such an *ortho* substituent, if it represents a good leaving group (halogen, methoxyl), can allow the production of the tetrahydrophenanthridinones without added iodine, as shown for the synthesis of benzo[*c*]phenanthridinone (**226**) ⟨73JCS(P1)1996⟩ from amide (**225**). A better yield was obtained in the cyclization of the *o*-methoxyamide (**227**) with control of the regiochemistry of the product (**228**); without the methoxyl group, but using iodine, both regioisomers in ring A were obtained ⟨75JCS(P1)762⟩. An *ortho* substituent can isomerize after the cyclization, appearing at the position next to the nitrogen atom (a 1,5-shift). Thus, among the *ortho* substituents in amides (**229**), the methoxyl group and the methoxycarbonyl group migrated, while the amino group directed cyclization to the other *ortho* position. Experiments with a monocyclic enamide showed that the amide group underwent some migration, but the carboxyl group was eliminated during photocyclization ⟨74CC81⟩.



(**222**)



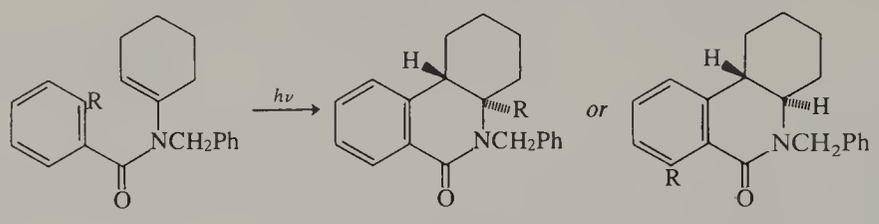
(**223**) *cis* and *trans* and dehydro



(**224**) $R^1 = R^2 = H$, R = Me, 52%

(**225**) $R^1 = R^2 = H$, $R^3 = Br$, R = Me
(**227**) R^1, $R^2 = OCH_2O$; $R^3 = MeO$; R = Me

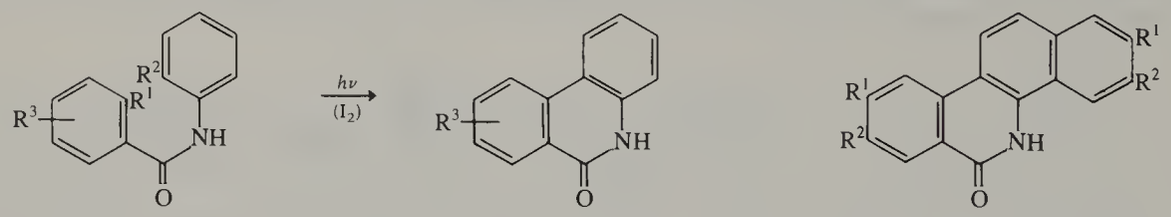
(**226**) $R^1 = R^2 = H$, R = Me
(**228**) R^1, $R^2 = OCH_2O$; R = Me



(**229**)

R = OMe, CO_2Me, $CONH_2$ R = NH_2

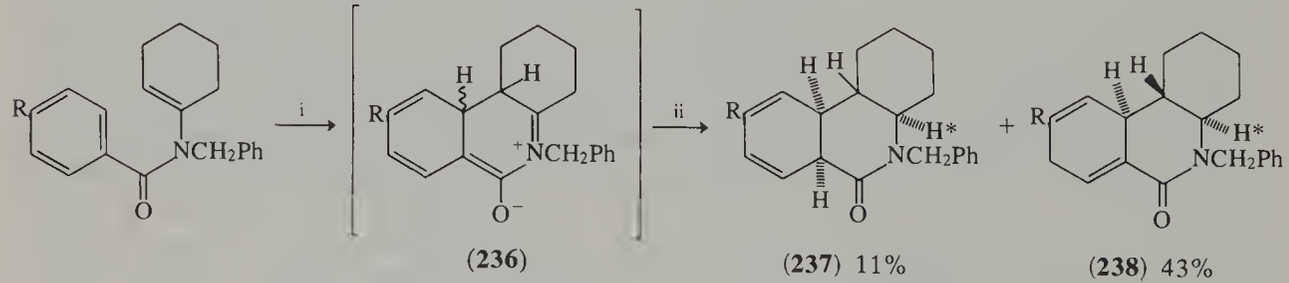
Benzoylanilides can be cyclized to phenanthridinones if irradiated in the presence of iodine ⟨67CC614⟩. In the examples given, phenanthridinone itself (**233**) has been prepared from benzanilide (**230**), from *o*-iodobenzoylaniline (**231**), and from benzoyl-*o*-iodoaniline (**232**); in the last two cases no iodine was necessary. A whole range of *o*-methoxybenzanilides (**234**) has been cyclized in moderate to excellent yields, if the benzene ring A contained at least one extra methoxyl group ⟨73CC647⟩. As expected, benzo[*c*]phenanthridinones such as compound (**235**) can be similarly prepared ⟨74TL2269⟩. The phenanthridinones can be converted into phenanthridines by standard procedures. Irradiation of *N*-cyclohexenylbenzamides in the presence of sodium borohydride or borodeuteride gives mixtures of dienes (**237**) and (**238**) ⟨81H(16)1137⟩. The labelling produced by the use of borodeuteride has provided a proof for the intermediacy of the zwitterionic intermediate (**236**).



(**230**) $R^1 = R^2 = R^3 = H$
(**231**) $R^1 = I$, $R^2 = R^3 = H$
(**232**) $R^2 = I$, $R^1 = R^3 = H$
(**234**) $R^1 = OMe$, $R^2 = H$, R^3 = various groups

(**233**) $R^3 = H$, 20%
9%
48%

(**235**) R^1, $R^2 = OCH_2O$, 70%



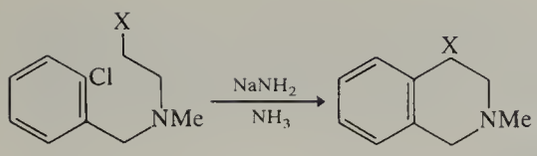
(**236**)

(**237**) 11%

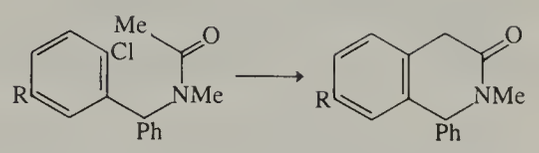
(**238**) 43%

i, *hν*, high pressure, Et_2O/MeOH; ii, $NaBH_4$ or $NaBD_4$; * labelled when $NaBD_4$ is used

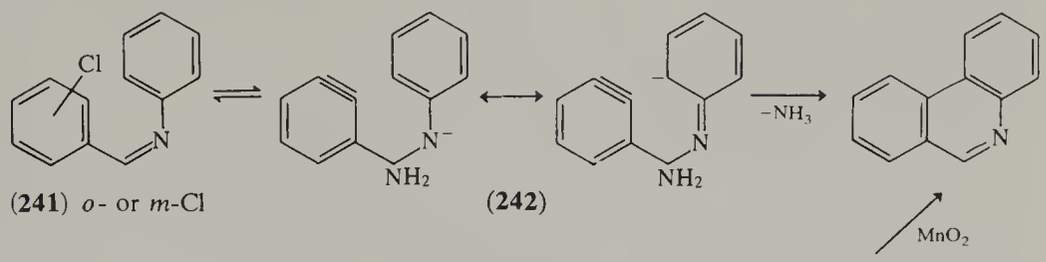
Some tetrahydroisoquinolines (**239**) ⟨68BSF310⟩ and some dihydroisoquinolin-3-ones (**240**) ⟨67JHC149⟩ can be prepared *via* benzyne intermediates. More interesting is the discovery that Schiff bases from *o*- or *m*-chlorobenzaldehyde (**241**) can cyclize *via* benzyne intermediates when treated with potassium amide ⟨69TL1155, 73T167⟩. The mechanism is assumed to involve addition of amide ion, thus providing the anionic centre in intermediate (**242**) which can react with the neighboring benzyne. The benzylaniline (**243**), where the anionic center is formed by deprotonation of the amine, can be cyclized in quantitative yield, the resulting dihydrophenanthridine being easily dehydrogenated by manganese dioxide ⟨73T167⟩. Benzo[*c*]phenanthridine (**244**) has been similarly prepared ⟨69TL1155⟩ and many substituted phenanthridines ⟨73T177⟩.



(**239**) X = CN, 46%
X = CO_2Me, 20%

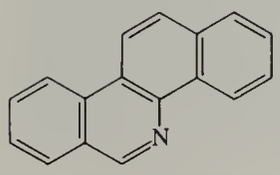


(**240**) R = H, 8%
R = CF_3, 14%

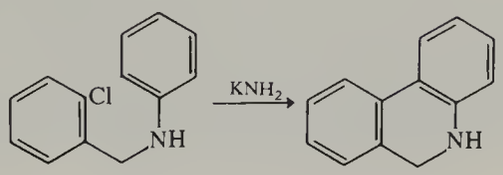


(**241**) *o*- or *m*-Cl

(**242**)

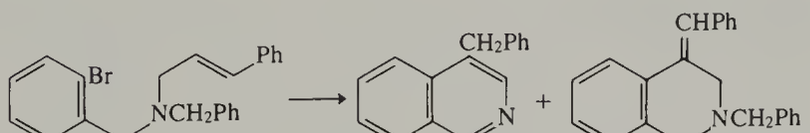


(**244**) 35%



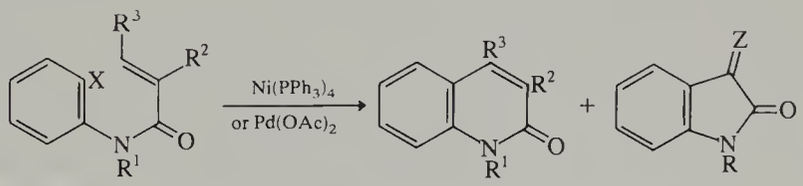
(**243**)

Finally, a few cyclizations of unsaturated side chains on *o*-halogeno-anilines or -benzenes have been catalyzed by transition metal complexes. Cyclization of the cinnamylbenzylamine (**245**) by palladium gives some 4-benzylisoquinoline and some of compound (**246**) ⟨77TL1037⟩. Acryloylanilines (**247**) and (**248**) can be cyclized by a nickel complex ⟨75MI20800⟩ or by a palladium complex ⟨79JA5281⟩. The mechanism for the latter reaction is given in equation (50).

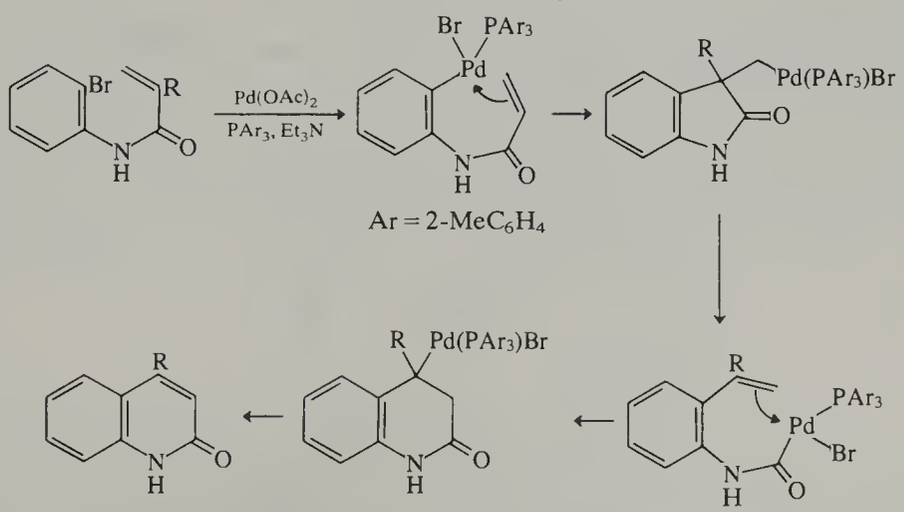


(**245**)

(**246**)



(**247**) X = Cl, R^1 = Me, R^2 = H, R^3 = H, CO_2Me or Ph
(**248**) X = Br, R^1 = R^2 = H, R^3 = Me or Ph



Ar = 2-MeC_6H_4

(50)

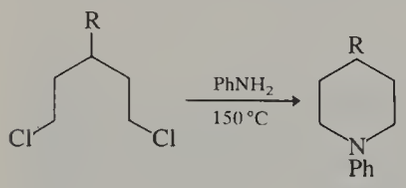
The Pschorr cyclization of the diazonium fluoroborate from *N*-methylanthranilamide can be used to make *N*-methylphenanthridinone ⟨67JCS(C)1513⟩.

2.08.2.2 Formation of Two Bonds

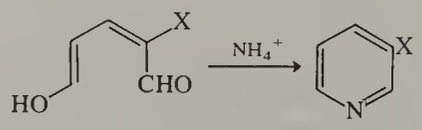
2.08.2.2.1 From [5+1] atom fragments

(i) From a nitrogen derivative and a five-carbon fragment

The boundary between reactions where six atoms are cyclized and those where a nitrogen-containing fragment reacts with a five-carbon chain is difficult to distinguish; some overlap is inevitable with Section 2.08.2.1. Thus, the synthesis of piperidines commencing from 5-chloropentanamines can equally well proceed from 1,5-dihalogenopentanes. Early syntheses of this type have been summarized ⟨08CB2156⟩, while more recent examples are provided by the preparation of 4-aminopiperidines (**249**) ⟨43HCA1132⟩. Glutaraldehyde can be cyclized to give pyridine in up to 53% yield by using an ammonium salt and a reducible dye, such as malachite green ⟨67BRP1077573⟩, or by copper(II) or iron(III) salts with halide counterions ⟨68BRP1102261⟩. Glutaconic aldehydes are unstable, and are usually obtained from pyridines, but they can be converted into pyridines (**250**) by treatment with ammonium acetate ⟨24CB1622, 25CB2018⟩. The more stable acetal (**251**), at the same oxidation level as glutaconic aldehyde, is reported to give pyridine in 91% yield ⟨54JAP5408029⟩; the thioenol ether (**252**) has been converted into a pyridine with an optically active *s*-butyl group in the 3-position, when treated with hydroxylamine hydrochloride ⟨76SC549⟩.



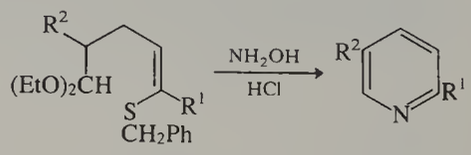
(**249**) R = NH_2 or NMe_2 (67% and 68%)



(**250**) X = H, Cl, Br, I

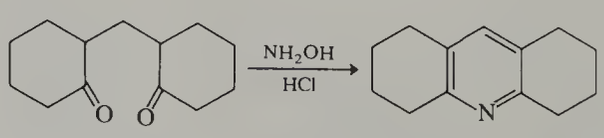
$(MeO)_2CHCH_2CH(OMe)CH_2CH(OMe)_2$

(**251**)



(**252**) R^2 = MeCHEt

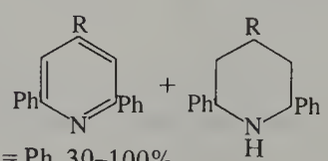
The cyclization of 1,5-diketone monoximes have been mentioned (Section 2.08.2.1); more commonly the diketones or dialdehydes are cyclized directly by treatment with a hydroxylamine salt, often in boiling ethanol. Glutaraldehydes give pyridines ⟨55BRP734381⟩ and octahydroacridines can be made by treatment of the diketone (**253**) with hydroxylamine hydrochloride ⟨52JA4923⟩. Quaternary salts are obtained from the diketone (**253**) and primary amines in the presence of acetic acid ⟨70ZOR404⟩. Condensation of aldehydes with acetophenones gives 1,5-diketones of general type (**254**). Such 1,5-diketones have been cyclized by hydroxylamine salts to give pyridines ⟨1898LA(302)240⟩, or by ammonia ⟨37AP(275)294⟩ or ammonium formate and formamide ⟨53JA6042⟩. In the last case and in the synthesis of the reduced quinoline (**255**) ⟨79JCS(P1)1411⟩ tetrahydropyridines or piperidines are also formed, indicating that disproportionation ensures aromatization. Dihydropyridines (**256**)–(**258**) are produced when ketones such as (**254**) are treated with amines or hydrazine ⟨37AP(275)294⟩, or the acid (**254**; R = CO_2H) with ammonia ⟨1887CB2756⟩; a close analogy with the Hantzsch synthesis (Section 2.08.2.4.2(i)) is provided by the isolation of the dihydropyridine (**259**) when 3,5-diacetylheptane-2,5-dione is treated with ammonia in alcohol ⟨1897CB2295⟩. Extra unsaturation in the starting material ensures production of a pyridine. Dienaminoiminium salts (**260**) can serve as masked keto aldehydes or diketones, and react with ammonia or



(**253**)

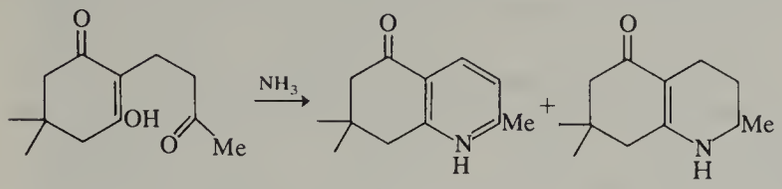
$PhCOCH_2CHRCH_2COPh$

(**254**)

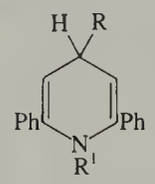


R = Ph, 30–100%

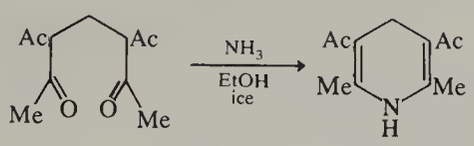
ammonium salts to give high yields of pyridines ⟨75LA874⟩. A ketene thioacetal is an intermediate in the production of 2,6-di(2-pyridyl)pyridine (**261**); the methylthio group is removed by Raney nickel desulfurization ⟨81JA3585⟩.



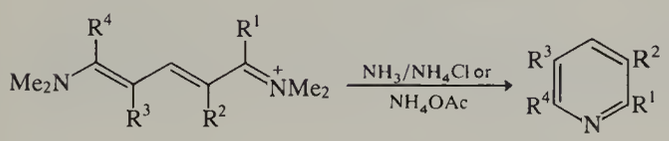
(**255**) 40% 31%



(**256**) R = Ph, $R^1 = NH_2$
(**257**) R = Ph, $R^1 = CH_2CH_2NH_2$
(**258**) R = CO_2H, R^1 = H



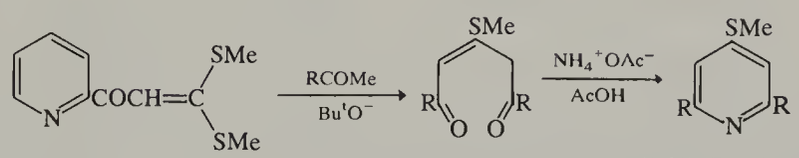
(**259**)



(**260**)

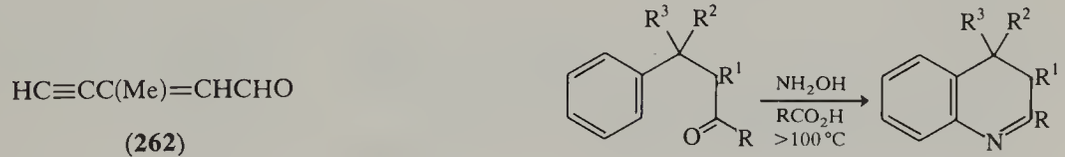
R^1	Ph	Ph	Ph	Ph	2-thienyl
R^2	H	Me	H	H	H
R^3	H	H	Ph	H	H
R^4	H	H	H	Ph	H
%	81	73	98	98	60

etc.

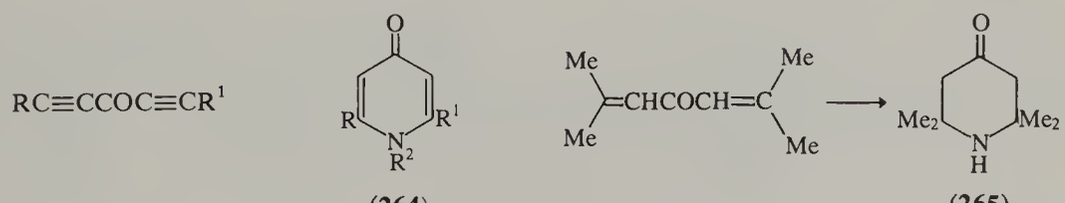


(**261**) R = 2-pyridyl

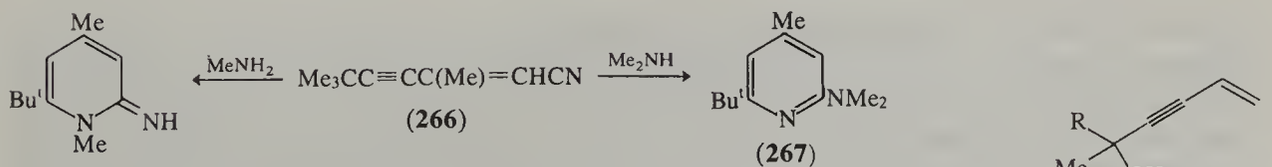
Ammonia or an amine can also be introduced between a terminal aldehyde or a ketone and a suitably placed double or triple bond, although the method is of limited use. A poor yield of 4-picoline is obtained when the aldehyde (**262**) is treated with ammonia or an ammonium salt ⟨49JCS1430⟩ and dihydroquinolines from the phenylethyl ketones (**263**) and hydroxylamine ⟨76MI20800⟩. More commonly, cyclization occurs by insertion of ammonia, amines or hydroxylamine between two triple or double bonds; in the former case, pyrid-4-ones (**264**) are obtained ⟨54BSF734⟩; in the latter, a piperid-4-one (**265**) results ⟨1897CB231⟩. Amines have also been used to give *N*-substituted piperid-4-ones ⟨70OMR(2)197⟩. In these cases a double 1,4-addition must be involved; in the cyclization of the unsaturated nitrile (**266**) by methylamine, 1,6-addition is presumably followed by 1,2-addition ⟨72ZOR2026⟩. It should be noted that dimethylamine initiates a six-atom cyclization to give the pyridine (**267**). Mixtures of pyridines are obtained when allylic alcohols (**268**) and ammonia are passed over catalysts such as cadmium oxide on alumina at 360–400 °C ⟨59IZV1629⟩.



(**262**) (**263**)



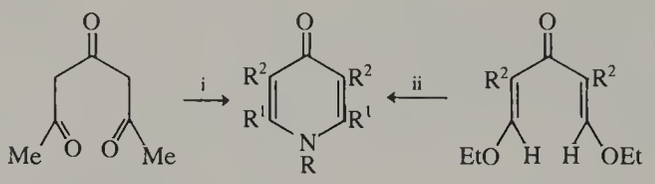
(**264**) (**265**)



(**266**) (**267**)

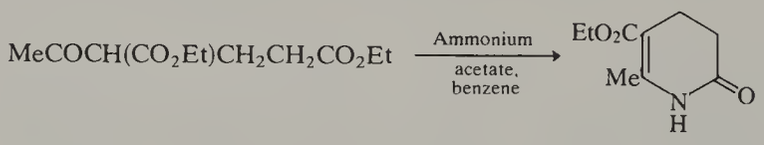
(**268**) R = H or Me

The synthesis of pyrid-4-ones can be achieved by reacting amines with 1,3,5-triketones (**269**) ⟨40USP2185243⟩, or from 1,5-diethoxy-1,4-dien-3-ones (**270**) with ammonia ⟨1898CB1682⟩. From 5-ketopentanoic acid derivatives and amines or ammonium salts the 3,4-dihydropyrid-2-one (**271**) ⟨54JOC1516⟩ or the mixture of hexahydroquinol-2-ones (**272**) and (**273**) ⟨76BSB11⟩ have been obtained; from the *o*-disubstituted benzenes (**274**) isoquinolin-3-ones are obtained ⟨71T4653⟩. Instead of the free aldehydes an enol ether (**275**) ⟨1898CB767⟩ or an acetal (**276**) can be used. In the former case a 4-hydroxypyrid-2-one was obtained, in the latter 4-aminopyrid-2-one (**277**) ⟨77JHC1295⟩ or *N,N'*-dialkyl-4-aminopyrid-2-ones (**278**) ⟨56CB876⟩. A dienaminoiminium salt (**279**), at a higher oxidation level than the compound (**260**), reacts with aniline to give a 2-phenylimino-*N*-phenylpyridine ⟨77JCR(S)100⟩.

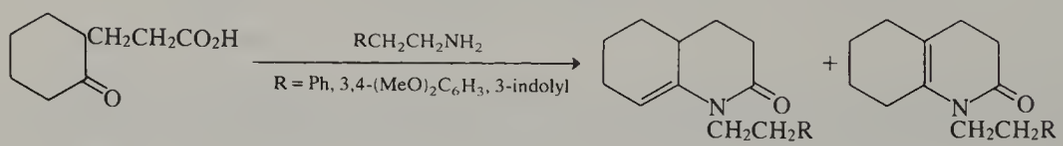


(**269**) (**270**)

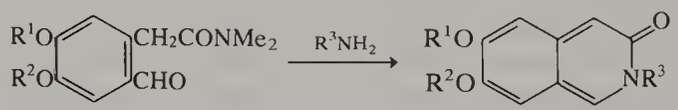
i, RNH_2, benzene, boil; R=Ph, Me, β-$C_{10}H_7$; gives R^1 = Me, R^2 = H; ii; NH_3; gives R = R^1 = H, R^2 = CO_2Et



(**271**)

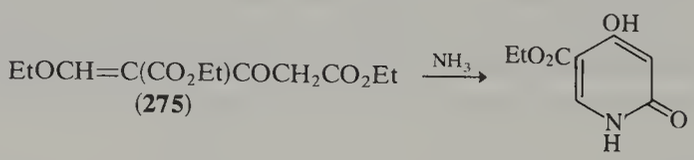


(**272**) (**273**)

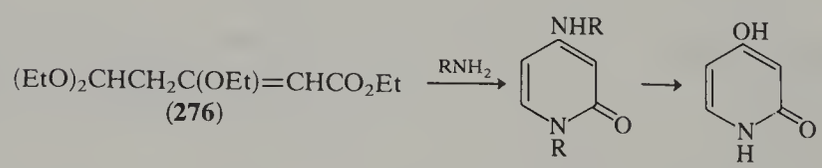


(**274**)

e.g. R^1, R^2, R^3 = Me, 73%; R^1, R^2 = OCH_2O, R^3 = CH_2Ph, 83%



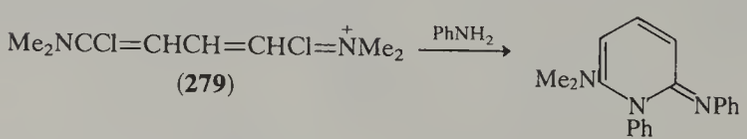
(**275**)



(**276**)

(**277**) R = H

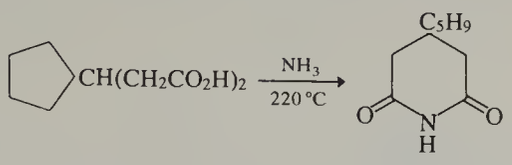
(**278**) R = C_6H_{11} or $PhCH_2$ (66%)



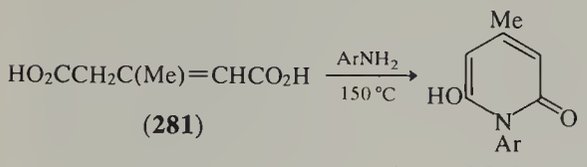
(**279**)

Glutaric acids can be converted into glutarimides (2,6-dioxopiperidines) by a variety of reagents. Examples are the synthesis of 4-cyclopentyl-2,6-dioxopiperidine (**280**) by ammonia ⟨54JA5548⟩, and of glutarimide itself ⟨50ZOR1145⟩. Once again, when an extra unit of unsaturation is introduced in the starting material, as in the glutaconic acid (**281**) ⟨56JA4683⟩ or during the reaction, as when a citric acid (**282**) is used ⟨56MI20800⟩, the products are 6-hydroxypyrid-2-ones. From β-ketoglutaric acid and ammonia the 4-amino derivative

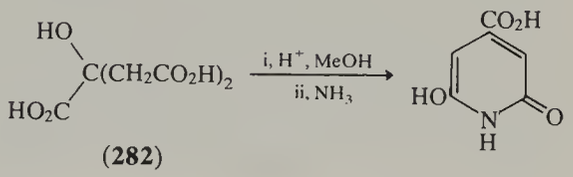
(**283**) ⟨16JPR(94)193⟩ can be obtained (and subsequently hydrolyzed to 4,6-dihydroxypyrid-2-one), while diethyl β-ketoglutarate with aniline gives the *N,N'*-diphenyl derivative (**284**) ⟨75JOC2135⟩, which can be hydrolyzed to *N*-phenyl-2,4,6-trioxopiperidine.



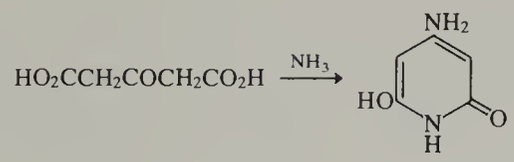
(**280**) 93%



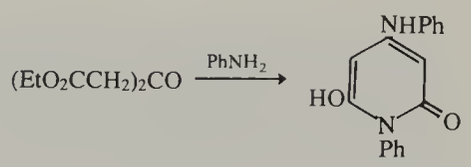
Ar = 4-MeC_6H_4, 30%



(**282**)



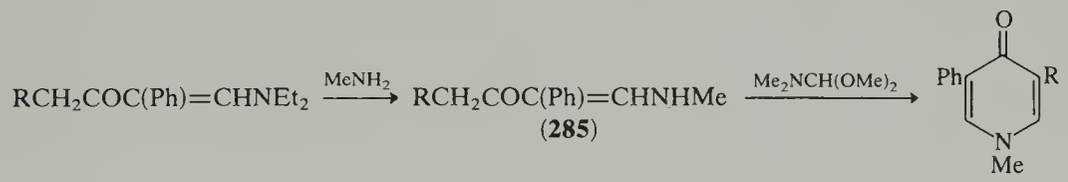
(**283**)



(**284**)

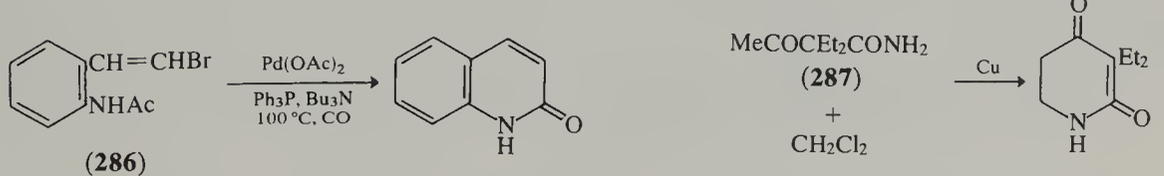
(ii) By insertion of the α-carbon atom

There are few examples of this class of synthesis, most being derived from the Pictet–Spengler isoquinoline synthesis. A few pyrid-4-ones have been obtained by reaction between the enaminoketones (**285**) and dimethylformamide dimethyl acetal ⟨77SC305⟩. Insertion of carbon monoxide into 1-(*o*-acetamidophenyl)-2-bromoethylene (**286**), using palladium(II) acetate, gives quinol-2-one ⟨79H(13)329⟩. A reaction of uncertain mechanism produces, from the β-ketoamide (**287**) and methylene chloride with copper powder, a diketopiperidine ⟨52JAP5201775⟩. Anthranilates react with the anion of DMSO to give compounds of general type (**288**); condensation with aldehydes then produces 2-substituted quinol-4-ones ⟨72JHC173⟩. This reaction has some similarity to the Pictet–Spengler synthesis. The last class of α-insertion reactions makes use of lithiated intermediates. The trilithio derivative (**289**) of 2-aminobiphenyl gives phenanthridinone with carbon dioxide and phenanthridine with DMF ⟨81T825⟩. Substituted phenanthridines can also be made by this method, with the limitation that substituents must be unchanged by *n*-butyllithium. Transmetallation of *o*-bromophenylethyl bromide gives a monolithiated intermediate (**290**) which reacts with aromatic nitriles to give 3,4-dihydroisoquinolines ⟨78JOC1606⟩. Nitriles with α-hydrogen atoms give poor yields (or no product) and the synthesis also fails with 1-cyanoadamantane.



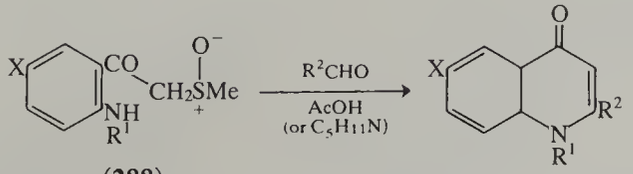
(**285**)

R = Ph, 4-$O_2NC_6H_4$, 4-$F_3CC_6H_4$



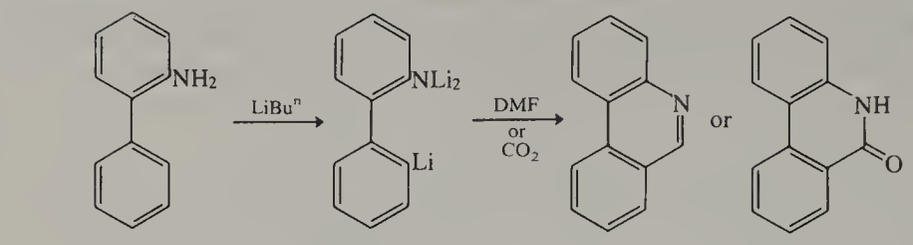
(**286**)

(**287**)

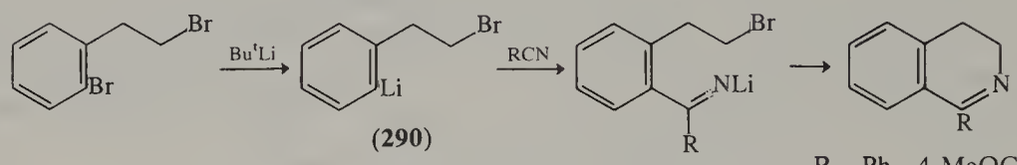


(**288**)

R^1 = Me, R^2 = X = H; R^1 = H, X = Cl, R^2 = 4-pyridyl, vanillyl, *etc.*



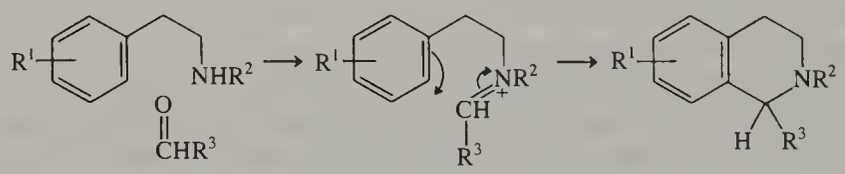
(289) 62%



(290)

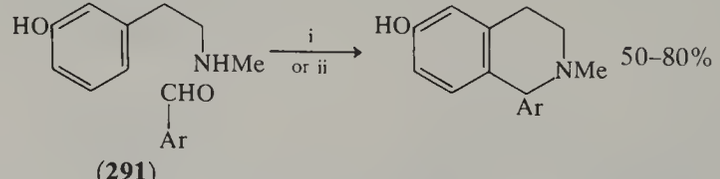
R	Ph	4-MeOC$_6$H$_4$
%	63	43

The synthesis of 1,2,3,4-tetrahydroisoquinolines, first discovered by Pictet and Spengler ⟨11CB2030⟩, is generalized in equation (51). Although it seems clear that the intermediate is an imine which cyclizes by electron donation from the aromatic ring (activation by electron-donating substituents is essential), the imine is rarely isolated (see ⟨13LA(395)342⟩). In the common form of the synthesis a one-carbon aldehyde function is inserted to become the α-carbon of the isoquinoline. The synthesis has been reviewed, with many examples taken from the literature before 1950 ⟨51OR(6)151⟩ and also more recently ⟨81HC(38-1)170⟩.



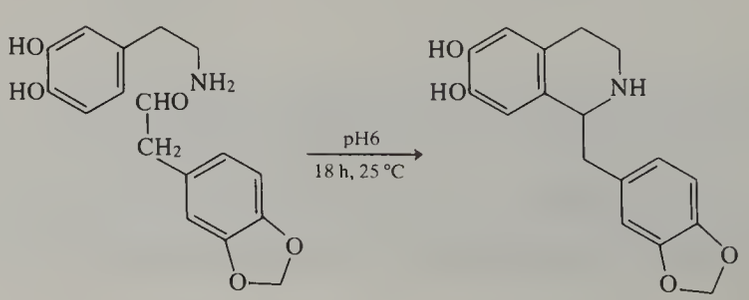
(51)

A phenolic or alkoxyl group *meta* to the side chain in the phenylethylamine assists the cyclization, and alkoxyl groups then appear in position 7 of the tetrahydroisoquinolines. Phenols, however, can give mixtures of 5- and of 7-substituted tetrahydroisoquinolines ⟨28M(50)341⟩. As cyclizing agents, hydrochloric, sulfuric or acetic acids have been used, and phenolic β-phenylethylamines (**291**) have been cyclized under neutral or basic conditions ⟨71JCS(C)2632⟩. The main feature of the Pictet–Spengler synthesis is the mildness of the cyclization conditions, and it has been much used to simulate biosynthetic pathways under 'physiological conditions'. A classic case is the synthesis of the tetrahydroisoquinoline (**292**) in 84% yield at pH 6 and 25 °C ⟨40LA(544)1⟩. It is interesting to note that all aldehyde had gone after two hours, although the maximum yield of product was not attained until 18 hours had elapsed. In this case, and many others, there was a decrease in yield if the phenolic hydroxyl group was alkylated. In another modification, pyruvic acid can be used to give a carboxylic acid ⟨11CB2030⟩. A free phenolic hydroxyl appears to be essential for the condensation in this case. With air and a mild base a product such as (**293**) undergoes decarboxylation and dehydrogenation to give a 3,4-dihydroisoquinoline ⟨76H(4)1645⟩.

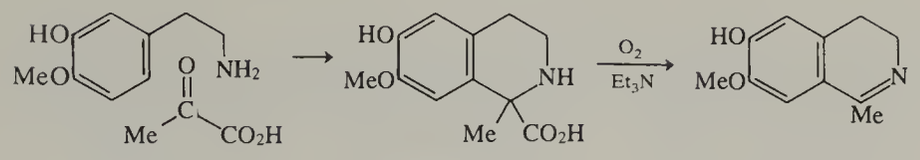


(291)

i, *e.g.* Ar = Ph, boil in EtOH; ii, *e.g.* Ar = 4-$NH_2C_6H_4$, pyridine

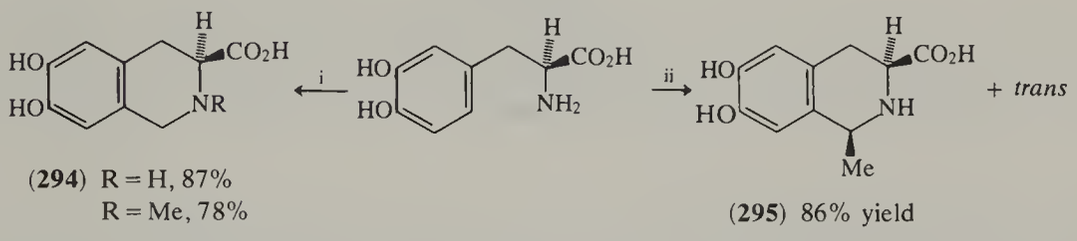


(292) 84%



(**293**)

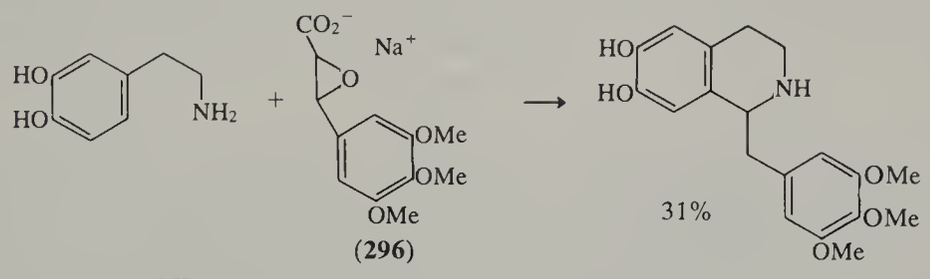
An additional indication of the mildness of the cyclization is provided by the synthesis of the chiral tetrahydroisoquinoline-3-carboxylic acid (**294**) ⟨72HCA15⟩; in the presence of hydrogen and palladium-on-charcoal the *N*-methyl derivative was obtained. Acetaldehyde gave a mixture of diastereoisomers in which the *cis* isomer (**295**) predominated (95:5). Unstable aldehydes can sometimes be generated *in situ*, as when the phenylglycidate (**296**) replaces the much less stable phenylacetaldehyde ⟨66T(S8)129⟩; acetals, enol ethers and chloromethyl methyl ethers have also been used. The mild conditions also allow the isolation of 4-hydroxytetrahydroisoquinolines (**297**) ⟨75H(3)311⟩. A review is available listing syntheses of 4-oxytetrahydroisoquinolines ⟨73AHC(15)99⟩.



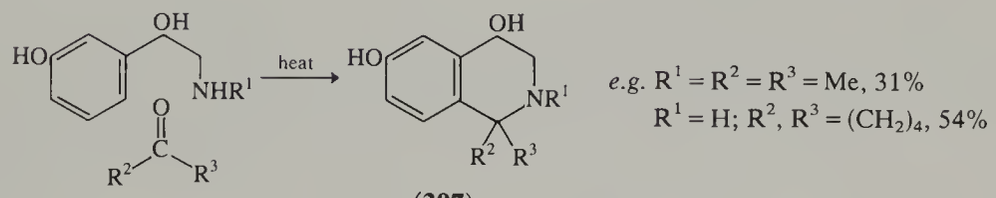
(**294**) R = H, 87%
R = Me, 78%

(**295**) 86% yield

i, CH_2O (with or without H_2/Pd), H^+; ii, MeCHO, H^+

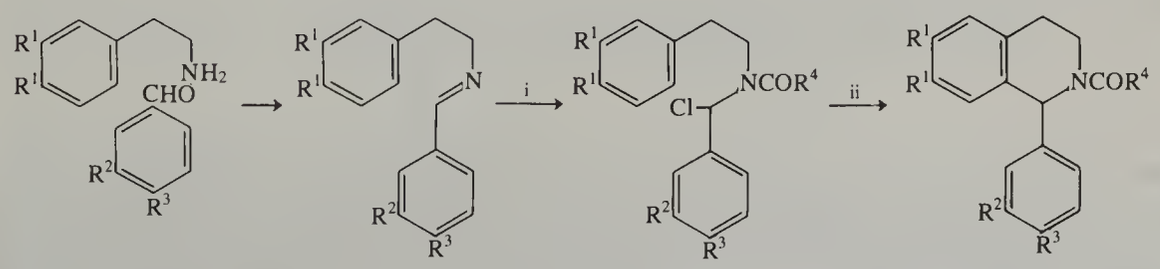


(**296**)



(**297**)

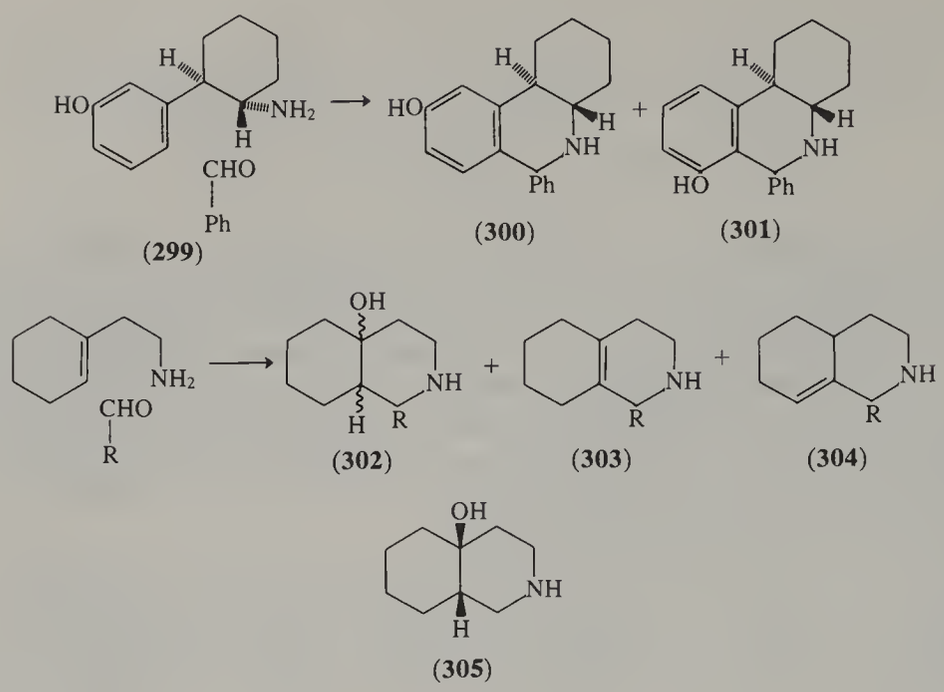
If the Schiff base intermediate is isolated, and treated with an acid chloride, α-chloroamides (**298**) can be obtained, and subsequently cyclized by aluminum chloride ⟨78S62⟩. If the phenylethylamine has an activating methoxyl group (R^1=MeO) the cyclization proceeds without aluminum chloride; the substitution pattern of the aromatic aldehyde has some bearing on the success of the synthesis, electron-donating groups lowering the yield. The octahydrophenanthridines (**300**) and (**301**) are obtained from the phenylcyclohexylamine (**299**) ⟨71JCS(C)1805⟩. This example again illustrates the formation of both regioisomers when a free phenolic hydroxyl group is present. A reaction which bears a superficial similarity to the Pictet–Spengler synthesis is that between 2-(cyclohex-1-en-1-yl)ethylamine and aldehydes or ketones, giving compounds of general structures (**302**)–(**304**) ⟨53LA(581)85⟩. The isolation of the *cis*-decahydroisoquinoline (**305**) when formaldehyde was used makes it unlikely that any free carbonium ion is formed during the cyclization ⟨66HCA2175⟩.



(**298**)

i, R^4COCl; ii, $AlCl_3$ when R^1 = H, no catalyst when R^1 = OMe

R^4 = Me, Ph
R^1 = H, R^2, R^3 = OMe
R^1 = R^2 = H, R^3 = NO_2, *etc.*



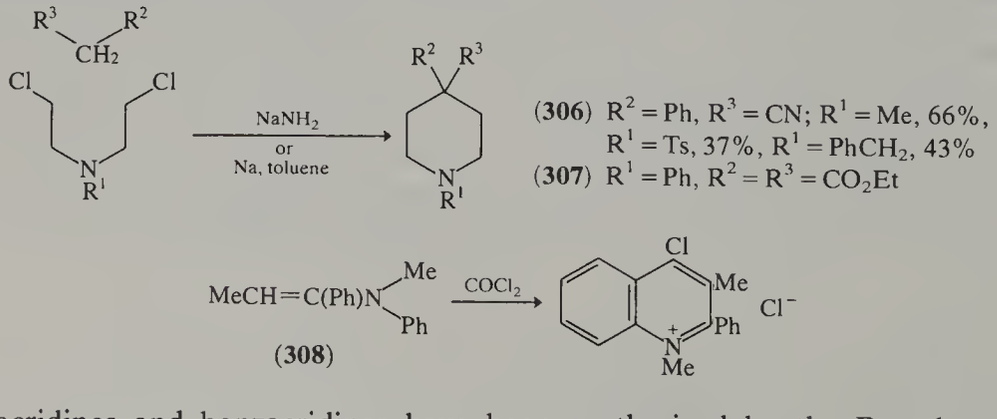
(299) (300) (301)

(302) (303) (304)

(305)

(iii) By insertion of the γ-carbon atom

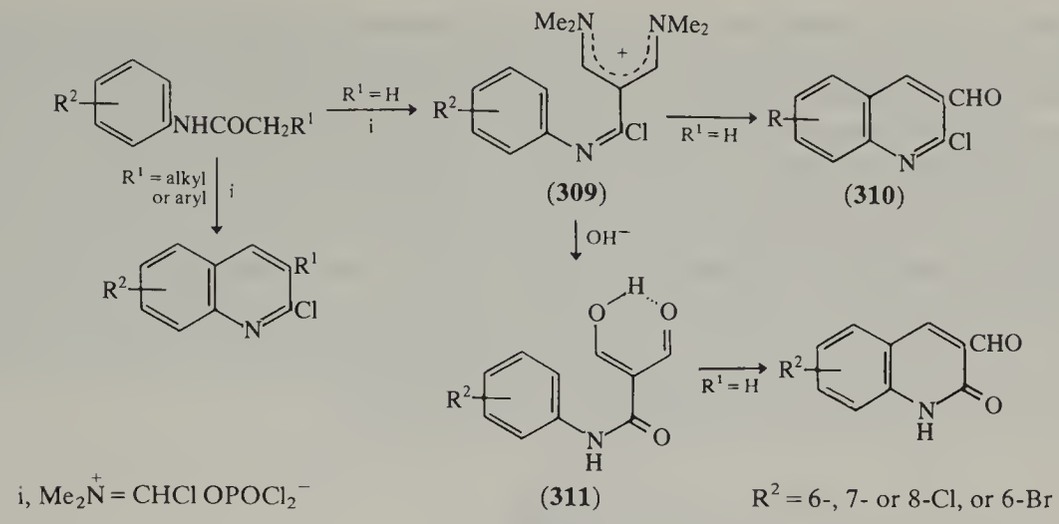
There are few examples of this type of synthesis to form pyridines or piperidines. Bis(2-chloroethyl)amines can react with the anions of active methylene compounds to give 4-substituted piperidines. Thus have been prepared the 4-cyano derivatives (**306**) from phenylacetonitriles ⟨41CB1433⟩ and the bis(ethoxycarbonyl)piperidines (**307**) from diethyl malonate ⟨45JCS917⟩. More common is the synthesis of di- or poly-cyclic systems when the inserting species generates a carbonium ion which can cyclize to an adjacent aromatic ring. The propenylaniline (**308**) reacts with phosgene to give a 4-chloroquinolinium salt ⟨75CB2300⟩. A more general synthesis appears to be by the treatment of *N*-acylanilines with the Vilsmeier–Haack reagent. If the *N*-acetylanilines are used the products are 2-chloroquinoline-3-carbaldehydes (**310**), and it has been established that the intermediates are the diiminium salts (**309**) ⟨81JCS(P1)1520⟩. The yields of quinolines are good (56–70%) for anilines bearing electron-donating groups (with the exception of *o*-methoxyacetanilide), but poor or zero for anilines bearing deactivating substituents. This difficulty can be overcome for mildly deactivated acetanilides (halogen substituents), by hydrolysis of the diiminium salts with base, and cyclization of the malonodialdehydes (**311**) by polyphosphoric acid to give quinol-2-one-3-carbaldehydes in 91–98% yield. The synthesis failed with nitroacetanilides, the iminium salts forming readily but being resistant to cyclization. The synthesis can be extended to the production of 3-alkyl-2-chloroquinolines, by using anilides with longer alkyl substitutents ⟨81JCS(P1)1537⟩; examples are shown in Scheme 2, and yields range from 13% (R^1=CN) to 95% (R^1 = Ph) with many above 70%. The reaction appears to be regiospecific, *meta*-substituted anilides giving 7-substituted quinolines.



(**306**) R^2 = Ph, R^3 = CN; R^1 = Me, 66%, R^1 = Ts, 37%, R^1 = $PhCH_2$, 43%
(**307**) R^1 = Ph, R^2 = R^3 = CO_2Et

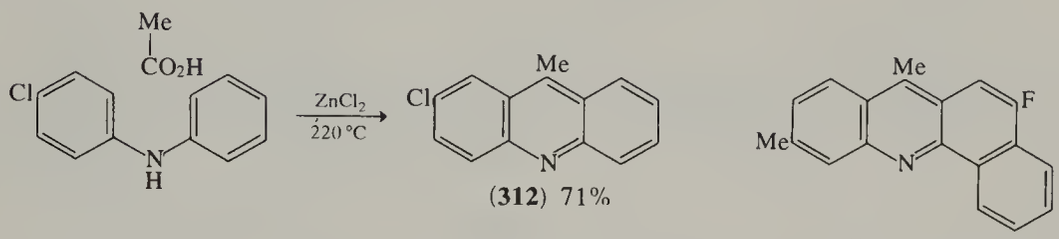
(**308**)

Many acridines and benzacridines have been synthesized by the Bernthsen reaction ⟨1884LA(224)1⟩ in which a diphenylamine is heated with a carboxylic acid and zinc chloride, with or without aluminum chloride. The reaction has been reviewed ⟨73HC(9)141⟩, and will be outlined here. The yields are not generally high; one of the better examples is the synthesis of 2-chloro-9-methylacridine (**312**) ⟨63BCJ1477⟩. In the synthesis of the

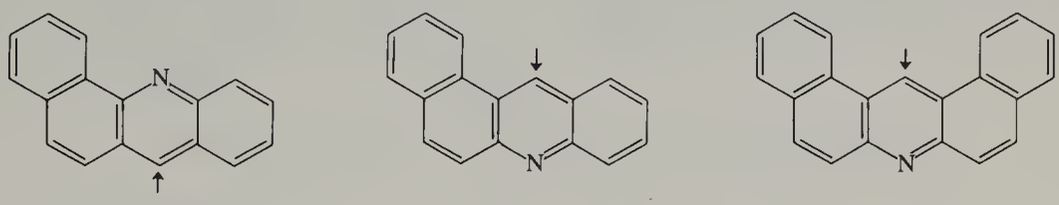


Scheme 2

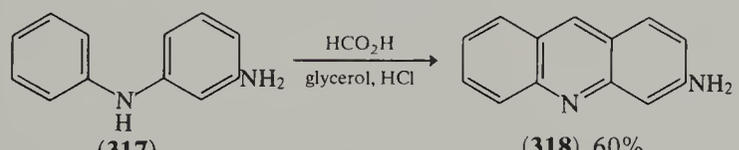
benz[*c*]acridine (**313**), zinc and aluminum chlorides were used, with acetic anhydride in place of the free acid ⟨62JOC527⟩, and polyphosphoric acid has been recommended for some difficult cases (for example *p*-aminobenzoic acid gave 9-(*p*-aminophenyl)acridine in 24% yield) ⟨62JOC2658⟩.



Pivalic acid reacts with phenylnaphthylamines or dinaphthylamines to give low yields of the parent polycycles (**314**)–(**316**), with loss of the *t*-butyl group ⟨66JCS(C)1792⟩. The loss of *t*-butyl groups is not general, and in these cases is thought to be due to some *meso* effect (or steric compression in two cases). Acridines with no substituent at position 9 such as 3-amino-acridine (**318**) can be obtained from diphenylamines, formic acid, hydrochloric acid and glycerol ⟨48JGS1225⟩. Evidence that 2-formyldiphenylamines are intermediate is provided by the cyclization of 2-formyldiphenylamine under the same conditions (acid and glycerol) to give acridine in 95% yield.



All synthesized using Bu^tCO_2H; → indicates position vacated by *t*-butyl group



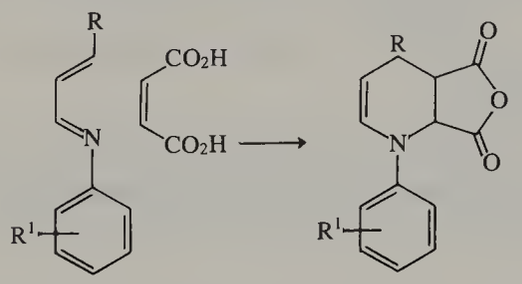
The formation of 4-chloroquinolinium salts from *N*-vinylanilines (**308**) and carbonyl chloride, mentioned earlier, is a reaction related to the Bernthsen synthesis.

2.08.2.2.2 From [4+2] atom fragments

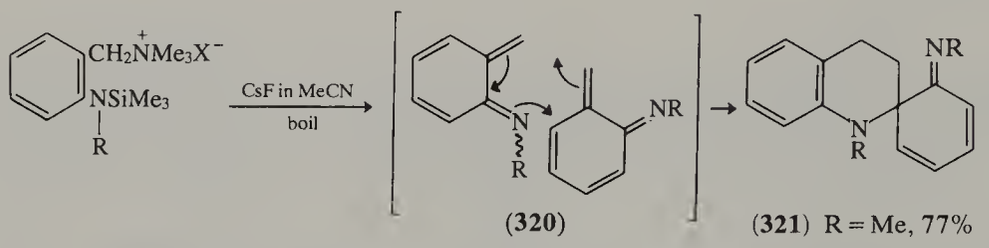
(i) Nitrogen in the 4-atom fragment

(a) Bonding to nitrogen. There are few $[_4\pi_s + _2\pi_s]$ cycloaddition reactions in which the diene component has a terminal nitrogen atom. A series of Schiff bases of unsaturated aldehydes are reported to react with maleic acid to give tetrahydropyridines (**319**)

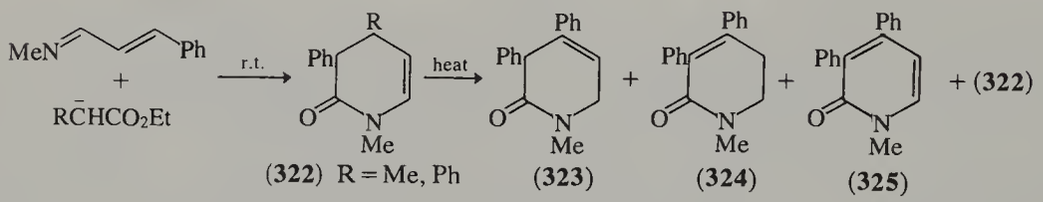
⟨73MIP20800⟩. The formation of the spirocyclohexadienyltetrahydroisoquinoline (**321**) is thought to proceed *via* the $[_8\pi_s + _2\pi_s]$ cycloaddition, although the intermediate (**320**) could not be trapped by added reactive dienophiles ⟨81JA5250⟩; an intramolecular cycloaddition to a suitably placed double bond gives a quinolizine. There is a report that intermediates such as (**320**) may rearrange by a 1,5-H-shift to aldimines ⟨82TL4501⟩. Unsaturated Schiff bases also react with the anions from substituted acetic acid esters to give dihydropyrid-2-ones (**322**) ⟨81TL3769⟩; on heating, compound (**322**; R = Ph) is converted into a mixture containing compounds (**323**)–(**325**). Benzoylacetonitriles are converted by treatment with morpholine or piperidine into 6-amino-3-cyano-2,4-diarylpyridines (**326**), *via* the enamines ⟨74JHC481⟩. A reaction between the β-chloroimino ether hydrochloride (**327**) and Meldrum's acid (2 molar equivalents) gives a piperid-2-one where carbon atoms 2 and 3 are derived from one of the molecules of Meldrum's acid ⟨81TL2255⟩.



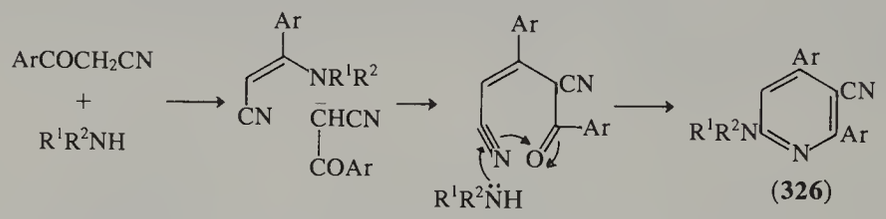
(**319**) R = H, Me, Ph, furyl, thienyl
R^1 = H, alkyl, OH, OEt, $OCH{=}CH_2$



(**320**) (**321**) R = Me, 77%

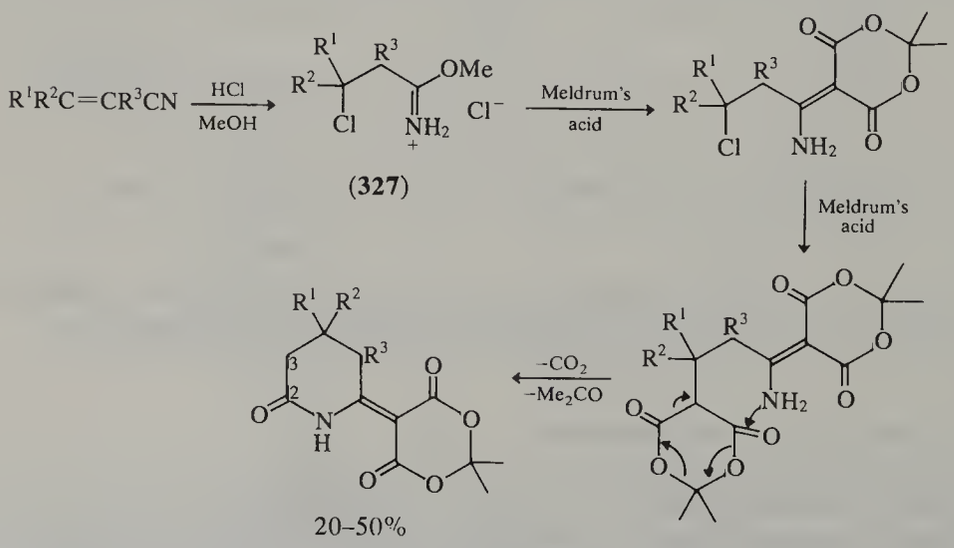


(**322**) R = Me, Ph (**323**) (**324**) (**325**)



(**326**)

R^1R^2NH = morpholine or piperidine; Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4

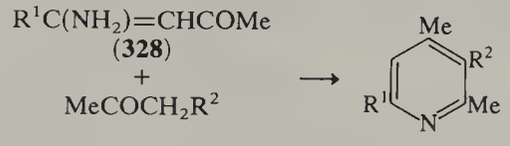


(**327**)

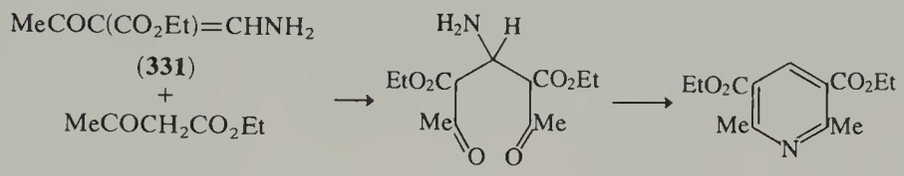
20–50%

Other pyridine-forming reactions of this class bear some resemblance to the Friedländer synthesis and its near relations. The enamino ketones (**328**) condense with 1,3-diketones

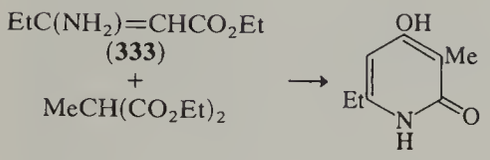
or β-keto esters (the diketones may be formed from the enamines during the reaction) to give 3-acetyl- (**329**) ⟨76TL4831⟩ or 3-ethoxycarbonyl-pyridines (**330**) ⟨51DOK(79)609⟩. There is a report that the very similar enamino ketone (**331**) condenses with ethyl acetoacetate to give the symmetrical pyridine (**332**); it is suggested that the intermediate Michael adduct undergoes loss of ammonia and that the ammonia thus produced causes the cyclization ⟨49CB41⟩. The enamino ester (**333**) condenses more normally to give, after hydrolysis and decarboxylation, a 4-hydroxypyrid-2-one ⟨42HCA1306⟩. The nitrogen atom in pyrid-2-ones can come from an enaminoketone (**334**), as in the condensation with diketene ⟨80MI20800⟩, or from a β-ketoamide, as in the synthesis of 6-hydroxypyrid-2-one (**335**) ⟨44RTC231⟩.

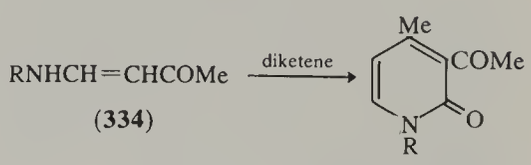


(**329**) R^1 = Me, R^2 = Ac, 90%
(**330**) R^1 = H, R^2 = CO_2Et

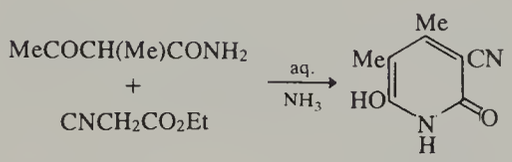


(**332**)



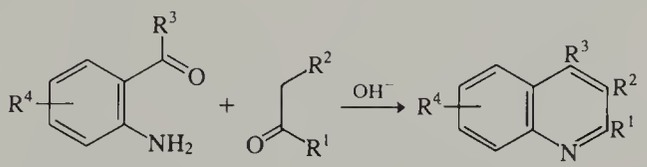


R = H, Me, C_6H_{11}



(**335**) 90%

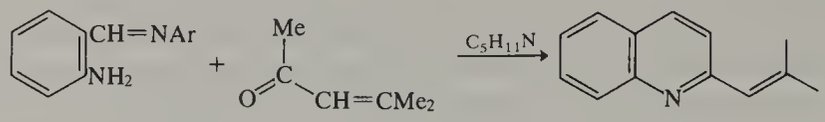
The most important synthesis in this class is that of quinolines, due to Friedländer, with its major modifications by Pfitzinger and by von Niementowski. The Friedländer synthesis has been comprehensively reviewed ⟨77HC(32-1)181, 82OR(28)37, 80T2359⟩, the last two reviews dealing only with the true Friedländer procedure. This is exemplified in equation (52), and the various possible modifications are indicated by the substituents.



(52)

Friedländer and Gohring originally used *o*-aminobenzaldehyde or simple ketones, with a strongly basic medium ⟨1883CB1833⟩. The synthesis is weakest when substituents in the benzenoid ring of the quinoline are required, because the necessary trisubstituted benzenes are difficult to obtain, but balancing this is the unambiguous positioning of the substituent (*cf.* Skraup and Doebner–von Miller syntheses where a *meta*-substituted aniline gives two products). The range of substituents which can be introduced in position 4 of the quinoline is also small (alkyl, aryl, CO_2R), but the major advantage of the synthesis is in the range of 2- or 3-mono- and 2,3-di-substituted quinolines which can be obtained. The *o*-aminobenzaldehydes are unstable and can often be replaced with advantage by the anils. 2-Isobutenylquinoline (**336**) is prepared in this way ⟨11JPR(85)90⟩ and another advantage is that a much milder base, piperidine, can be used. Aldehydes should give 3-substituted quinolines but many cannot tolerate the strongly basic conditions. It has been reported that long-chain aldehydes, such as heptanal, will react with *o*-aminobenzaldehyde without a basic catalyst at 180 °C ⟨22CB3779⟩ to give 3-pentylquinoline (**337**). Arylacetaldehydes give 3-arylquinolines. Ketones must usually be symmetrical, or with potential enolization in

only one direction, or mixtures result. Acetophenones give 2-arylquinolines and the use of mesityl oxide is illustrated below.



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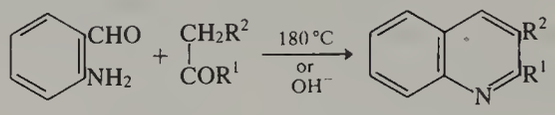
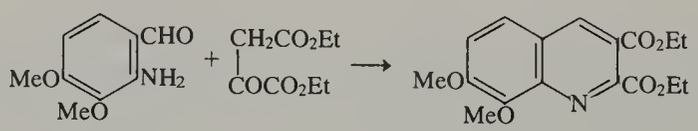
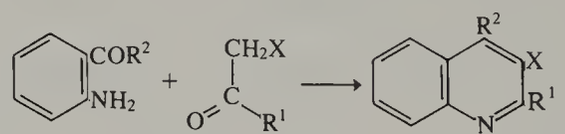


(337) $R^1 = H, R^2 = C_5H_{11}$
(338) $R^1 = CO_2H, R^2 = CH_2Ph$

By using α-keto acids, 3-substituted quinoline-2-carboxylic acids can be obtained. In the example given the product (**338**) can be converted into the acid chloride and cyclized by aluminum chloride to give a benzacridinol ⟨37LA(532)127⟩. Oxaloacetates give quinoline-2,3-dicarboxylates such as compound (**339**) ⟨52CB204⟩, and pyruvic aldoxime with an anil (**340**) gives a quinaldoxime ⟨43LA(554)269⟩. Mixtures are obtained generally from ketones with two enolic forms (see later for acid catalysis), but if the enolization in one direction can be enhanced, as in a β-keto ester, a high yield of one component can be obtained. Examples of this type, dealt with in detail in the review ⟨77HC(32-1)181⟩, are summarized in equation (53). It is worth noting that a β-diketone can be used if one carbonyl group has greater reactivity, as in benzoylacetone. With β-keto esters and β-diketones, hydrolysis can be a major problem, but it is often possible to use weaker bases, such as piperidine. Some substituents of ketones are transformed during the reaction, notably halides. Thus, the bromo ketone (**341**) forms a 3-hydroxy-2-arylquinoline with lactonization by the *ortho*-carboxyl group ⟨51HCA1050⟩. A 3-aminoquinoline can be made by two routes. In the first a phthalimidomethyl ketone gives a 3-phthalimidoquinoline (**342**), which can be hydrolyzed to a 3-amino ketone ⟨45JCS867⟩. In the second route, methazonic acid is used, preferably in a two-stage reaction, to give a 3-nitroquinoline (**343**), easily reduced to the 3-amino compound ⟨50JCS395⟩. A modification of the latter route uses nitroacetaldehyde dithioacetal to give a 3-nitro-2-methylthioquinoline (**344**) ⟨76JPR(318)39⟩ or, if the aniline derivative is used, a 2-anilino-3-nitroquinoline (**345**).

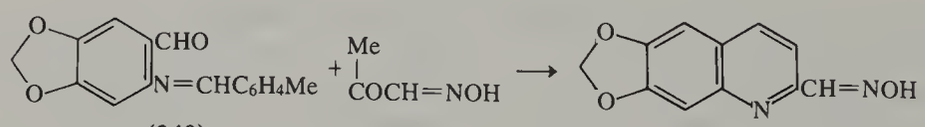


(339) 75%

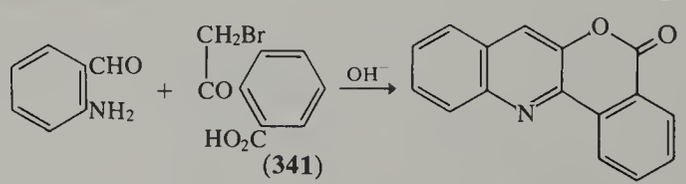


(53)

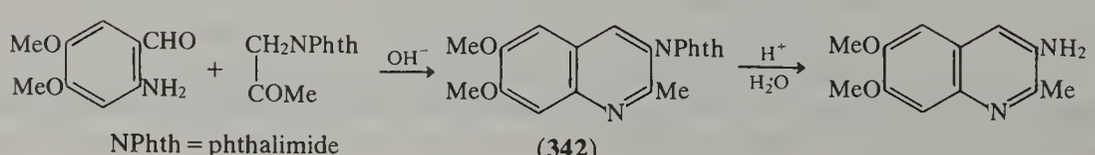
X = CN, CO_2R, COR, CONHR, SO_2R



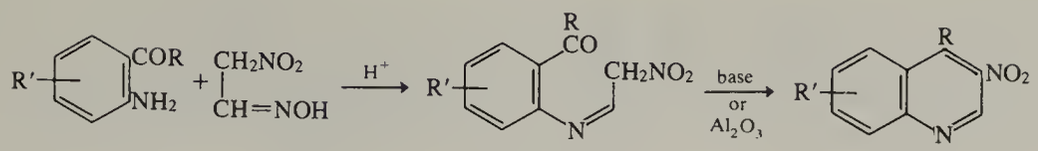
(340) 6,7-$(MeO)_2$, 68%



(341)

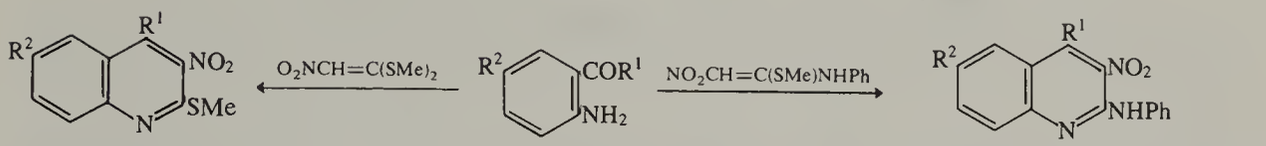


NPhth = phthalimide (342)



(**343**)

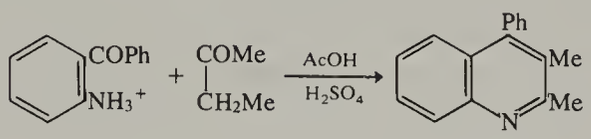
R = Me, Ph, anisyl, 2-pyridyl; R′ = 5-, 6- or 7-NO_2, 5-, 6-, 7- or 8-Cl; yields often 100%



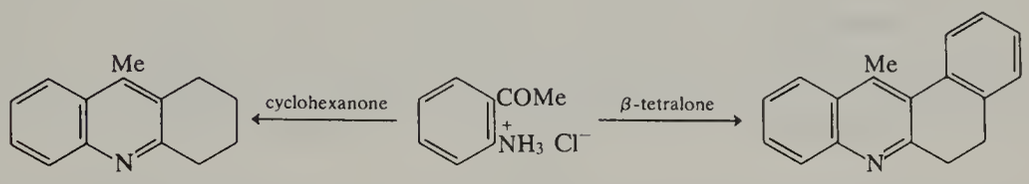
(**344**) 52–76%

(**345**) *e.g.* R^1 = Ph, R^2 = Cl, 46%

The other major modification of the Friedländer synthesis is the use of acid catalysis, first reported by Clemo and Felton ⟨52JCS1658⟩ but much developed by Fehnel and by Kempter. One of the major advantages of the acid-catalyzed procedure is its greater regioselectivity. Methyl ethyl ketone is reported to react with *o*-aminobenzophenone to give a high yield of 2,3-dimethyl-4-phenylquinoline (**346**) ⟨66JOC2899⟩. The acid-catalyzed process also works particularly well with cyclic ketones; with the appropriate ketones, *o*-aminoacetophenone hydrochloride gives the tetrahydroacridine (**347**) ⟨64CB16⟩ and the benz[*b*]acridine (**348**) ⟨64CB316, 65ZC154⟩.



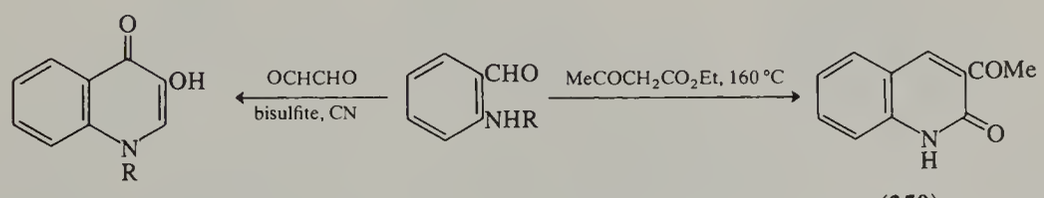
(**346**) 86%



(**347**) 90%

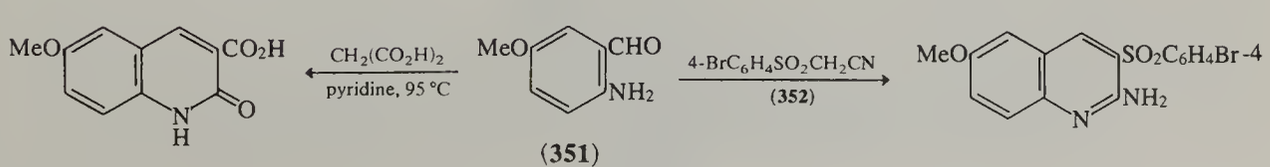
(**348**)

Other modifications to the Friedländer synthesis are the use of a glyoxal bisulfite compound, which with *o*-aminobenzaldehyde gives 3-hydroxyquinol-4-one (**349**) ⟨74AJC537⟩, and the use of malonic ester derivatives, acetoacetates or cyanoacetates. Friedländer and Gohring reported that ethyl acetoacetate could react with *o*-aminobenzaldehyde in two ways. If the two components are heated to 160 °C 3-acetylquinol-2-one (**350**) is formed ⟨1883CB1833⟩. In a similar manner the aminobenzaldehyde (**351**) reacts with malonic acid to give a 3-carboxyquinol-2-one ⟨27JPR(117)97⟩. Here the analogy with the ready cyclization of *o*-nitrobenzylidenemalonic acid on reduction is obvious (Section 2.08.2.1.1). Cyanoacetates react similarly, giving 3-cyanoquinol-2-ones ⟨27JPR(117)97⟩, while substituted acetonitriles such as (**352**) give 2-aminoquinolines. Some phenols can undergo Friedländer condensation; from phloroglucinol, presumably *via* a small amount of keto form, the acridinediol (**353**) is obtained ⟨54MI20802⟩. A more distantly related synthesis is shown by the production of the tetrahydroquinoline (**354**) from methyl vinyl ketone ⟨76JHC131⟩.

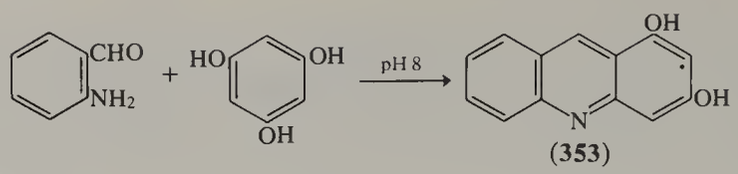


(**349**) R = H, 64%; R = Me, 33%

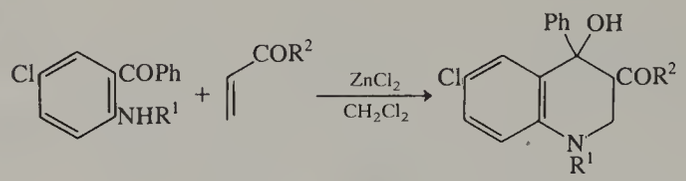
(**350**)



(**351**)

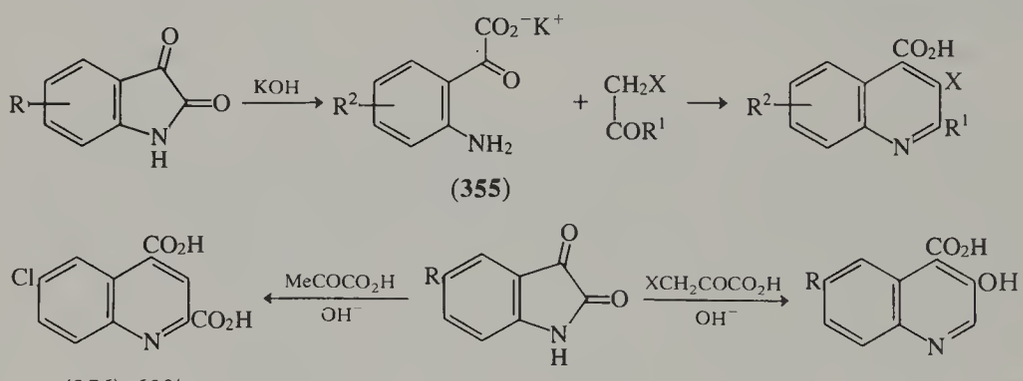


(353)



(354) R^1, R^2 = Me, 74%

The most widely used variant on the Friedländer synthesis is that due to Pfitzinger (equation 54) ⟨1886JPR(33)100⟩. Isatin in potassium hydroxide solution reacts as potassium isatogenate (**355**), and hence gives quinoline-4-carboxylic acids. It is possible to use the isatogenate; the carboxylic acids can be decarboxylated in reasonable yields. The variations in, and the drawbacks to, the Pfitzinger synthesis are largely the same as those of the Friedländer procedure and the reaction has been reviewed ⟨77HC(32-1)197⟩ so that minimal details will be given here. Not too many substituted isatins are available, so that only limited variations in benzene ring substituents are possible, but the position of substitution in the benzenoid ring is unambiguous. Most Pfitzinger reactions have used ketones, because aldehydes undergo self condensation, but aldoximes can be used ⟨02JPR(66)263⟩. Ketones with two enolizable positions give mixtures; if one direction of enolization is favoured (*β*-keto esters, *β*-cyano ketones, *etc.*) a variety of 3-substituted quinoline-4-carboxylic acids can be obtained (equation 54, X = CN, CO_2R). While pyruvic acid gives quinoline-2,4-dicarboxylic acids, as shown for the synthesis of the 6-chloro derivative (**356**) ⟨46JA2962⟩, halopyruvic acids give 3-hydroxyquinoline-4-carboxylic acids (**357**) with loss of the 2-carboxyl group ⟨53JOC552⟩. Oxaloacetates give quinoline-2,3,4-tricarboxylic acids ⟨21CB3090⟩. The instability of *β*-keto aldehydes to alkali makes them unsuitable but their enol ethers or acetals can be used; best yields of the 3-acetylquinoline-4-carboxylic acid (**358**) are obtained in a two-stage condensation ⟨66M135⟩. A number of other variations are summarized in Scheme 3.



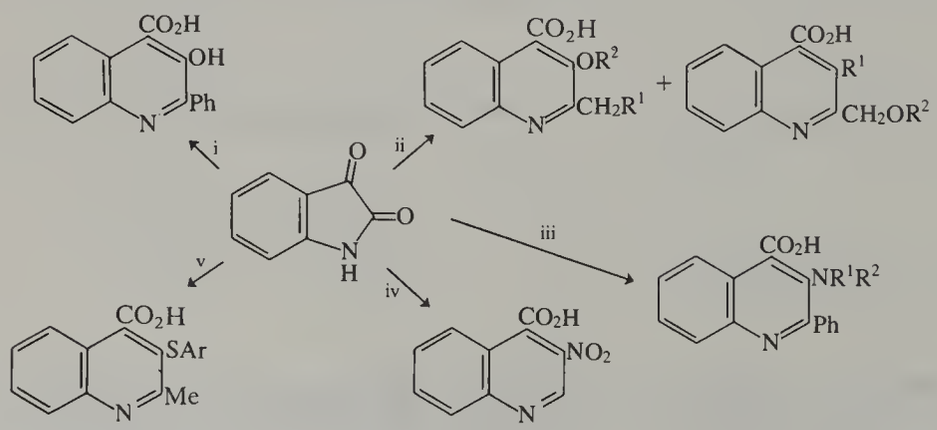
(54)

(355)

(356) 62%

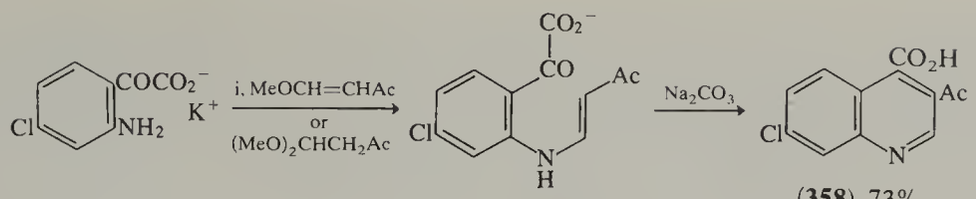
(357)

R	H	Cl	Me	Me
X	Cl	Cl	Cl	Br
%	71	79	24	14



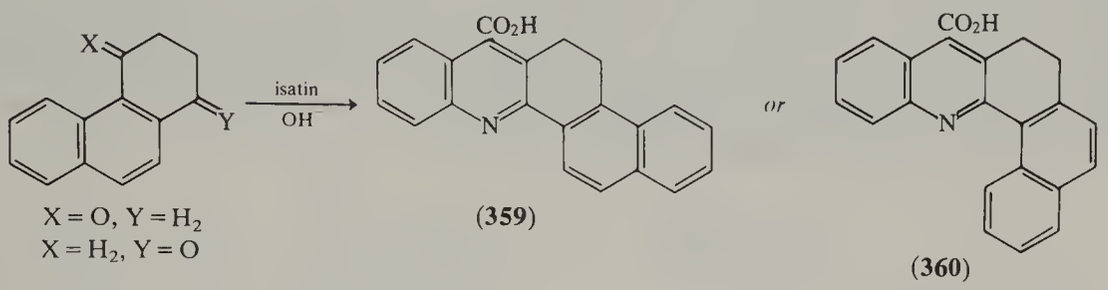
i, XCH_2COPh, X = Cl, Br, OH, OAc; ii, $R^2OCH_2COCH_2R^1$; iii, $PhCOCH_2NR^1R^2$; iv, $O_2NCH_2CH{=}NOH$; v, $ArSCH_2COMe$

Scheme 3



(**358**) 73%

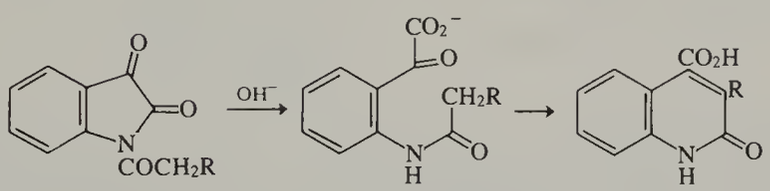
Steric hindrance from the ketonic component can lower the yields of quinolines or in extreme cases prevent the reaction entirely; in this context, a substituent in the 4-position of the isatin can make things worse. The use of the Pfitzinger synthesis to produce polycycles is illustrated by the preparation of the isomeric naphthacridines (**359**) and (**360**) ⟨43CR(216)447⟩. Both were dehydrogenated and decarboxylated to give the fully aromatic compounds. The Camps synthesis (Section 2.08.2.1.3) and the Pfitzinger synthesis are combined when an *N*-acylisatin is treated with base, the ring opens, and an intramolecular cyclization occurs as in equation (55). In reactions comparable with the modified Friedländer synthesis, isatin gives with malonic acid a 4-carboxyquinol-2-one, and with phenylacetic acid it gives the 3-phenyl analogue.



X = O, Y = H_2
X = H_2, Y = O

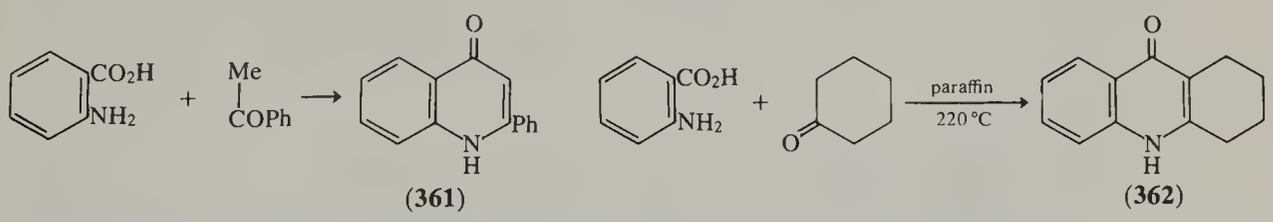
(**359**)

(**360**)



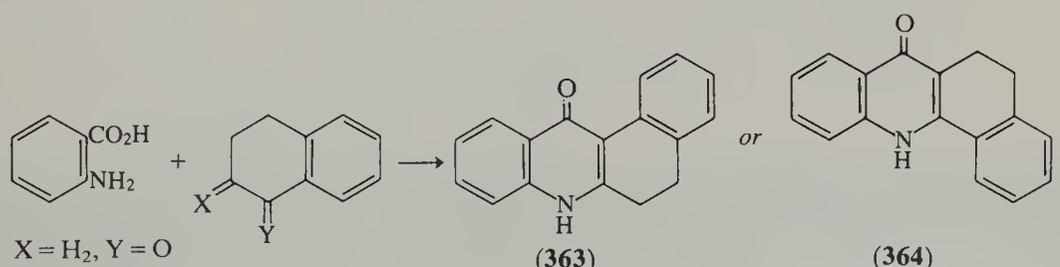
(55)

The second major modification of the Friedländer synthesis is due to von Niementowski ⟨1894CB1394⟩, who reported that poor yields of 2-phenylquinol-4-one (**361**) were obtained on heating anthranilic acid with acetophenone. As examples of the original procedure, cyclohexanone and the two tetralones give respectively the tetrahydroacridone (**362**) ⟨09CB621⟩, and the dihydrobenzacridones (**363**) ⟨69JHC361⟩ and (**364**) ⟨63ZOB3961⟩, while 3-amino-2-naphthoic acid and cyclohexanone give the tetrahydrobenzo[*b*]acridanone (**365**) ⟨48JCS1284⟩. A more unusual example uses the cyclopropanephosphonium salt (**366**) to produce a quinol-2-one instead of the usual quinol-4-one ⟨75TL4353⟩.



(**361**)

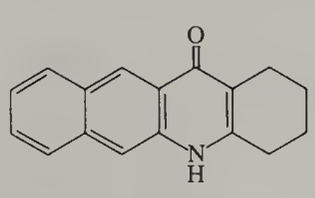
(**362**)



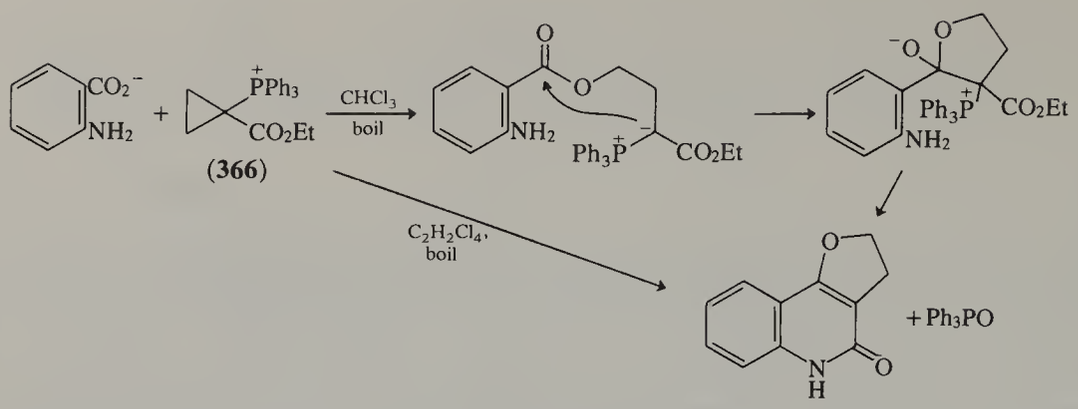
X = H_2, Y = O
X = O, Y = H_2

(**363**)

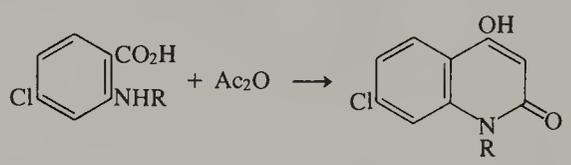
(**364**)



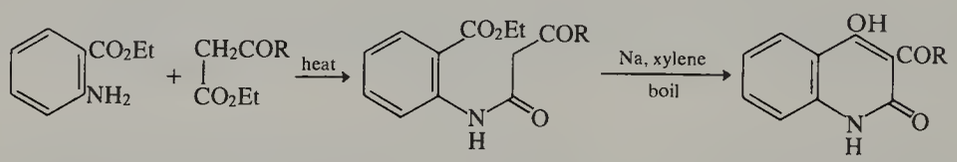
(**365**)



Among the variations of the von Niementowski synthesis are the use of acetic anhydride and an anthranilic acid to give a 4-hydroxyquinol-2-one (**367**) ⟨46JA1810⟩, the use of diketene with an anthranilic ester to give 4-hydroxyquinolone itself in 89% yield ⟨70GEP1924362⟩, and condensation of anthranilates with esters to give *N*-acylanthranilates which are cyclized under Dieckmann conditions to give 3-acyl-4-hydroxyquinol-2-ones (**368**) ⟨51YZ1100⟩. Improvements in yield are claimed when enol ethers or ketals are used with anthranilates, as in the synthesis of 2-arylquinol-4-ones (**369**) ⟨46JA1270⟩. Finally, the use of methazonic acid to produce 3-nitroquinol-4-ones is exemplified by the synthesis of the quinolone (**370**) ⟨47JA365⟩ and of the benzoquinolone (**371**) ⟨48JCS1284⟩.

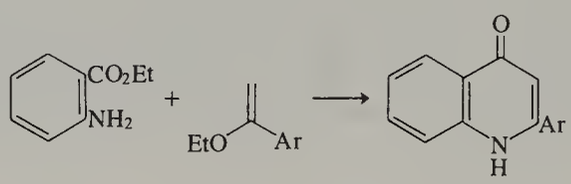


(**367**) R = Me, 43%

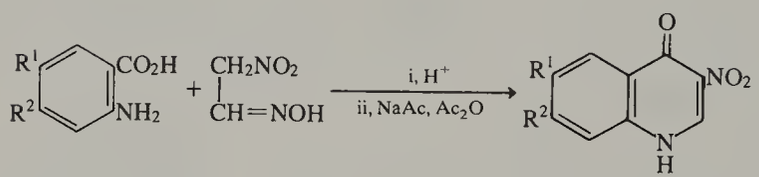


(**368**)

R	Me	Et	Me_2CHCH_2	Ph
%	30	59	14	26

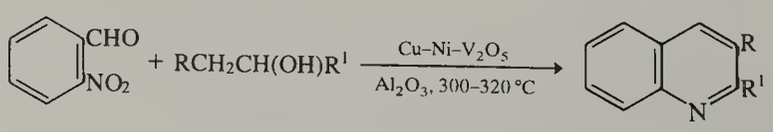


(**369**) Ar = 4-ClC_6H_4, 74%



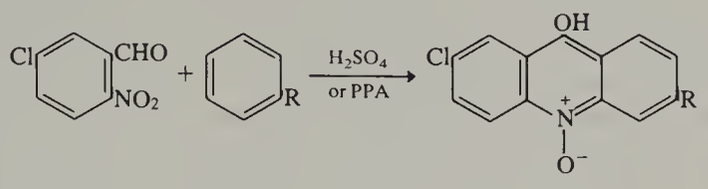
(**370**) $R^1 = R^2 = H$, 43–45%
(**371**) R^1, R^2 = CH=CHCH=CH, 50%

A reaction which formally resembles a Friedländer synthesis is that between *o*-aminobenzaldehyde and iodobenzene, the resulting 2-formyldiphenylamine being cyclized by acid to give acridine ⟨17CB1306⟩. Quinolines (**372**) can be synthesized by passing mixtures of *o*-nitrobenzaldehyde and alcohols over a Cu–Ni–V_2O_5 catalyst at 300–320 °C ⟨76MI20801⟩.

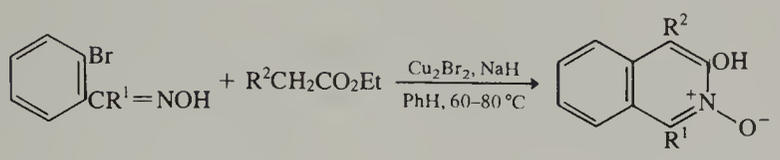


(**372**) 27–38%; R, R^1 = H; R = Me, R^1 = H; R = H, R^1 = Me

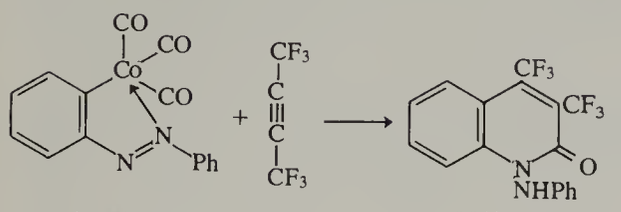
The reaction of *o*-nitrobenzaldehydes with some benzene derivatives in the presence of strong acid (H_2SO_4, PPA) is a classical synthesis of acridinol *N*-oxides (**373**) ⟨37BSF240⟩. The synthesis works for benzyl alcohol, benzene, toluene and halobenzenes, but not for benzoic acid, benzonitrile, dimethylaniline, or nitrobenzene. Isoquinoline *N*-oxides (**374**) have been obtained from *o*-bromobenzaldoxime or the acetophenone derivative, and active methylene compounds with copper(I) bromide and sodium hydride ⟨77S760⟩. The azobenzene cobalt tricarbonyl (**375**) reacts with hexafluorobut-2-yne to give a quinol-2-one ⟨72CC1228⟩, and the 3,4,5-tricyanopyridine (**376**) is formed when tetracyanoethylene reacts with an enaminonitrile ⟨80S471⟩.



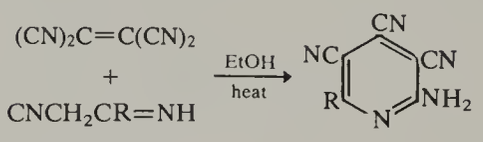
(**373**)



(**374**) R^1 = H, Me; R^2 = Ac, Bz, CN, CO_2Et

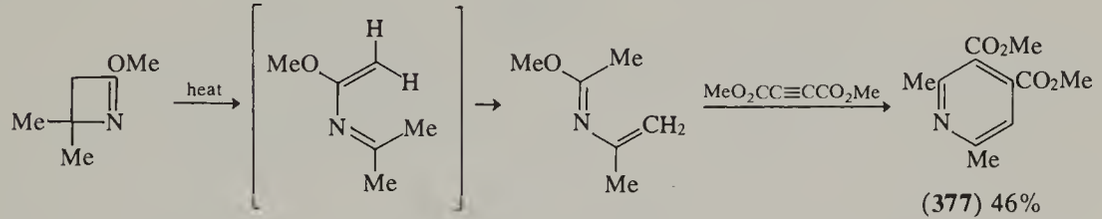


(**375**) 30%

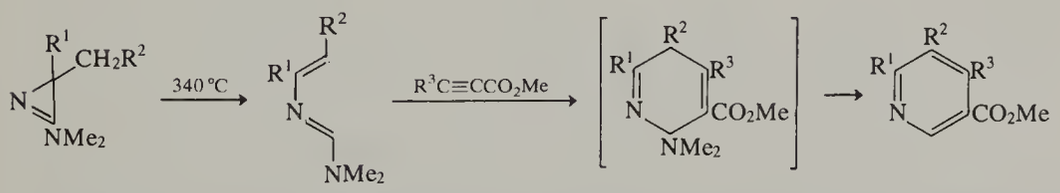


(**376**) R = Me, Ph, 4-ClC_6H_4

(*b*) *Bonding α to nitrogen.* There are few examples of pyridine synthesis by a thermal $[_4\pi_s + _2\pi_s]$ cycloaddition using azadienes. The examples shown use a 4-methoxy-2-azabutadiene to give the pyridine diester (**377**) ⟨75JOC1349⟩, and two different dimethylamino-2-azabutadienes (**378**) and (**379**) to give a diester ⟨75JA4409⟩ and a triester ⟨81AG(E)296⟩ respectively. If 1,4-naphthoquinone is used as the dienophile with diene (**378**), a benzo[*g*]isoquinolinequinone (**380**) is obtained; conversely the diene (**381**) reacts with methyl propiolate to give a 5,6,7,8-tetrahydroquinoline ⟨75JA4409⟩.

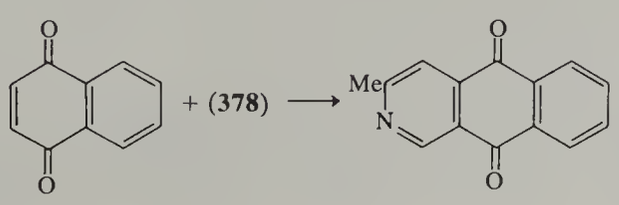


(**377**) 46%

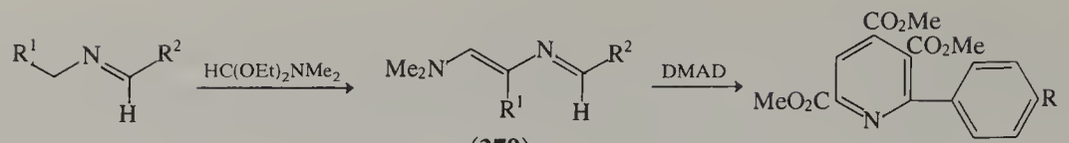


(**378**) R^1 = Me, R^2 = H
(**381**) R^1, R^2 = $CH_2CH_2CH_2CH_2$

R^1 = Me, R^2 = H, R^3 = CO_2Me, 58%
R^3 = H, R^1, R^2 = $CH_2CH_2CH_2CH_2$, 30%



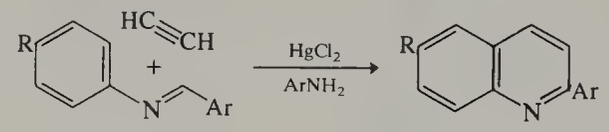
(**380**)



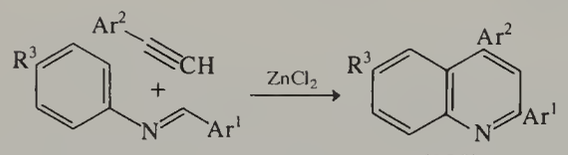
(379)

R	H	Cl	Me
%	41	38	15

A number of syntheses of quinolines are based on reaction between anils and alkynes, or anils and substituted alkenes. Although formally $[4\pi+2\pi]$ reactions, most are initiated by salts or by Lewis acids, and are presumably electrophilic substitutions on the benzene ring during the cyclization step. Kozlov and his coworkers have exhaustively examined the reaction between Schiff bases and acetylene, using a wide range of metal salts as catalysts. One example is given in equation (56) ⟨63ZOB1079⟩; many others are mentioned in a review ⟨77HC(32-1)132⟩. It should be noted that amine exchange can occur, a simple anil reacting in the presence of *p*-anisidine to give a 6-methoxyquinoline. Yields vary from 27 to 76%. Arylalkynes condense with Schiff bases when treated with zinc chloride to give 2,4-diarylquinolines (**382**) ⟨79NKK1514⟩; the same reaction converts the benzaldehyde anil of 1-naphthylamine into 2,4-diphenylbenzo[*h*]quinoline (**383**). The chloroimines (**384**) and phenylacetylene, with tin(IV) chloride, can also give good yields of 2-aryl-4-phenylquinolines ⟨64AG991⟩. The only reaction of this type which is truly a $[_4\pi_s+_2\pi_s]$ cycloaddition is that between benzyne and the anil of benzaldehyde; the product (**385**), obtained in poor yield, results from cyclization followed by substitution by a second molecule of benzyne ⟨75BCJ1063⟩.

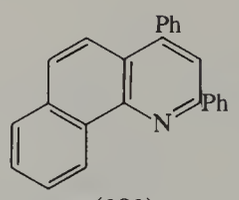


(56)

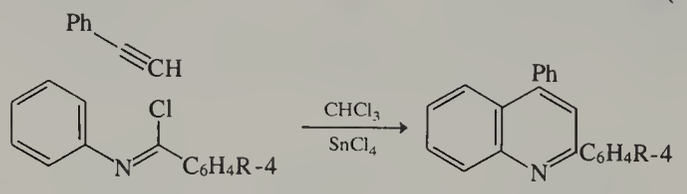


$Ar^1 = 4\text{-}R^1C_6H_4$; $Ar^2 = 4\text{-}R^2C_6H_4$

(382)

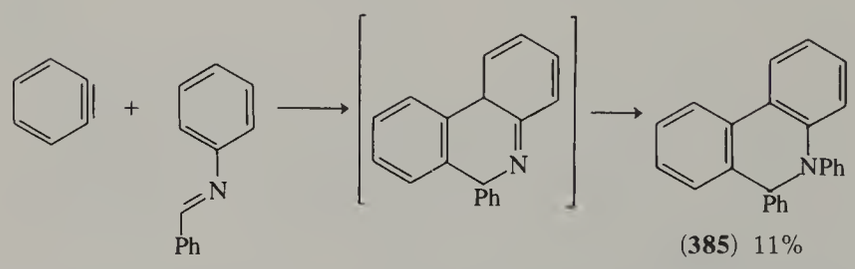


(383)



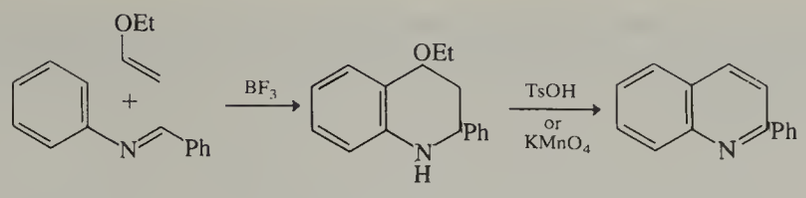
(384)

R	H	Me	Cl	NO_2
%	56	68	69	70

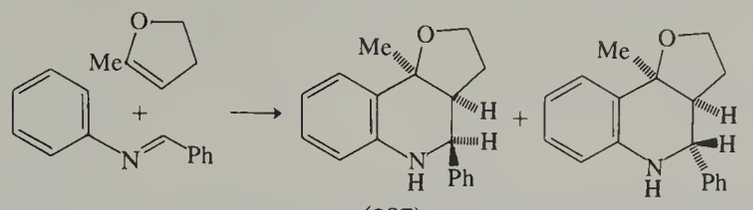


(385) 11%

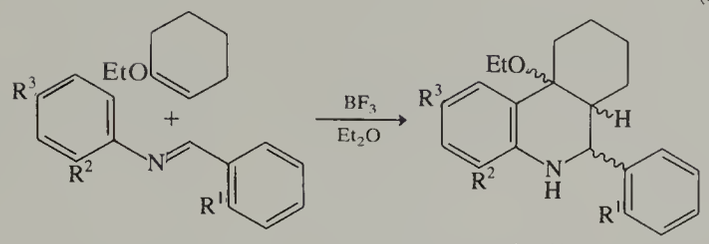
Most of the cyclization reactions between anils and alkenes use enol ethers to give, as intermediates or final products, 4-alkoxytetrahydroquinolines. In one version of the synthesis the reaction is catalyzed by boron trifluoride or aluminum tribromide. A simple example shows the synthesis of 2-phenylquinoline *via* the intermediate tetrahydroquinoline (**386**) ⟨65IZV2163⟩; the yield of 50% would appear to be the highest attainable in the aromatization step. The addition of cyclic ethers such as dihydrofurans has been shown to be stereospecific as well as regiospecific; in the example shown the products (**387**) and (**388**) are both *cis* fused, and it was suggested that this may indicate an electrocyclic mechanism ⟨69JHC597⟩. A cyclohexene gives octahydrophenanthridines (**389**) ⟨66IZV337⟩ which can be oxidized to 1,2,3,4-tetrahydrophenanthridines.



(**386**) 63% 50%



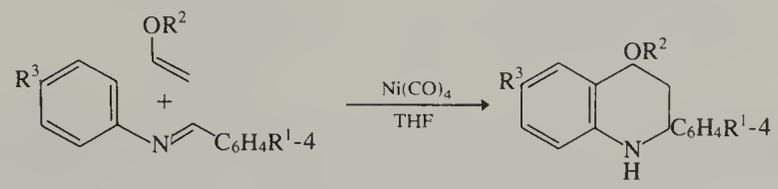
(**387**) (**388**) 73% total



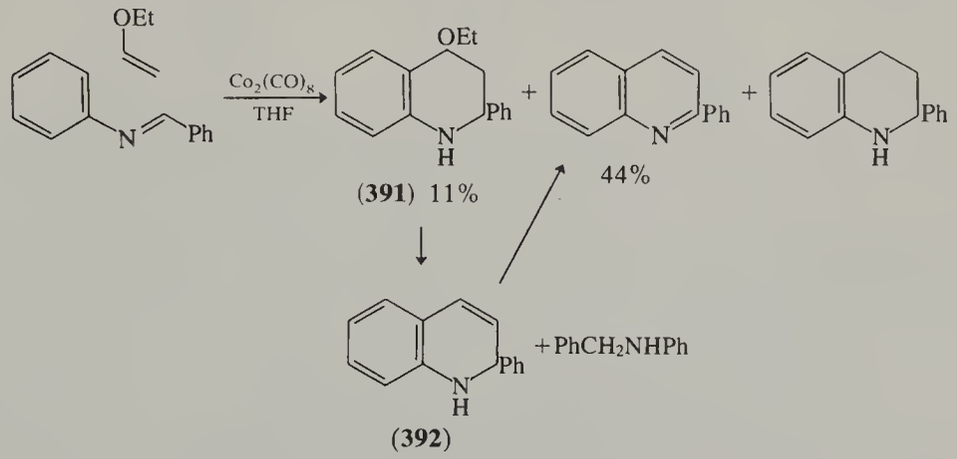
R^1	H	OH	H	H
R^2	H	H	H	H
R^3	H	H	Br	CO_2H
%	57	53	63	28

(**389**)

The second major mode of reaction between enol ethers and anils uses transition metal carbonyls. The yields can be excellent, as shown in the reaction using nickel tetracarbonyl to give the tetrahydroquinoline (**390**) ⟨72JAP720067⟩. The reaction using dicobalt octacarbonyl has been thoroughly examined. The products were the tetrahydroethoxyquinoline (**391**), 2-phenylquinoline, shown to be formed from the tetrahydro derivative, probably *via* the dihydroquinoline (**392**), 1,2,3,4-tetrahydroquinoline, and *N*-phenylbenzylamine ⟨67TL4199⟩.



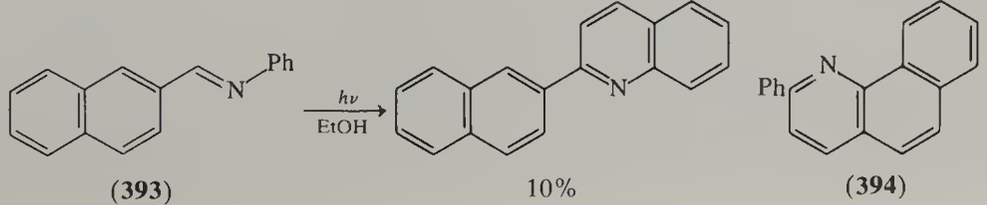
(**390**) *e.g.* $R^1 = H$, $R^2 = Me$, $R^3 = OMe$, 87%



(**391**) 11% 44%

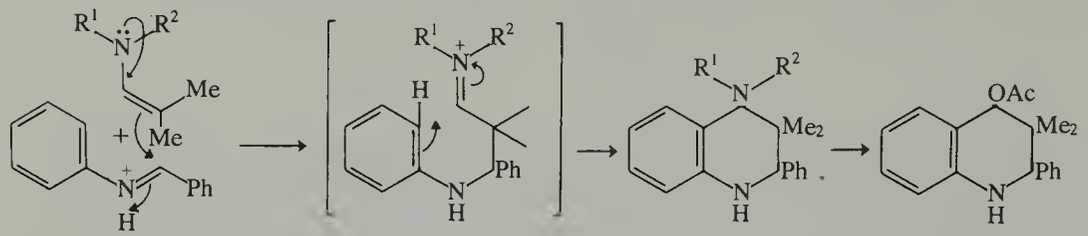
(**392**)

A reaction which could involve the vinyl alcohol tautomer of acetaldehyde is the synthesis of 2-(2-naphthyl)quinoline by photolysis of the anil (**393**) in ethanol ⟨68TL3685⟩. From the benzaldehyde anil of α-naphthylamine by a similar reaction, 2-phenylbenzo[*h*]quinoline



(**393**) 10% (**394**)

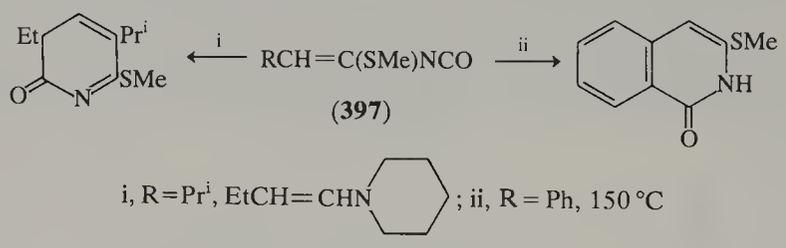
(**394**) is obtained. An enamine (**395**) reacts with Schiff bases in glacial acetic acid to give 4-morpholino-1,2,3,4-tetrahydroquinolines, which were converted into the 4-acetoxy derivatives (**396**) ⟨78CL267⟩.



(**395**)

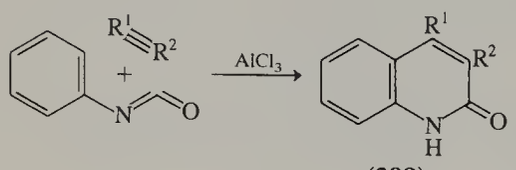
(**396**) 81%; also 4-Cl, NO_2, MeO

Unsaturated isocyanates can react with activated double or single bonds to produce pyridones, quinolones, or phenanthridinones. The thiomethyl isocyanates (**397**) react with an enamine to give a product assigned the 3*H*-pyridin-2-one structure when R is an isopropyl group; when heated to 150 °C they give an isoquinolin-1-one if R is a phenyl group ⟨78JOC402⟩. A range of substituted alkynes react with phenylisocyanate and aluminum chloride to give 3,4-disubstituted quinol-2-ones (**398**) ⟨74BSF1949⟩; ynamines react without a catalyst, giving 4-dimethylaminoquinol-2-ones (**399**) ⟨69HCA2641⟩. Benzyne undergoes a cycloaddition with phenyl isocyanate to give phenanthridinone (**400**) ⟨65JOC3247⟩. The bis(trifluoromethyl)ketenimine (**401**) and ethoxyacetylene give a 4-ethoxyquinoline, while vinyl ethers react with loss of alcohol to give 2-(hexafluoropropan-2-yl)quinoline ⟨76IZV858⟩. The phosphorane (**402**) reacts with *p*-nitrophenylisocyanate to give a quinol-2-one, possibly *via* a zwitterionic intermediate ⟨75ZN(B)766⟩.



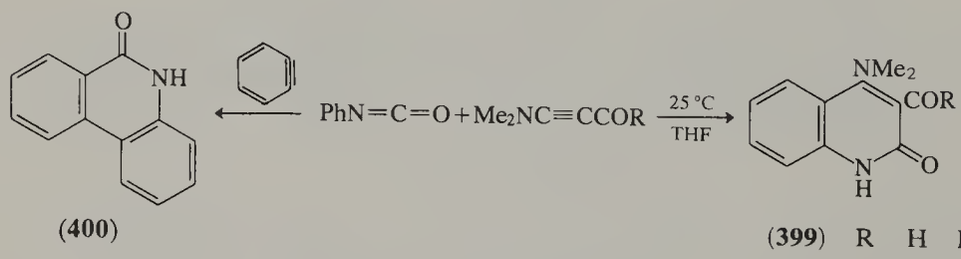
(**397**)

i, R=Pr^i, EtCH=CHN⟨cyclohexyl⟩; ii, R = Ph, 150 °C



(**398**)

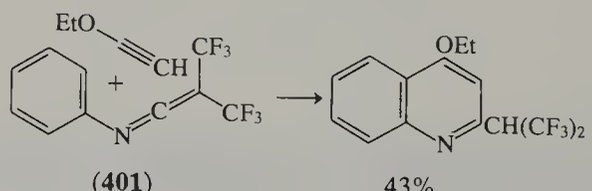
R^1	Ph	Ph	Et	Bu^n	$SiMe_3$	H
R^2	H	$SiMe_3$	Et	$SiMe_3$	$SiMe_3$	$SiMe_3$
%	43	44	—	50	57	25



(**400**)

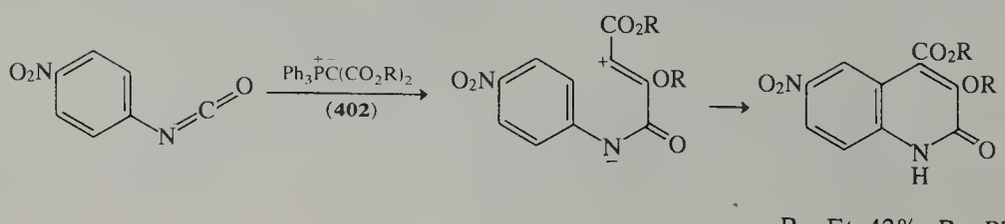
(**399**)

R	H	Me	OMe	
%	75	70	58	



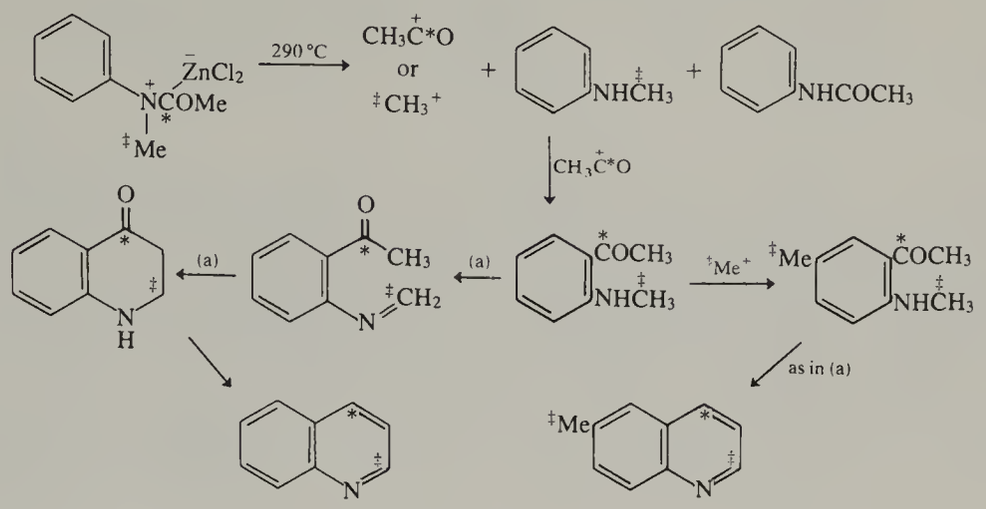
(**401**)

43%



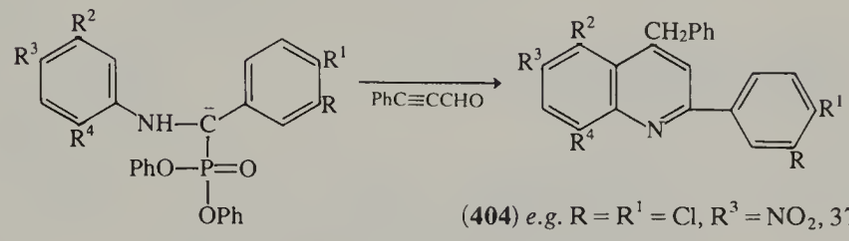
R = Et, 42%; R = Ph, 55%

To close this section there are three reactions which fit in none of the previous categories. It has recently been shown by ^{13}C labelling studies that the production of quinoline and 6-methylquinoline by heating *N*-acetyl-*N*-methylaniline with zinc chloride goes by the complex mechanism shown in Scheme 4 ⟨80CJC1806⟩; the yields are very small. The phosphoranes (**403**) react with phenylpropargaldehyde to give 2-aryl-4-benzylquinolines (**404**) ⟨78JHC1237⟩, and diphenylcarbodiimide with a substituted acetaldehyde gives a mixture of mono- and di-anilinoquinolines, possibly *via* the azete (**405**) ⟨74JOC3516⟩.



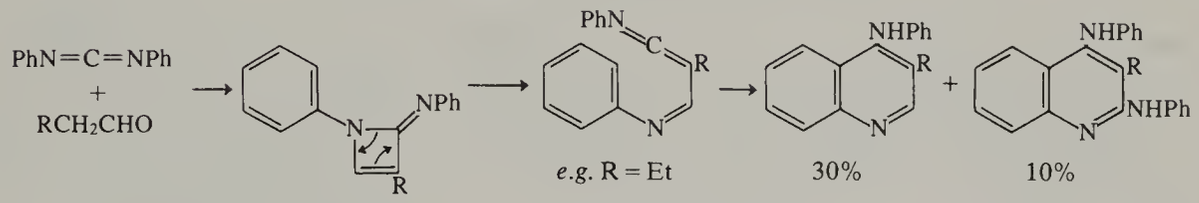
* Label (1), ‡ label (2)

Scheme 4



(**403**)

(**404**) *e.g.* R = R¹ = Cl, R³ = NO₂, 37%



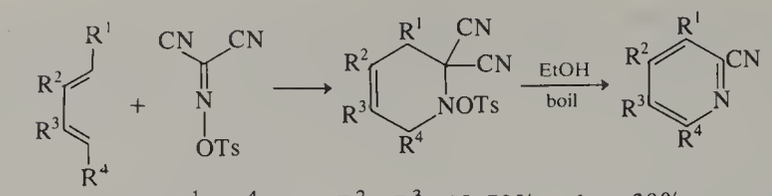
(**405**)

e.g. R = Et 30% 10%

(ii) Nitrogen in the 2-atom fragment

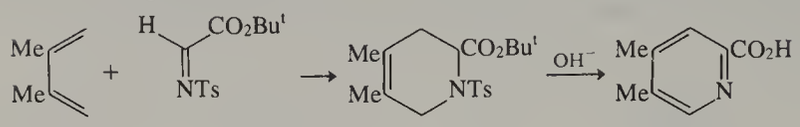
The sub-division in this section is based on reaction type.

(a) Electrocyclic reactions. Cycloaddition reactions take place between 1,3-dienes and carbon to nitrogen double or triple bonds. In the examples shown in equations (57) to (60) the C=N group carries electron-withdrawing groups and the dienes are conventional. All give tetrahydropyridines; in equation (57) ⟨78BSF(2)147⟩ and in equation (58) ⟨65CB1431⟩ the tetrahydropyridines are shown to be easily converted into the pyridine. In equation (57), equation (59) ⟨72LA(106)762⟩ and equation (60) ⟨72T791⟩, the cycloaddition is regioselective, but not always consistent. The orientation of addition has been discussed ⟨72LA(762)106, 78BSF(2)147⟩; when the trichloromethylimine (**406**) is used with vinyldihydronaphthalene to prepare an azasteroid intermediate (**407**) the addition occurs in a sense opposite to that expected from the study on simpler dienes as shown in equation (60) ⟨72TL1425⟩. The imines often carry groups which by subsequent elimination can contribute to the final unsaturation. In a similar manner the chloroimines (**408**), obtained from amides by treatment with phosphoryl chloride, can lose hydrogen chloride after cycloaddition to give 1,2-dihydropyridines ⟨58BSF1331⟩. From a styrene the chloroimine gives a 3,4-dihydroquinoline (**409**). Benzocyclobutene (**410**), on heating, gives an *o*-quinodimethane which reacts with an added Schiff base to give an isoquinoline as a single isomer, indicating regioselectivity ⟨74T1047⟩.

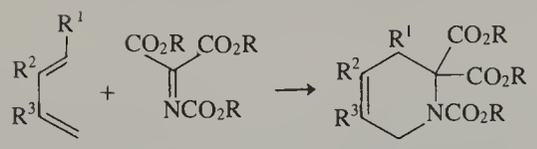


(57)

e.g. $R^1 = R^4 = Me$, $R^2 = R^3 = H$, 70%; others 30%

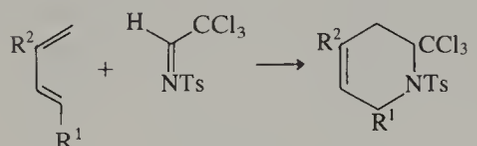


(58)



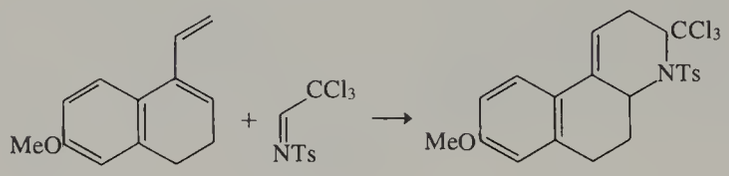
$R = Et$, $R^1 = H$, $R^2 = R^3 = Me$, 57%
$R = Et$, $R^1 = Ph$, $R^2 = R^3 = H$, 66%

(59)



R^1	Me	Ph	H	H	H
R^2	H	H	Me	Ph	H
%	70	72	82	86	90

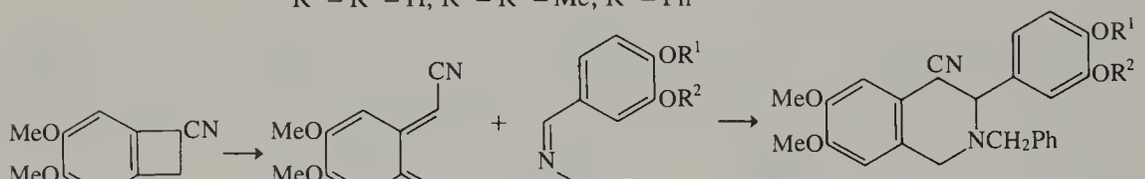
(60)



(406) (407)

(408) (409)

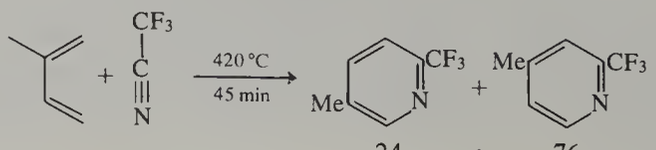
$R^1 = R^4 = R^5 = H$, $R^2 = R^3 = Me$
$R^2 = R^3 = R^5 = Me$, $R^1 = R^4 = H$
$R^1 = R^4 = H$, $R^2 = R^3 = Me$, $R^5 = Ph$



(410)

$R^1 = R^2 = Me$, 41%
$R^1, R^2 = CH_2$, 25%

The reaction between dienes and nitriles has been studied in detail. A review is available ⟨67MI20800⟩ on the cycloaddition reaction using cyanogen, closely related nitriles with strongly electron-withdrawing groups, and some simple nitriles. The tables included in the review indicate that the conversions are only good for nitriles carrying electron-withdrawing groups; the reaction requires high temperatures, and for simple nitriles some catalyst. In the example given in equation (61) ⟨64JOC569⟩ it can be seen that unsymmetrical dienes give mixtures of pyridines. When one pyridine predominates it is that in which a positive charge can be visualized as developing on a tertiary carbon during a stepwise addition. It should be noted that pyridines, not dihydropyridines, are obtained. Acrylonitrile and butadiene give a mixture of 2-vinylpyridine and of cyanocyclohexene ⟨55JA3143⟩. A related reaction is that in which octa-1,7-diyne reacts with nitriles in a $[\pi_2 + \pi_2 + \pi_2]$cycloaddition (catalyzed by a cobalt carbonyl) to give 5,6,7,8-tetrahydroisoquinolines (**411**) ⟨77AG(E)708⟩. The tetraphenylbutadiene cobalt complex (**412**) reacts with nitriles to give pyridines, and with methyl isocyanate to give a pyrid-2-one ⟨73CC280⟩; other unsymmetrical diene–cobalt complexes show regioselectivity in reaction.



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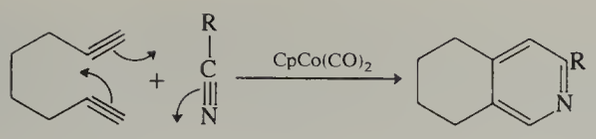
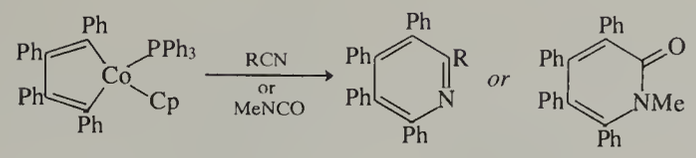
(61)



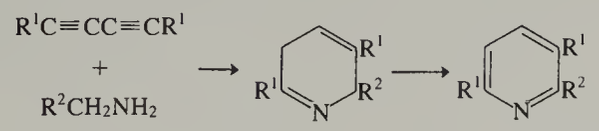
(411)	R	Ph	Bu^n	Me	CH_2OMe	CO_2Et	CH_2CO_2Et
	%	70	77	81	62	5.9	47



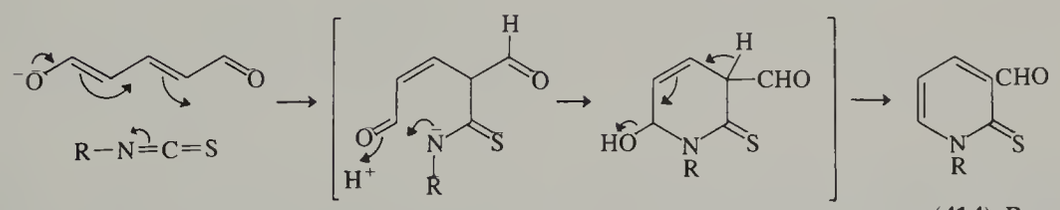
	R	Me	Ph	$CH{=}CH_2$
	%	33	30	72

(412)

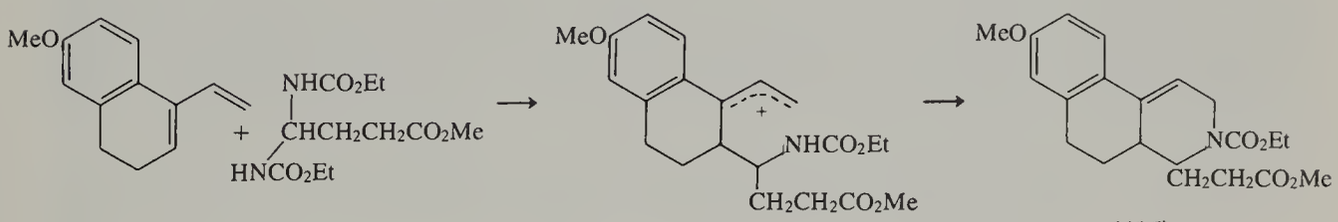
(*b*) *Other diene or diyne reactions.* Primary amines of the type RCH_2NH_2 react on heating with 1,3-diynes to give trisubstituted pyridines (**413**) in 50–70% yield ⟨74T1387⟩; the *N*-oxides can be obtained if air or oxygen is present. Glutaconic dialdehyde anion reacts with isothiocyanates (but not with thiocyanic acid) in what seems to be a two stage reaction to give 2-thioxopyridine-3-carbaldehydes (**414**) ⟨76ACS(B)863⟩. Isobutene is lost from the *N*-*t*-butylpyridinethione (**414**; R=Bu^t) on pyrolysis to give the *N*-unsubstituted thione. A similar addition reaction is observed with isoselenocyanates ⟨77ACS(B)843⟩. A hexahydrobenzo[*f*]isoquinoline (**416**) is obtained when the diene (**415**) is treated with a Lewis acid and a dicarbamate ⟨70TL383⟩.



(**413**) R^1 = Me, $PhOCH_2$, Ph, 3-MeC_6H_4
R^2 = $PhCH_2$, Ph, 4-MeC_6H_4, C_6H_{11}, n-C_8H_{17}

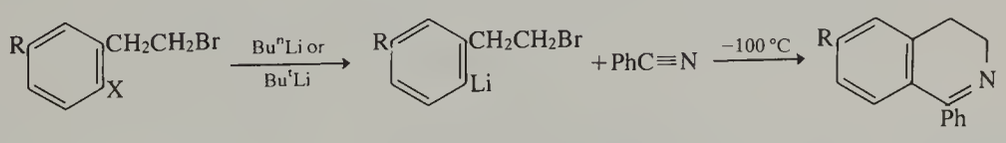


(**414**) R = aryl, 45–97%

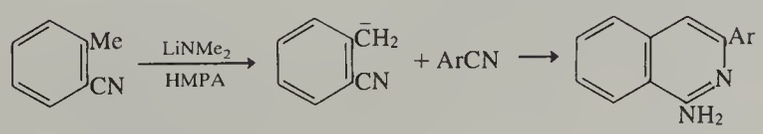


(**415**) (**416**)

(*c*) *Base-catalyzed cyclizations.* When an *o*-halogenophenethyl bromide is treated with an alkyllithium a monolithio derivative is obtained, and at −100 °C this reacts with benzonitrile to give a dihydroisoquinoline (**417**) ⟨77TL4145⟩. Similarly, reaction between the anion from *o*-toluonitrile and excess starting material, or with other added aromatic nitriles, gives 1-amino-3-arylisoquinolines (**418**) ⟨74S805⟩. The anion from diethyl acetonedicarboxy-

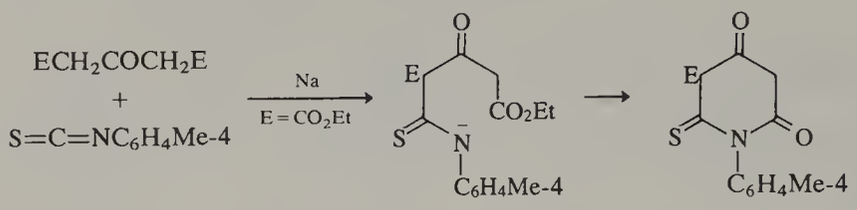


(**417**) R = H, Me

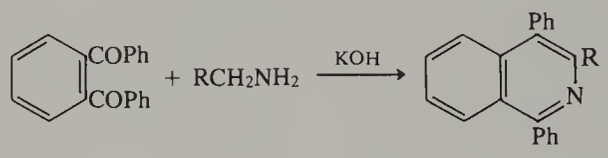


(**418**)	Ar	Ph	2-MeC_6H_4	3-C_5H_4N
	%	70	80	50

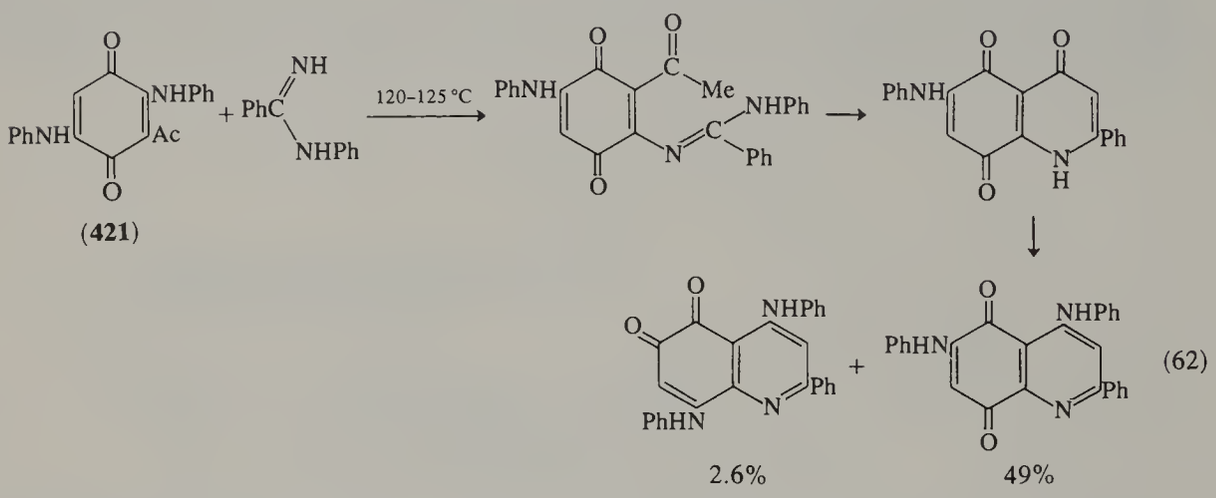
late condenses with *p*-tolylisothiocyanate to give the pyridine derivative (**419**) ⟨39JA2966⟩, and 1,2-dibenzoylbenzene reacts with primary amines in the presence of potassium hydroxide to give trisubstituted isoquinolines (**420**) ⟨80H(14)789⟩. The *p*-benzoquinone (**421**) reacts with *N*-phenylbenzamidine to give quinolinequinones (mainly 5,8) by the route shown in equation (62) ⟨77LA1445⟩.



(**419**)

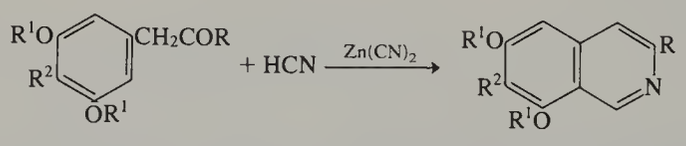


(**420**) R = Ph, Pr, CO_2Et, CN



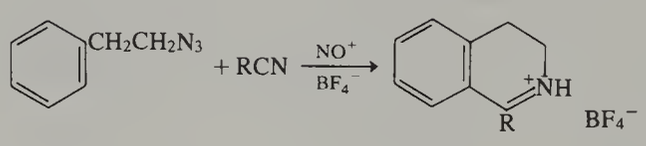
(62)

(*d*) *Cyclizations involving electrophiles.* Gatterman syntheses on ketones of type (**422**) give, in rather poor yield, a series of 3-substituted isoquinolines ⟨71JCS(C)3590⟩. Phenethyl azide reacts with nitriles and nitrosonium fluoroborate to give salts (**423**) of 3,4-dihydroisoquinolines ⟨75JHC263⟩, and phenylacetyl chloride and an alkyl isothiocyanate with tin(IV) chloride gives 3-hydroxy-1-methylthioisoquinolines (**424**) ⟨76CC695⟩.

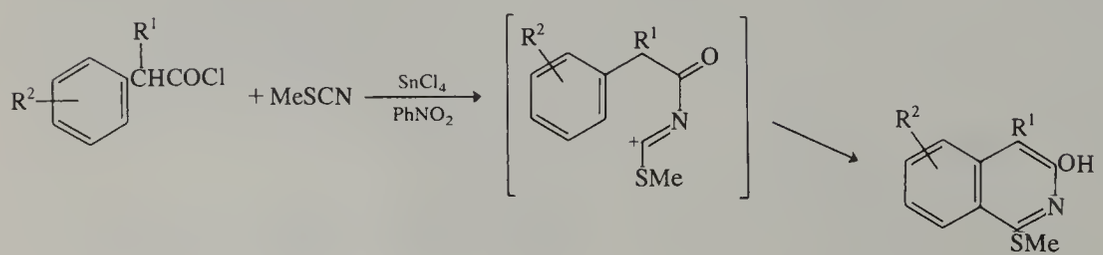


(**422**)

R^1 = Me, R^2 = H; R = Me, Pr^i, Bu, Et
R^1 = H, R^2 = Me, R = Me, Et



(**423**) R = Me (71%), Ph (54%)



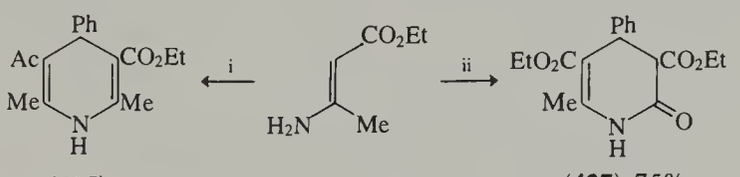
(**424**) R^1 = H or Me, R^2 = Me or OMe, 10–65%

2.08.2.2.3 From two three-atom fragments

The most obvious major division of this section is based on the nature of the three-atom segments. The first sub-section describes syntheses using two acyclic or alicyclic fragments, giving pyridines or tetrahydro-quinolines or -isoquinolines. The second sub-section contains syntheses from one acyclic or alicyclic and one aromatic fragment, and the third contains syntheses from two aromatic fragments. Within the first sub-section a further division depends on the nature of the nitrogen-containing fragment. Thus, historically, the first syntheses used enamines of some type; after this come syntheses using cyanoacetamide, cyanoacetates, malonamides and finally malononitriles. These syntheses are very well reviewed, in greater detail than can be achieved here, with many tables ⟨60HC(14-1)355⟩. The sub-section concludes with some miscellaneous syntheses.

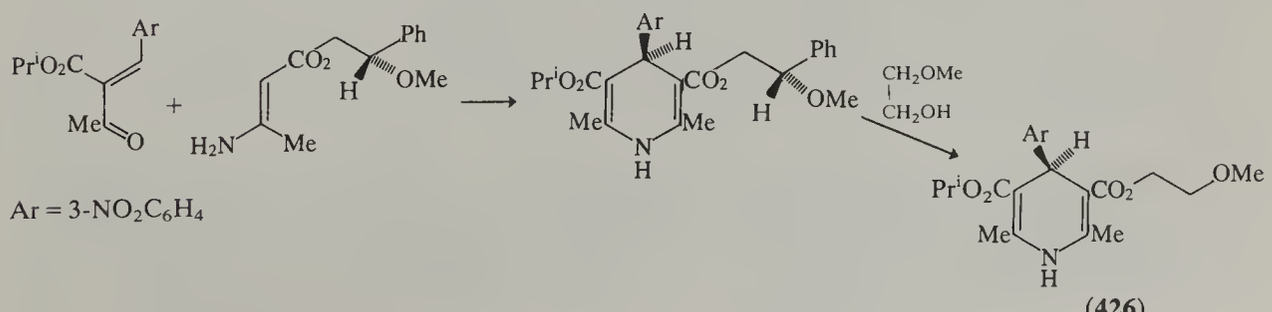
(*i*) *Two acyclic or alicyclic fragments*

(*a*) *Syntheses using enamines.* The Hantzsch synthesis of pyridines is dealt with in Section 2.08.2.4.2.i, but it is generally accepted that at an intermediate stage a β-aminoacrylate and an α,β-unsaturated ketone are present. Knoevenagel set the pattern for many syntheses by reacting together preformed enamino esters or ketones and α,β-unsaturated carbonyl compounds to obtain 1,4-dihydropyridines. Thus, from α,β-unsaturated ketones tetrasubstituted 1,4-dihydropyridines (**425**) are obtained, and these can be oxidized easily (for example, with dilute nitric acid) to the pyridines ⟨1898CB1025⟩. The 4-carbon atom is chiral, and a review ⟨81AG(E)762⟩ gives an example in which the optically pure form of a cerebral vasodilator (**426**) can be obtained by a diastereoselective synthesis; the final stage is selective alkanolysis of the chiral ester group. From an α,β-unsaturated ester and β-aminocrotonate a dihydrohydroxypyridine or pyridone (**427**) is obtained ⟨1898CB761⟩. Mumm and his coworkers ⟨17CB1568, 21CB726⟩ are credited with the discovery that the pyridines (**428**) (rather than dihydropyridines) can be obtained by condensing 1,3-diketones with β-aminocrotonates, but Claisen had used ethoxymethyleneacetoacetate (a masked β-keto aldehyde) much earlier to obtain the 2,3-dimethylpyridine-3,5-dicarboxylate (**429**) ⟨1893CB2729⟩. The less stable β-keto aldehydes are used in protected form, as an enol ether acetal (**430**) ⟨39CB1548⟩ or as the tetramethoxybutane (**431**) ⟨53CB797⟩. In such cases condensation gives only one of the possible isomers, with an unsubstituted 4-position. When 1,3-diketones are used the most electrophilic carbonyl carbon atom appears as the 4-carbon in the pyridine; when there is little distinction between the two carbonyl groups mixtures are obtained. In a case where prediction might have been difficult, that of ethyl ethoxymethyleneacetylpyruvate (**432**), the concealed aldehyde function leads to a pyridine with a free 4-position, and the yield was 82% ⟨51JA4380⟩. Hydroxymethylenecyclohexanone is reported to give a hexahydroquinoline (**433**), one of the few examples where the intermediate carbinolamine has been obtained ⟨57LA(530)131⟩. Hydroxymethylcyclohexanone is reported to give a small yield of the hexahydroquinoline (**434**) (a 1,4-dihydropyridine). This product seems likely to have been formed by retro-aldol reaction to give formaldehyde, followed by a Hantzsch synthesis ⟨37JCS1526⟩, a view supported by the isolation of some 2,6-dimethylpyridine-3,5-dicarboxylate.



(**425**) (**427**) 75%

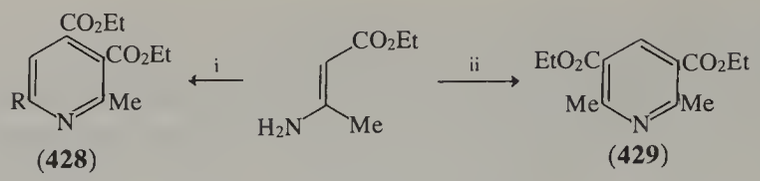
i, PhCH=C(Ac)COMe, water bath; ii, PhCH=C(CO$_2$Et)$_2$, 130–150 °C



Ar = 3-NO$_2$C$_6$H$_4$

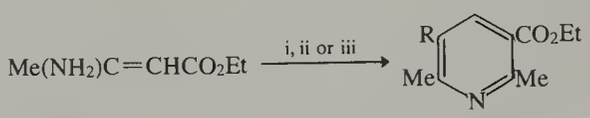
(**426**)

R	Et	Pr^n	Pr^i	Bu^t
%	80	89	90	64

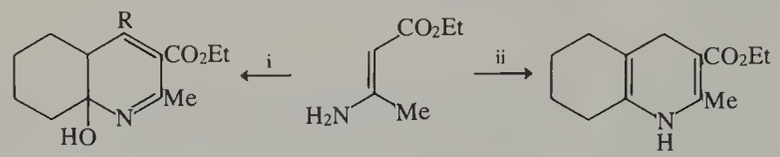


(**428**) (**429**)

i, $ROCH_2COCO_2Et$, heat; ii, $MeCOC(CO_2Et)=CHOEt$, heat



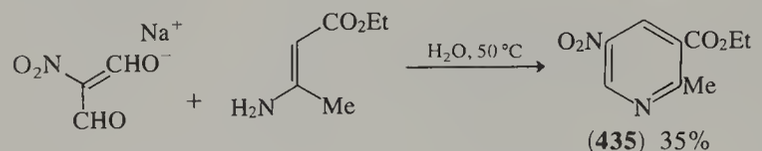
i, $Me(EtO)C=CHCH(OEt)_2$, (**430**), R = H, 40%; ii, $Me(EtO)_2CCH_2CH(OEt)_2$, (**431**), R = H, 35%; iii, $EtO_2CCOC(Ac)=CHOEt$, (**432**), R = Ac, 82%



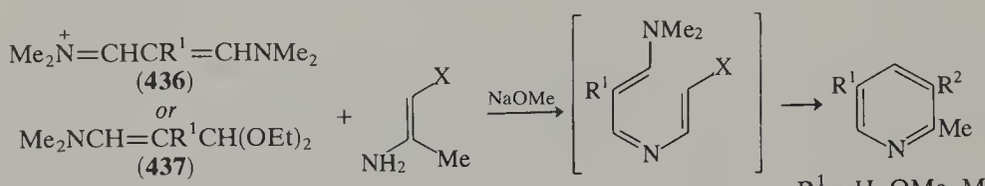
(**433**) R = H, CO_2Et (**434**)

i, 2-formylcyclohexanone; ii, 2-hydroxymethylcyclohexanone

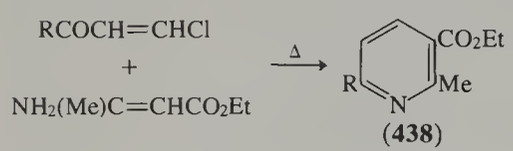
Malonic dialdehydes are difficult to prepare and use, but the sodium salt of nitromalonodialdehyde condenses with ethyl β-aminocrotonate at 50 °C to give the 5-nitronicotinate (**435**) ⟨53JA737⟩. Masked 1,3-dialdehydes are provided by the iminium salts (**436**) or the enamino acetals (**437**), and these condense with β-aminocrotonates or crotononitriles to give trisubstituted pyridines in 52–95% yield ⟨77S326⟩. A synthon for a β-keto aldehyde is a β-chlorovinyl ketone (obtainable by addition of acyl or aryl chlorides to alkynes), and a number of these have been shown to react with ethyl β-aminocrotonate to give 2,6-disubstituted nicotinates (**438**) ⟨51DOK609, 59ZOB1657⟩.



(**435**) 35%



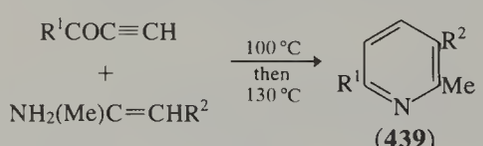
R^1 = H, OMe, Me, Ph; R^2 = CN, CO_2Et



R	Me	C_5H_{11}	Ph	2-ClC_6H_4	4-ClC_6H_4	4-$O_2NC_6H_4$
%	75	46	51	55	63	66

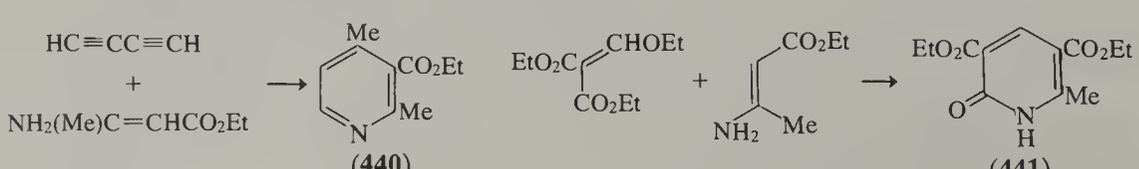
(**438**)

Ethynyl ketones also react on heating with β-aminocrotonate or with crotononitrile to give 2,3,6-trisubstituted pyridines (**439**) in excellent yield ⟨65GEP1190164⟩. Buta-1,3-diyne gives ethyl 2,4-dimethylnicotinate (**440**) when reacted with ethyl β-aminocrotonate ⟨72ZOR1328⟩, and a number of dialkylaminovinylacetylenes and alkoxyvinylacetylenes react with the same reagents to give mixtures of disubstituted nicotinates ⟨72ZOR1575⟩. Condensation of an aminocrotonate with ethoxymethylenemalonate gave a poor yield of the pyrid-2-one diester (**441**) ⟨41CB1111⟩, while substituted malonates, with an alkoxide catalyst, gave the 4-hydroxypyrid-2-one esters (**442**) ⟨66CB244⟩ and (**443**) ⟨60CB1848⟩.

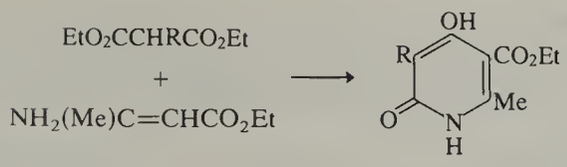


R^1	Me	Ph	Me	Ph
R^2	CO_2Et	CO_2Et	CN	CN
%	90	80	90	80

(**439**)

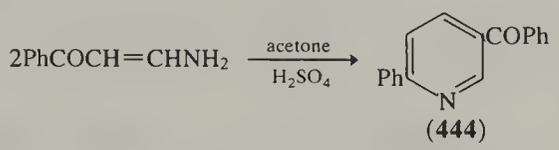


(**440**) (**441**)

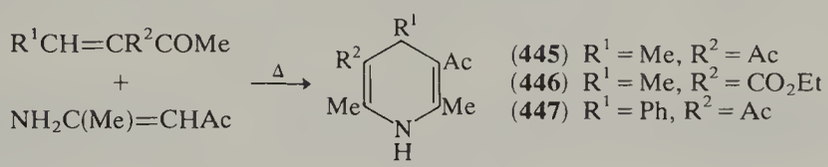


(**442**) R = NO_2, 35%
(**443**) R = Bu^n, 50%

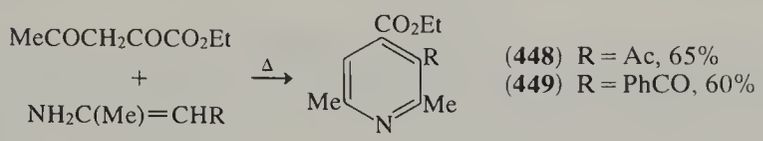
The second major class of enamines contains the enamino ketones, made from ammonia or an amine and a 1,3-diketone. By this route the same 1,3-diketone can provide both halves of the resulting pyridine; such an example is provided by the synthesis of 5-benzoyl-2-phenylpyridine (**444**) ⟨54YZ259⟩. As in the case of the crotonates, the first examples of the condensation of an enamino ketone with an α,β-unsaturated ketone were provided by Knoevenagel and Ruschhaupt ⟨1898CB1025⟩, who prepared the range of 3-acetyldihydropyridines (**445**) to (**447**). Similarly, Mumm and Böhme obtained the 3-acetyl- and 3-benzoyl-2,6-dimethylpyridines (**448**) and (**449**) from ethyl acetylpyruvate ⟨21CB726⟩.



(**444**)

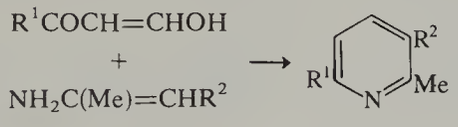


(**445**) R^1 = Me, R^2 = Ac
(**446**) R^1 = Me, R^2 = CO_2Et
(**447**) R^1 = Ph, R^2 = Ac

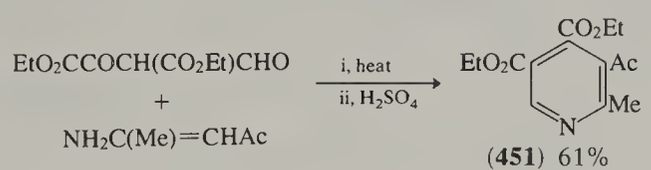


(**448**) R = Ac, 65%
(**449**) R = PhCO, 60%

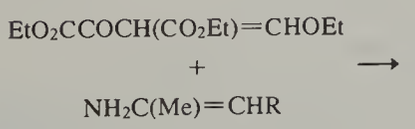
A number of α-hydroxymethylene ketones were shown to condense with enamino ketones to produce pyridines (**450**) without a substituent at position 4 ⟨35JIC665⟩. That the balance is delicate is shown by the production of pyridines (**451**) with a free 6-position when hydroxymethyleneoxaloacetates are used ⟨51JA5224, 55USP2724714⟩; the cyclization stage required acid conditions. By contrast, aminocrotononitrile and hydroxymethyleneoxaloacetate gave the pyridine (**452**) with a vacant 4-position ⟨51JA5224⟩. To add to the confusion, ethoxymethyleneoxaloacetate is reported to react with three types of enamine to give, in all cases, 2,3,5,6-tetrasubstituted pyridines (**453**) ⟨51JA4380⟩. The protected malonic aldehyde (**454**) reacts with 3-aminocyclohex-2-enones to give the reduced quinolinones (**455**) ⟨76BRP1432379⟩; the protected keto aldehyde (**456**) gives 3-acetyl- or 3-benzoyl-2,6-dimethylpyridine ⟨39CB1548⟩.



(**450**) R^1 = Ph, *p*-tolyl; R^2 = Ac, COPh

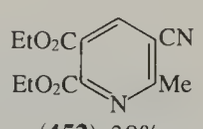


(**451**) 61%

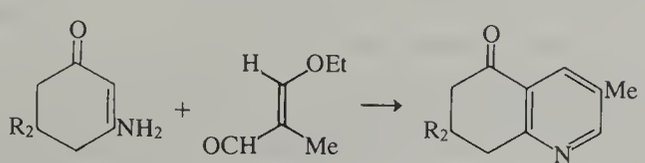


(**453**)

R	CN	Ac	CONHPh
%	70	65–70	69



(**452**) 38%

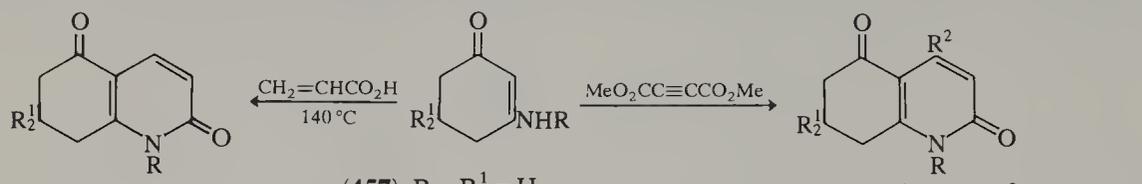


(**454**)

(**455**) R = H, Me; 40–72%

$EtOC(Me)=CHCH(OEt)_2$ (**456**) + $NH_2C(Me)=CHCOR$ → 2,6-dimethyl-3-COR-pyridine (Me, N, Me) R = Me, 30–34%; R = Ph

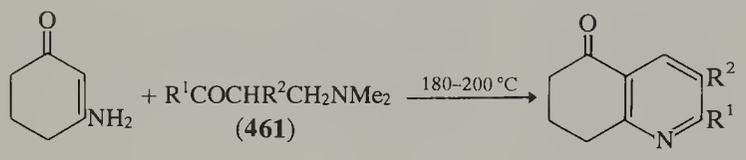
Chlorovinyl ketones and alkynyl ketones react with enamino ketones in the same manner as with aminocrotonates ⟨56IZV213, 65GEP1190164⟩, and also react with vinylacetylenes to give mixtures of pyridines ⟨72ZOR1575⟩. Reaction between aminocyclohexenone (**457**) and acrylic acid gives a tetrahydroquinoline-2,5-dione (**458**) in 95% yield ⟨81JOC3719⟩ while the hydrazinocyclohexenone (**459**) with acetylenedicarboxylate gives a dihydroquinolinedione (**460**) ⟨79ZN(B)102⟩. Aminocyclohexenone and the Mannich bases (**461**) react at 180–200 °C to give dihydroquinolin-5-ones in good yields ⟨77AP48⟩.



(**458**) R = R¹ = H, 95%

(**457**) R = R¹ = H
(**459**) R = NMe_2, R¹ = Me

(**460**) R = NMe_2, R¹ = Me, R² = CO_2Me



R¹ = Ph, 2-naphthyl; R² = Me, Ph, *e.g.* R¹ = Ph, R² = Me, 70%

(*b*) *Syntheses using cyanoacetic or malonic acid derivatives.* When a 1,3-dicarbonyl compound reacts with cyanoacetamide or cyanoacetic esters the products are pyrid-2-ones. The early examples were reactions between 1,3-diketones and cyanoacetamide; in a detailed discussion of the mechanism Bardhan reported on the direction of condensation when unsymmetrical diketones were used ⟨29JCS2223⟩. In the examples given in equation (63), the products clearly reflect the difference in electrophilic activity between the two carbonyl carbon atoms. By using the two enol ethers of an unsymmetrical diketone Basu was able to isolate both the isomeric pyrid-2-ones (**462**) and (**463**), but the yield of the 'abnormal' isomer (**463**) was much lower ⟨30JIC481⟩; a tetrahydroquinolin-2-one (**464**) was also prepared. The direction of condensation is rarely exclusive; careful examination of crystallization residues from reaction between ethoxyacetylacetone and cyanoacetamide after removal of the 'normal' product (**465**) showed the presence of 15% of the 'abnormal' isomer (**466**) ⟨46JOC751⟩.

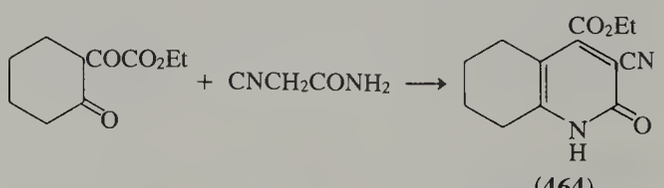
$R^1COCH_2COR^2$ + $CNCH_2CONH_2$ → 3-CN-2-oxo-1,2-dihydropyridine (R¹, R²) *or* (R², R¹) (63)

Product A Product B

R¹ = Ph, R² = Me, Product A
R¹ = Me, R² = CO_2Et, Product B

(**462**) R¹ = Ph, R² = Me, 84%
(**465**) R¹ = Me, R² = CH_2OEt, 75%

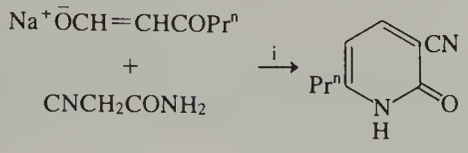
(**463**) R¹ = Ph, R² = Me, 30%
(**466**) R¹ = Me, R² = CH_2OEt, 15%



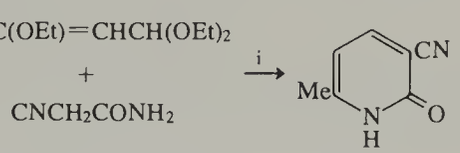
(**464**)

Ketoaldehydes as sodium salts condense with cyanoacetamide to give 6-substituted pyrid-2-ones, such as compound (**467**) ⟨51JA1368⟩. It is more common to use a protected aldehyde in the form of an enol ether or an acetal as in the synthesis of pyridone (**468**) ⟨40CB153⟩. The thioacetals (**469**) condense with cyanoacetamide to give 4-methylthiopyrid-2-ones when the group R^2 is hydrogen or phenyl, but if the group R^2 is a methyl or methylene group an alternative pathway leads to pyridone (**470**) ⟨78JCS(P1)549⟩. In a similar reaction the enamino ketones (**471**) condense with cyanoacetamides with an isopropoxide catalyst to give 4-amino-3-cyanopyrid-2-ones ⟨82S214⟩. Malonic aldehyde condenses in a protected

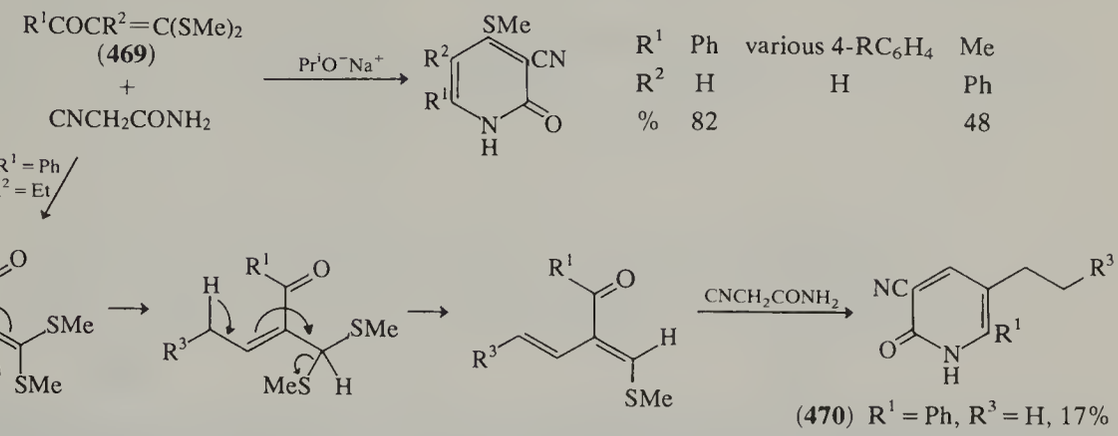
form to give 3-cyanopyrid-2-one (**472**) ⟨40CB153⟩ and nitromalonaldehyde gives 5-nitro-3-cyanopyrid-2-one (**473**) ⟨55JA1045⟩. The examples chosen illustrate the range of bases used in the condensation, from diethylamine or piperidine, through Triton B, to sodium alkoxides.



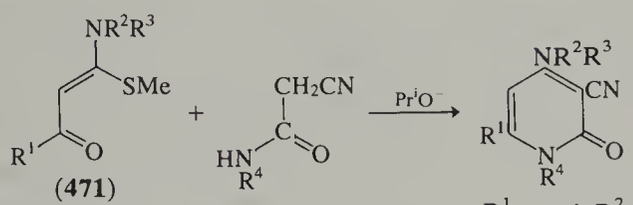
i, piperidine acetate (**467**) 37%



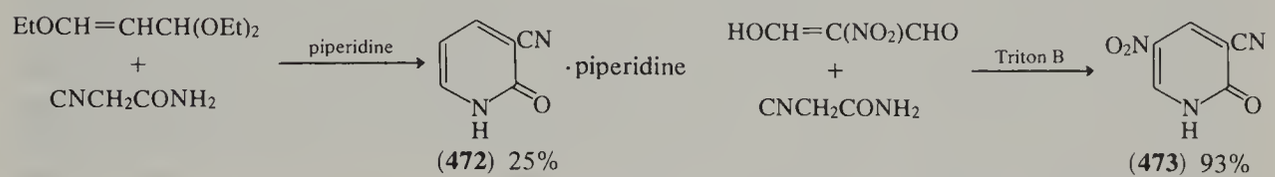
(**468**)



(**470**) R^1 = Ph, R^3 = H, 17%

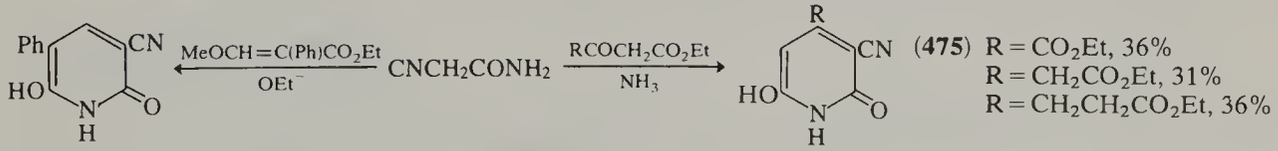


R^1 = aryl, R^2 = alkyl, aryl; R^4 = H, Me; 50–71%

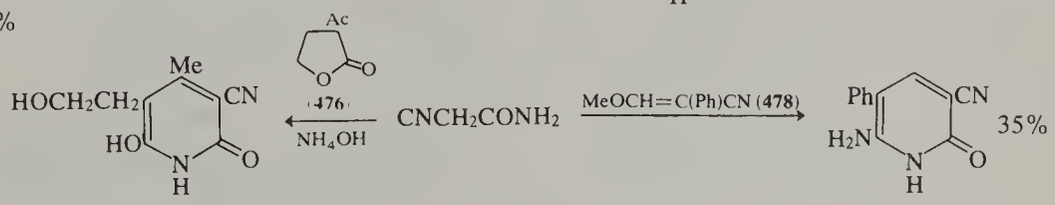


(**472**) 25% (**473**) 93%

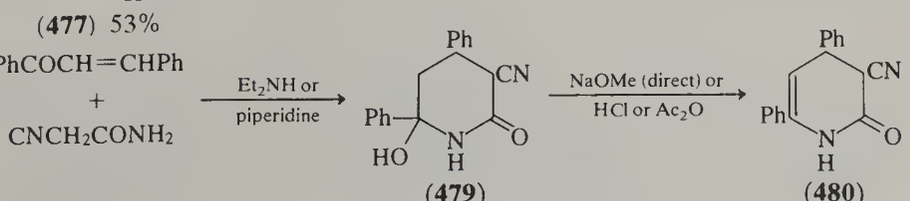
Protected β-aldehydo esters and β-keto esters react with cyanoacetamide to give 6-hydroxypyrid-2-ones (**474**) and (**475**) respectively, with or without a substituent in position 4 ⟨53JCS3548, 43JA449⟩. The γ-lactone (**476**) gives the pentasubstituted pyridine (**477**) ⟨42JA1093⟩, and the protected cyano aldehyde (**478**) gives a 6-aminopyrid-2-one ⟨53JCS3548⟩. Cyanoacetamide reacts with α,β-unsaturated ketones to give either a 3,4-dihydropyrid-2-one (**480**) (with sodium ethoxide) or the intermediate piperidone (**479**) (with diethylamine or piperidine) ⟨30JIC321⟩. With alkynyl ketones pyrid-2-ones (**481**) are obtained ⟨30JIC851⟩; *N*-methylcyanoacetamide gives *N*-methylpyridones, but the yields are poorer with alkylalkynyl ketones. Ethyl propiolate and cyanoacetamide react in the presence of sodium methoxide to give, in high yield, 3-cyano-6-hydroxypyrid-2-one (**482**) ⟨80AG390⟩.



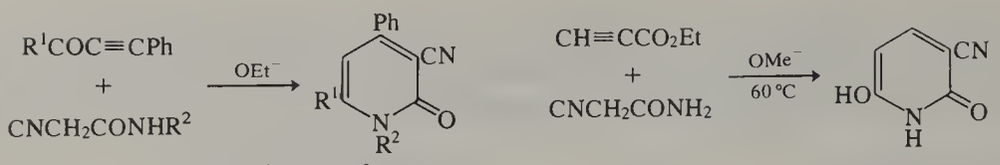
(**474**) 15% (**475**) R = CO_2Et, 36%; R = CH_2CO_2Et, 31%; R = $CH_2CH_2CO_2Et$, 36%



(**477**) 53% 35%



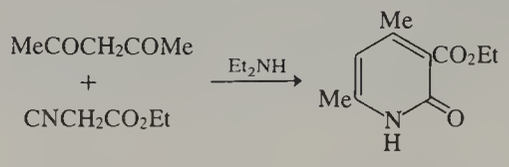
(**479**) (**480**)



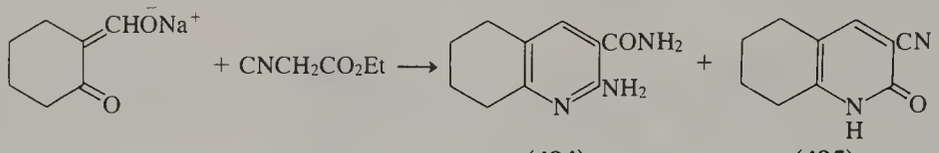
(**481**) R^1 = Ph, R^2 = H, 60%

(**482**) 79%

Ethyl cyanoacetate reacts with 1,3-diketones to give 4,6-disubstituted 2-oxopyridine-3-carboxylates such as compound (**483**) ⟨15JCS792⟩, and with hydroxymethylenecyclohexanone to give a mixture of tetrahydroquinolines (**484**) and (**485**) ⟨55AP174⟩.

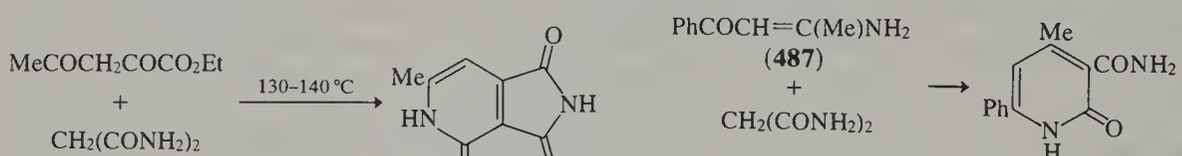


(**483**)

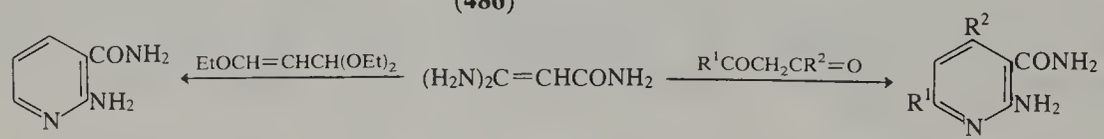


(**484**) (**485**)

Malonic acid diamide (malonamide) has been less frequently used for pyridine synthesis. Direct heating together of malonamide and ethyl acetylpyruvate gives a cinchomeronic acid imide (**486**) ⟨60G1399⟩. In the reaction between malonamide and the enamine (**487**) the pyridine nitrogen atom could come from either component, and indeed the same enamine reacts with ethyl cyanoacetate to give a pyridone in a [4 + 2] cyclization ⟨35JIC299⟩. Amidines can be used instead of malonamides; reaction with an enol acetal (a malonic dialdehyde synthon) gives 2-aminonicotinamide (**488**) ⟨49CB257⟩, while the sodium salt of acetoacetaldehyde gives the homologue (**489**) and acetylacetone gives the 4,6-dimethyl derivative (**490**) ⟨51CB296⟩. The diaminoacrylate (**491**) is at the oxidation level of an amidoacetate; it reacts with nitromalonic aldehyde to give the aminonicotinate (**492**), and with alkylidene- and arylidene-acetoacetates to give 1,4-dihydropyridines (**493**) ⟨77LA1895⟩. Similarly, imino ethers such as compound (**494**) react with keto aldehydes or 1,3-diketones to give 2-aminopyridines; examples of compounds thus obtained are shown by formulae (**495**) ⟨51CB296⟩, (**496**) ⟨40CB542⟩, and (**497**) ⟨55AP174⟩.

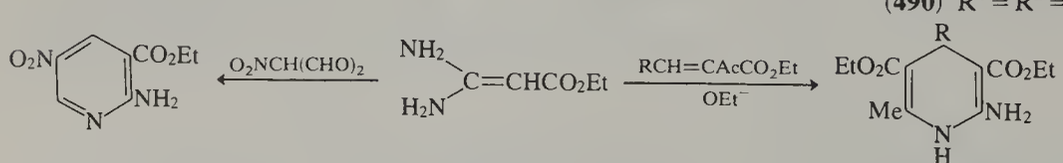


(**486**)



(**488**) 25%

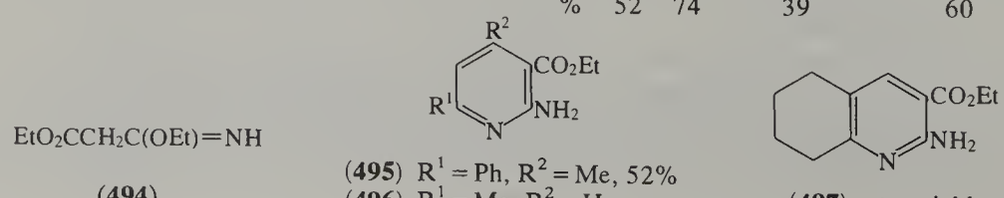
(**489**) R^1 = Me, R^2 = H, 56%
(**490**) R^1 = R^2 = Me, 60%



(**492**) (**491**)

(**493**)

R	Me	Ph	2-$O_2NC_6H_4$	3-$O_2NC_6H_4$	2-Furyl
%	52	74	39	60	82

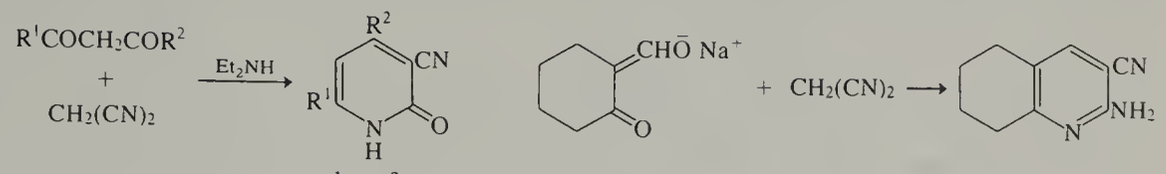


(**494**)

(**495**) R^1 = Ph, R^2 = Me, 52%
(**496**) R^1 = Me, R^2 = H

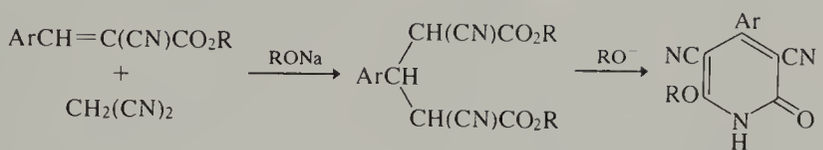
(**497**) poor yield

Malononitrile can function as the three-carbon fragment in a synthesis or as the provider of one nitrogen atom and two carbons. In reactions similar to those already described, malononitrile reacts with diketones to give pyrid-2-ones (**498**); the general rules for condensation follow those of cyanoacetamide with mixtures formed from compounds where the carbonyl groups have approximately equal reactivity ⟨30JIC815⟩. The sodium salt of hydroxymethylenecyclohexanone is reported to give 2-amino-3-cyanotetrahydroquinoline (**499**) ⟨55AP174⟩. With arylidenecyanoacetates, pyridones (**500**) are formed in 78–92% yield ⟨78S681⟩.



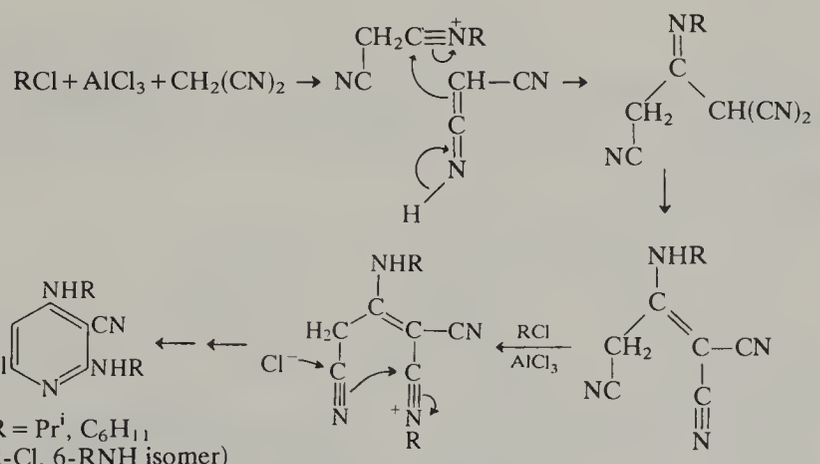
(**498**) *e.g.* $R^1 = R^2 = Me$, 77%

(**499**)



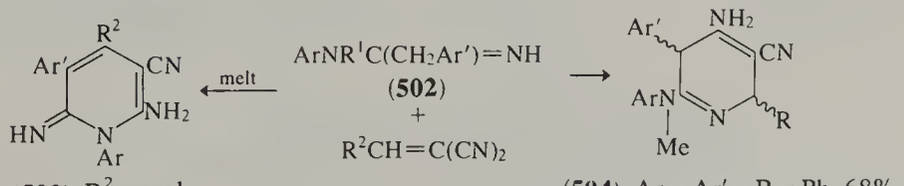
(**500**)

Malononitrile dimer or some close relative takes part in some pyridine syntheses, and can provide all six ring atoms. From malononitrile and an alkyl halide, with aluminum chloride, 2,4-diaminopyridines (**501**) are obtained ⟨80LA946⟩. The mechanism is shown in equation (64). A number of syntheses involve alkylidene- or arylidene-malononitriles. A wide range of 2,4-diaminopyridines (**503**) can be obtained by reaction between alkylidenemalononitriles and the amidines (**502**) ⟨80H(14)461⟩. When *N*,*N*-disubstituted amidines are allowed to react with the alkylidenemalononitrile, and the products cyclized under Thorpe condensation conditions, 2,5-dihydropyridines (**504**) are obtained ⟨80TL2097⟩; these can be dehydrogenated to give 2,4-diaminopyridines. The aminotrinitrile (**505**) behaves as an aminoacrylonitrile and provides dicyanomethylenepyridines (**506**) in good to excellent yields ⟨64M1201⟩. Ethoxymethylenemalononitrile is reported to react with thiols to give 6-alkylthio-2-aminopyridines (**507**); a plausible mechanism can be written *via* the malononitrile dimer (**505**) ⟨61JOC79⟩.



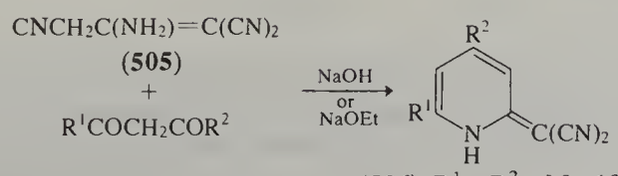
(64)

(**501**) R = Pr^i, C_6H_{11}
(some 2-Cl, 6-RNH isomer)

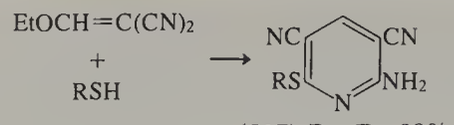


(**503**) R^2 = aryl

(**504**) Ar = Ar′ = R = Ph, 68%
cis : *trans* = 15 : 10

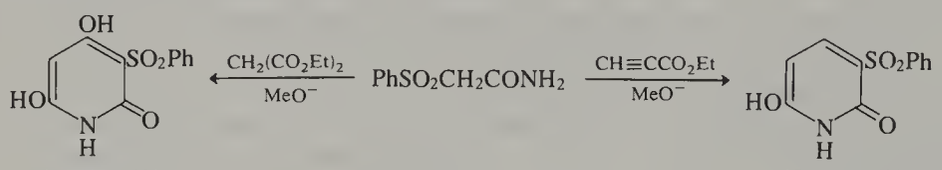


(**506**) $R^1 = R^2 = Me$, 100%

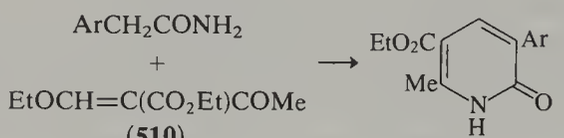


(**507**) R = Et, 80%

(*c*) *Syntheses using miscellaneous molecules providing two carbon atoms and one nitrogen atom.* A number of substituted acetamides can be used in the synthesis of pyridines, the substituent providing extra activation for the methylene group. Benzenesulfonylacetamide condenses with diethyl malonate, under basic conditions, to give the 4,6-dihydroxypyrid-2-one (**508**), and with ethyl propiolate to give the 6-hydroxypyrid-2-one (**509**) ⟨80AG390⟩. The masked β-keto aldehyde (**510**) reacts with 2-quinolylacetamide to give the pyrid-2-one (**511**) ⟨74CPB744⟩; a more general synthesis is provided by the reaction between α,β-unsaturated ketones and the pyridinium salts (**512**) ⟨57CB711⟩. In this synthesis the elimination of the pyridinium group introduces the final unsaturation; the use of a Mannich base instead of the α,β-unsaturated ketone is illustrated by the synthesis of tetrahydrocarbostyril (**513**). Acetoacetamide provides a useful starting material. With a 1,3-diketone or keto aldehyde it can be used to obtain 3-acetylpyrid-2-ones (**514**), in some cases in excellent yields ⟨76CPB303⟩. Its imine (aminocrotonamide) can be used to prepare nicotinamides (**515**) ⟨77H(6)547⟩. With acrylic esters acetoacetamide reacts by Michael addition followed by cyclization to produce acetylglutarimide (**516**) (together with many other products) ⟨74CPB2947⟩. The nitrodiamines (**517**) react with ethoxymethylenemalononitrile to give *N*-substituted 2-iminopyridines (**518**) ⟨78ZC335⟩.

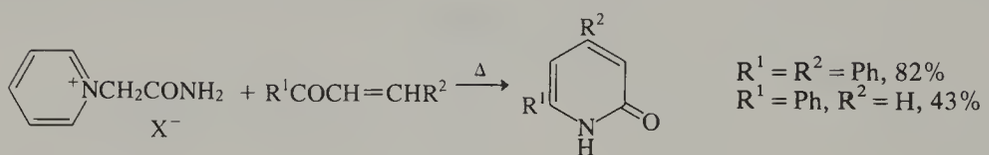


(**508**) 36% (**509**) 48%

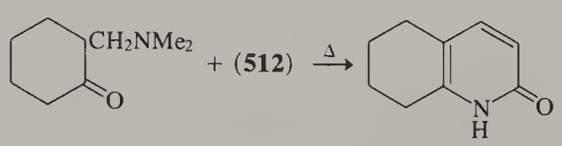


(**510**)

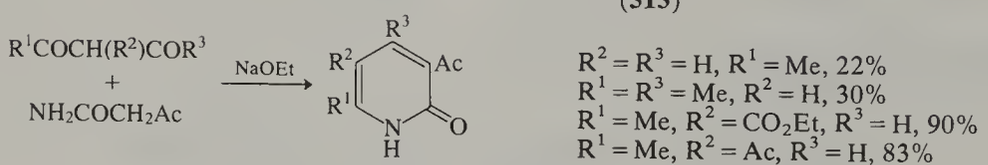
(**511**) Ar = 2-quinolyl



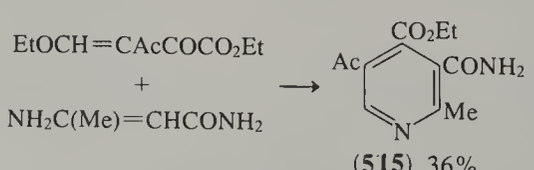
(**512**)



(**513**)



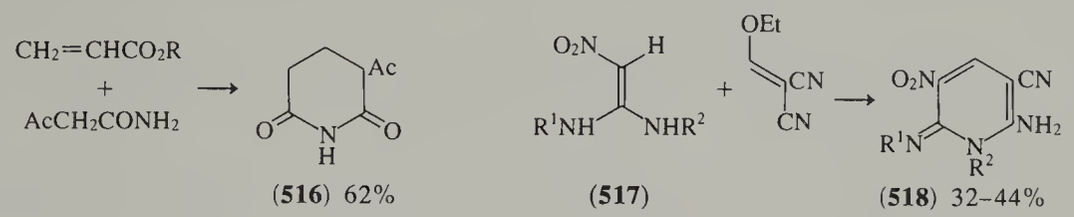
(**514**)



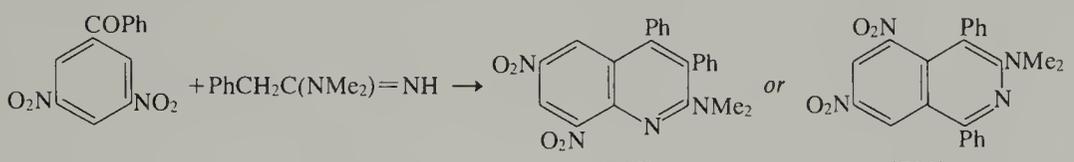
(**515**) 36%

In an unusual reaction, involving a Meisenheimer intermediate, 3,5-dinitrobenzophenone reacted with *N*,*N*-dimethylphenylacetamidine to give either a quinoline (**519**) or an isoquinoline (**520**) ⟨77JOC435⟩. Enamines (**521**) react with diethyl maleate and aluminum chloride at room temperature to give good yields of the unusual 3,6-dihydropyrid-2-ones (**522**)

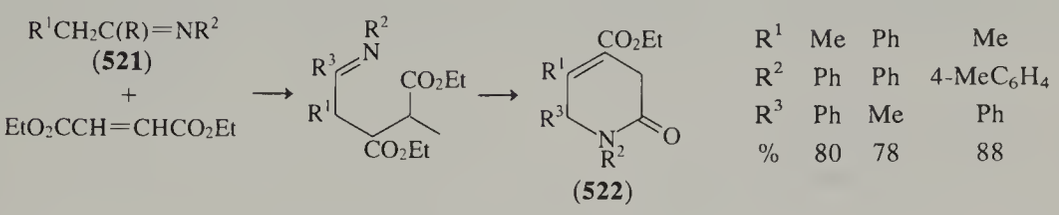
⟨75S643⟩. Acetonitrile and other simple nitriles can be used in a synthesis with malonyl chloride to give at room temperature 6-chloro-4-hydroxypyrid-2-ones (**523**). Bromomalonyl chloride and ethyl cyanoacetate give compound (**524**) ⟨62JCS3638⟩. Pyridine-2-thiones (**525**) and (**526**) can be prepared from benzoylisothiocyanate and enamino ketones ⟨75H(3)108⟩. Condensation between ethoxymethyleneacetoacetate and the nitroamine (**527**) gives a tetrahydropyridin-4-ol (**528**), which is dehydrated easily by acids to a 1,2-dihydropyridine ⟨53HCA37⟩; the primary amine condenses but does not cyclize. Another amine, with 4-formyl-4,5-dihydrofuran-3-one, gives, after oxidation, a 1,4-dihydropyridine (**529**) ⟨56USP2734063⟩.



(**516**) 62% (**517**) (**518**) 32–44%

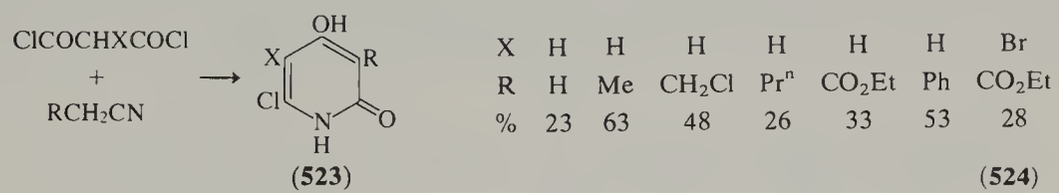


(**519**) (**520**)



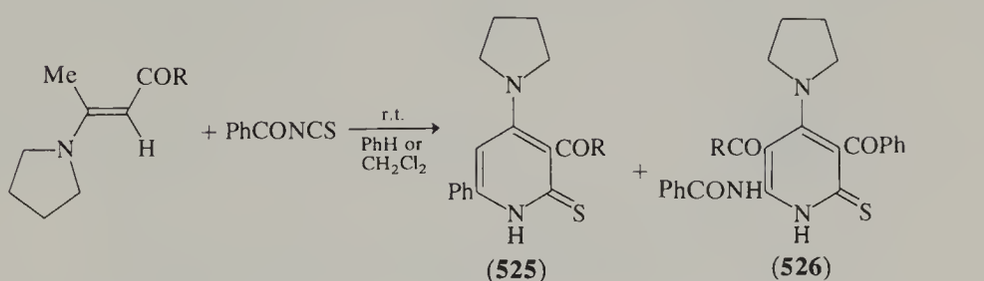
R^1	Me	Ph	Me
R^2	Ph	Ph	4-MeC_6H_4
R^3	Ph	Me	Ph
%	80	78	88

(**522**)

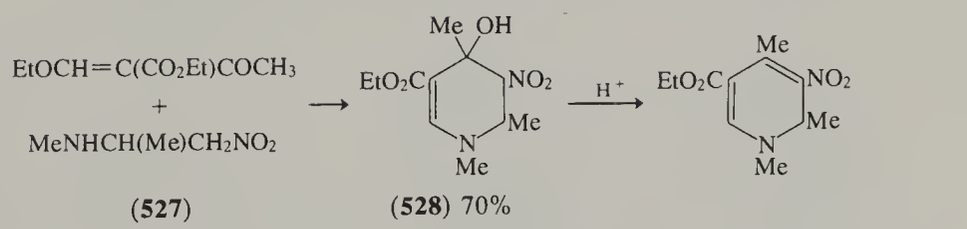


X	H	H	H	H	H	H	Br
R	H	Me	CH_2Cl	Pr^n	CO_2Et	Ph	CO_2Et
%	23	63	48	26	33	53	28

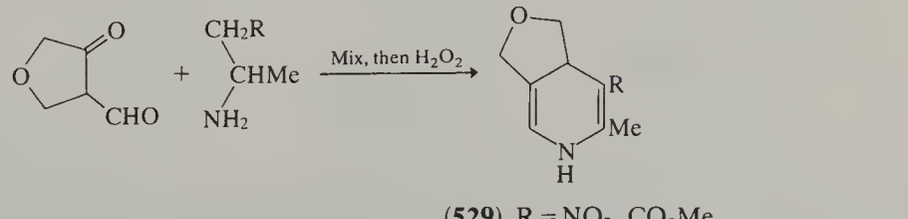
(**523**) (**524**)



(**525**) (**526**)



(**527**) (**528**) 70%



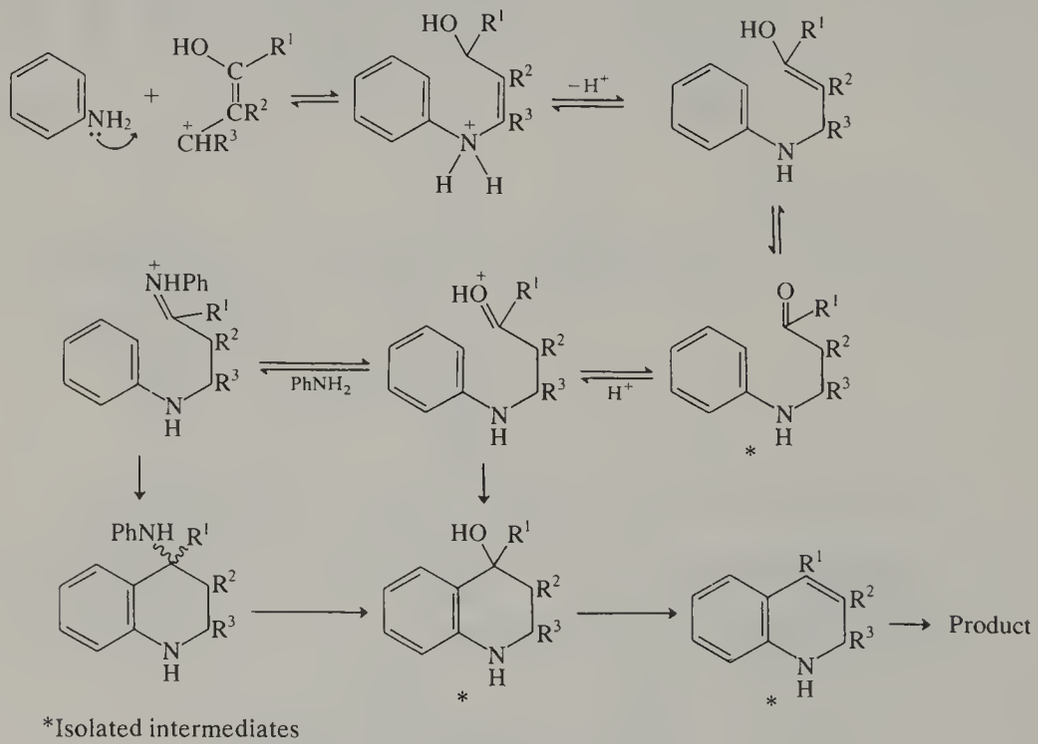
(**529**) R = NO_2, CO_2Me

(ii) One acyclic fragment and one fragment containing an aromatic ring

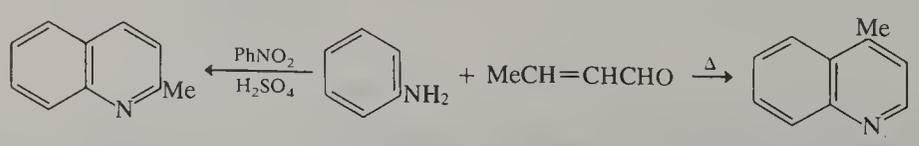
(a) Syntheses of quinolines. The best known synthesis of quinolines, that due to Skraup, clearly belongs to this category; the Doebner–von Miller synthesis is so closely related that it will be dealt with here, although in practical terms it can fall into the category [3+2+1].

Skraup's original mixture was glycerol, nitrobenzene and concentrated sulfuric acid, but he found a considerable improvement in yield if aniline was added ⟨1881M(2)139⟩, and this mixture with minor modifications has provided yields of quinoline as high as 90%. The active agent in the Skraup synthesis is felt to be acrolein or some simple derivative of acrolein, although attempts to use acrolein in place of glycerol have been almost completely unsuccessful. The assumed intermediacy of acrolein in the Skraup reaction provides a rationale for the synthesis due to Doebner and von Miller ⟨1881CB2812⟩. They originally used ethylene glycol instead of glycerol but deducing that crotonaldehyde might be the crucial intermediate, replaced the ethylene glycol with paraldehyde and greatly improved the yield of 2-methylquinoline. The two syntheses provide routes to a very large variety of quinolines and of 2- and 4-substituted quinolines, their particular charm being the variety of substituents possible in the benzenoid ring. A comprehensive review is available ⟨77HC(32-1)100⟩ and only the main features will be given here.

The mechanism of the Doebner–von Miller synthesis has been very thoroughly studied and is shown in Scheme 5. The assumption is made that the Skraup synthesis is a particular case of the more general Doebner–von Miller synthesis, and so labelling evidence from either reaction will be given. Labelling by ^{15}N has established that virtually all of the nitrogen in the quinoline comes from aniline rather than nitrobenzene ⟨64T2773⟩. Labelling of the α,β-unsaturated carbonyl component was originally by methyl groups (crotonaldehyde was shown to give 2-methylquinoline), but ^{13}C labelling of C-3 in acrolein diacetate ⟨61YZ855⟩, and of C-1 and C-3 in glycerol used to synthesize 8-nitroquinoline ⟨75CPB2682⟩ established the same course of addition for *py*-unsubstituted quinolines. Carbonyl-labelled but-2-en-3-one gave ^{13}C-labelled 4-methyl-8-nitroquinoline with C-4 labelling ⟨75CPB2682⟩. For the rest of the mechanism, Badger and his coworkers isolated β-amino ketones and showed that they could be converted into quinolines ⟨63AJC814⟩, Jones and Evans isolated 4-hydroxytetrahydroquinolines ⟨12JCS1376⟩, and more recently two groups have isolated 2-methyl-1,2-dihydroquinolines from a mixture of acetaldehyde with arylamines ⟨78H(9)281, 78CJC632⟩. By contrast, crotonaldehyde and aniline react in the gas phase over an aluminosilicate catalyst to give 4-methylquinoline as in equation (65) ⟨70JPR263⟩.



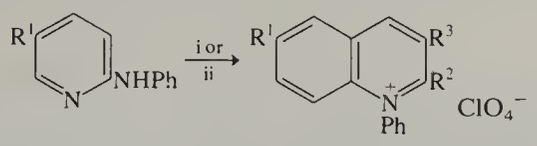
Scheme 5



(65)

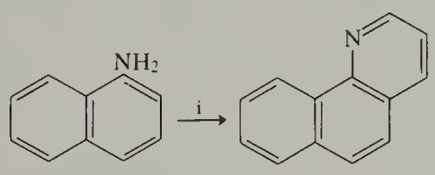
In practical terms, the major advantage of the Doebner–von Miller and Skraup syntheses is the wide range of *o*- and *p*-substituents in the aniline which are tolerant of the acid conditions. Thus, 6- and 8-substituted quinolines can be made where the substituent is an

alkyl, aryl, hydroxyl or ether, carboxyl, aroyl, sulfide, sulfone, or sulfoxide group, or a halogen. In the Doebner–von Miller procedure the same range of substituents can be used, and it is possible to produce 2-, 3-, or 4-alkyl- or -aryl-substituted quinolines. A few groups are unstable to the acid conditions, in particular to the strongly acidic medium in the Skraup synthesis (for example, a cyano group is hydrolyzed and the resulting carboxylic acid may decarboxylate) but the major disadvantage of these syntheses lies in the production of mixtures of 5- and of 7-substituted quinolines when *meta*-substituted arylamines are used. Nitrogen-containing substituents other than the amino group can provide the quinoline nitrogen atom. The use of nitro compounds by Skraup has been mentioned; azobenzenes, phenylhydroxylamines, and acetylamines have also been used. Only the last represents any real advantage, the amine apparently being released slowly during the reaction, with improved yields ⟨41MI20800⟩. The use of diphenylamine in the Doebner–von Miller synthesis gives *N*-phenylquinolinium salts (**530**) ⟨59ZOB1129⟩. More recently, diarylamines have been shown to react with acrolein, hydrochloric acid, and nitrobenzene to give arylquinolinium salts (**531**) without substituents in the pyridine ring ⟨78T363⟩. The other major modification of the aromatic amine is to use polycycles; thus α-naphthylamine gives benzo[*h*]quinoline (**532**) ⟨1881M(2)162⟩, and β-naphthylamine gives benzo[*f*]quinoline (**533**) ⟨1883M(4)436⟩. In the latter case, the use of 1-bromo- or 1-nitro-2-naphthylamine also gives compound (**533**) while 2-aminonaphthalene-1-sulfonic acid, with paraldehyde, gives the methyl derivative (**534**) ⟨71GEP2117361⟩. The reaction between β-naphthylamine and phenylpropynal gives the phenylbenzoquinoline (**535**), which was also obtained by a Doebner synthesis (Section 2.08.2.3.1.iii). Naphtho[2,1-*f*]quinolines (**536**) can be prepared in excellent yield from 2-aminophenanthrene ⟨66T(S7)287⟩. Other polycycles similarly prepared are shown in formulae (**537**) to (**539**) ⟨66T(S7)287⟩.

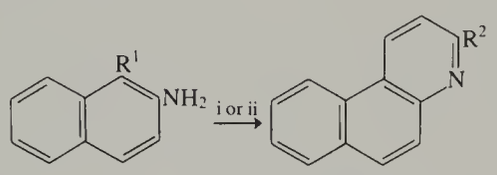


(**530**) R^1 = H, R^2 = Et, R^3 = Me
(**531**) $R^1 = R^2 = R^3$ = H, 48%

i, $MeCH_2CHO$, H^+, $PhNO_2$; ii, CH_2=CHCHO, HCl, $PhNO_2$

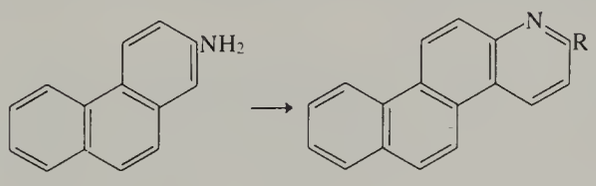


(**532**)

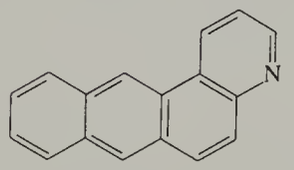


(**533**) R^2 = H
(**534**) R^2 = Me
(**535**) R^2 = Ph

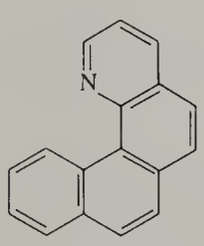
i, glycerol, H_2SO_4, $ArNO_2$; ii, MeCHO, H_2SO_4, oxidant



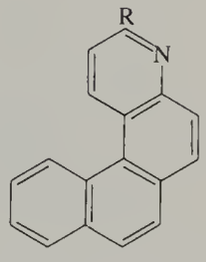
(**536**) R = H, 80–90%; R = Me, 49%



(**537**) 43%



(**538**) 75%

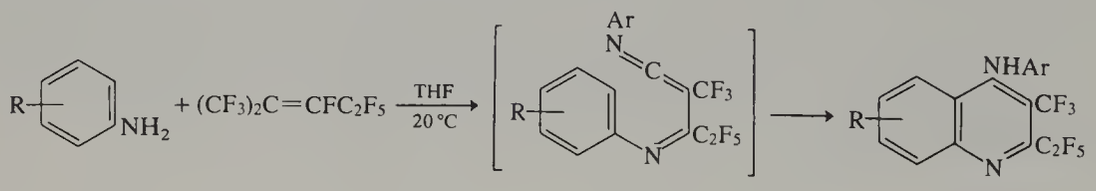


(**539**) R = H, 64%

Modifications in the three-carbon fragment include the use of acrolein or of acrolein acetals or diacetates to replace glycerol (α,β-unsaturated ketones are often used in the Doebner–von Miller synthesis). Substituted acroleins include 2-chloroacrolein giving 3-chloroquinolines, and 2-bromoacrolein diacetate to give 3-bromoquinolines (2-bromoacrolein gives halogen-free quinolines). Almost anything which might form acrolein (or,

more generally, α,β-unsaturated ketones) can be used: 2,3-dichloro- or 2,3-dibromo-acrolein, 3-chloro-3-hydroxy- or 3-ethoxy-propionaldehyde, the acetals of 3-ethoxyacrolein or 3-ethoxypropionaldehyde, β-hydroxy, β-chloro, or β-dialkylamino ketones, and (for 4-methylquinolines) 2,2,4-trimethoxybutane.

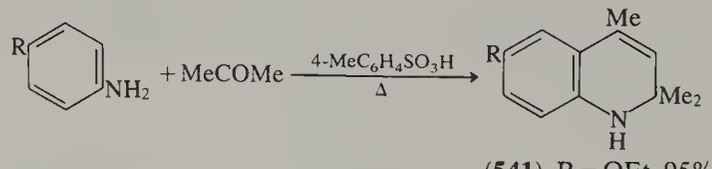
The most popular medium for the Skraup synthesis remains sulfuric acid, although polyphosphoric acid has been recommended when acroleins are used. The most important additive can be iron(II) sulfate or boric acid to moderate the legendary violence of the reaction. A very large number of oxidizing agents have been used, but an aryl nitro compound remains the most common, often the nitro compound corresponding to the arylamine or an involatile nitro compound such as nitrosulfonic acid. In the Doebner–von Miller synthesis the classical medium is a mixture of ethanol and hydrochloric acid, although sulfuric acid is not uncommon. No oxidizing agent is needed although iron(III) chloride or arsenic acid is often added, and zinc chloride can improve the yield if the quinoline is precipitated as a chlorozincate and the salt washed with isopropanol ⟨77JOC911⟩. This modification is also claimed to give 7-substituted quinaldines free from 5-substituted isomers when *meta*-substituted arylamines are used. A reaction with some similarity to the Skraup synthesis is that between an arylamine and perfluoro-2-methylpent-2-ene to give 4-arylaminoquinolines such as compound (**540**) *via* a ketenimine ⟨74CC134⟩; benzo[*h*]quinolines are obtained from 1-naphthylamine.



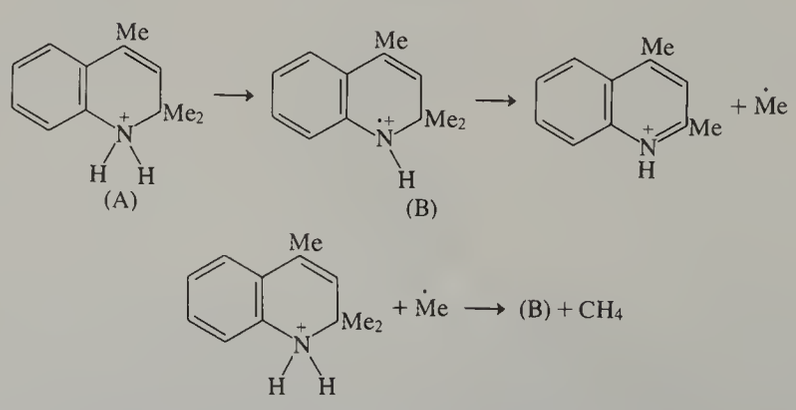
(**540**)

R = 6,8-$(MeO)_2$, Ar = 2,4-$(MeO)_2C_6H_3$, 74%

Closely related to the Doebner–von Miller synthesis is that of 2,2,4-trimethyl-1,2-dihydroquinolines (**541**) from an aromatic primary or secondary amine and acetone. Iodine is often used as a catalyst. This synthesis has been reviewed ⟨77HC(32-1)117⟩. Polymerization inhibitors are recommended, and continuous processes have been developed ⟨74JAP7435388⟩, because the 6-ethoxy analogue is an important antioxidant for foods. The use of diacetone alcohol or of mesityl oxide in place of acetone accentuates the similarity with the Doebner–von Miller synthesis ⟨77JAP(K)116478⟩. The most interesting question arises from the thermal conversion of the 2,2,4-trialkyldihydroquinolines (**541**) into 2,4-dimethylquinolines with loss of methane. Sodium amide or sodium anilide ⟨55OSC329⟩ give high yields of 2,4-dimethylquinolines; the reaction is generally accelerated by radical accelerators, such as hydrogen chloride, with production of extra, radical-derived, products. The mechanism proposed is given in Scheme 6.



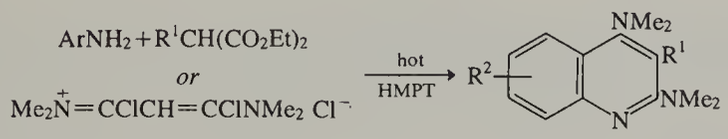
(**541**) R = OEt, 95%



(A) + Ṁe → Various trimethylquinolines

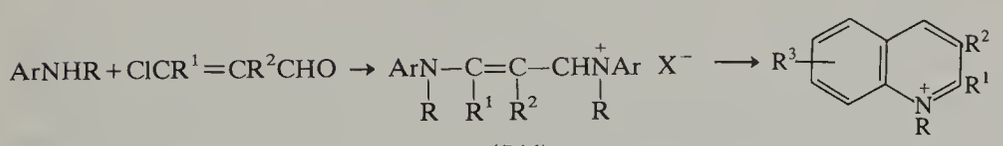
Scheme 6

Although the Combes synthesis, the Knorr synthesis, and the Conrad–Limpach synthesis have been dealt with in Section 2.08.2.1.3, it is worth noting here that they are often performed as [3+3] syntheses in which, for example, an amine is heated with a β-keto ester or a β-diketone. A variation of the malonic ester synthesis, which normally produces 4-hydroxyquinol-2-ones, has been reported ⟨76ACS(B)133⟩. By using hot HMPT as solvent, it is possible to obtain 2,4-bis(dimethylamino)quinolines (**542**); some 3-substituted quinolines have been obtained by using diethyl alkylmalonates. The same products can be obtained from the dichlorodiiminium chloride (**543**) by reaction, in high dilution, with arylamines ⟨76C189⟩. A close relative of the Combes synthesis makes use of an arylamine and a chlorovinyl aldehyde ⟨70JCS(C)2488⟩. The reaction proceeds *via* dianilinium salts (**544**) and thus resembles the modified Combes synthesis in mechanism; the use of secondary arylamines gives quaternary quinolinium salts. From aniline and 2-chlorocyclohex-1-enal, 1,2,3,4-tetrahydroacridine (**545**) is obtained in 77% yield. Another synthesis of 2,2-dimethyl-1,2-dihydroquinolines makes use of arylaminoacetylenes (**546**) ⟨62JOC4713⟩; in the example shown the arylamine and chloromethylacetylene are heated together to give a 4-vinyl derivative (**547**) ⟨74MIP20800⟩, but in early cases the preformed arylaminoalkyne was cyclized with an amine hydrochloride, copper(I) chloride, and copper bronze. Tetrahydrobenzo- and naphtho-quinolines can be prepared in modest yields by heating together an arylamine, its hydrochloride, tin(IV) chloride, and 2-hydroxymethylcyclohexanone. Thus, anilines give tetrahydrophenanthridines (**548**) ⟨37JCS1169⟩ while β-naphthylamine gives, in roughly equal proportion the tetrahydrobenzacridine (**549**) and tetrahydrobenzophenanthridine (**550**) ⟨37JCS1526⟩. Maleates and fumarates react with *o*-iodoanilines and palladium(II) acetate to give 2-oxoquinoline-4-carboxylates (**551**) ⟨78JOC2952⟩; iodobenzene reacts with *o*-aminocinnamic acid to give 4-phenylquinol-2-one, but this is clearly a six-atom cyclization.



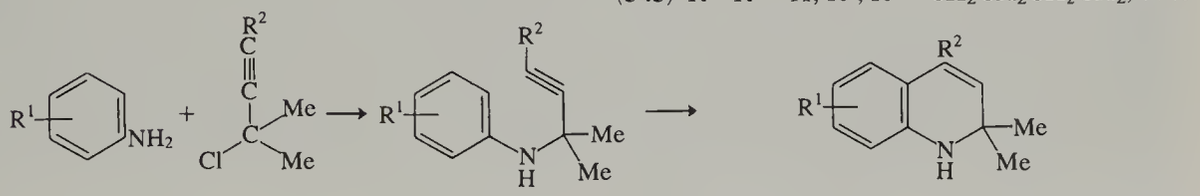
(**543**)

(**542**)	R^1	H	H	H	H	H	Et
	R^2	6-Me	6-MeO	6-Cl	8-MeO	H	H
	%	25	26	29	25	30	5



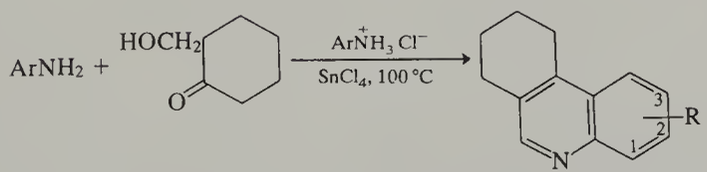
(**544**)

(**545**) R = R^3 = H; R^1, R^2 = $CH_2CH_2CH_2CH_2$, 77%

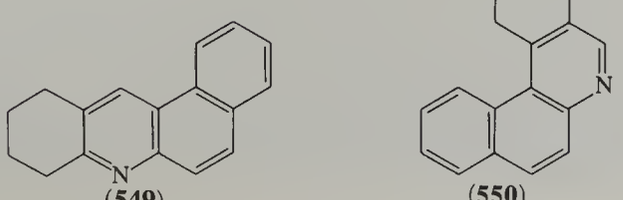


(**546**)

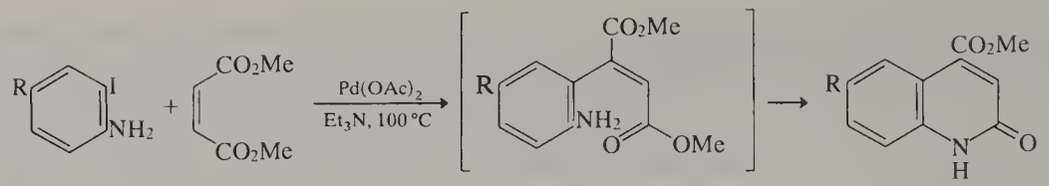
(**547**) R^2 = CH=CH_2; R^1 = H, 6-Me, 8-Me



(**548**)	R	H	3-Me	3-Br	3-MeO
	%	20	27	23	34



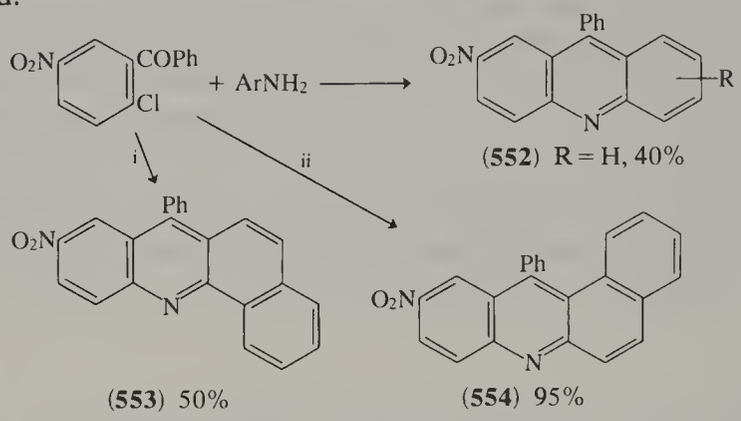
(**549**) (**550**)



(**551**) R H Br OH
% 71 55 33
From fumarate R = H, 47%

(iii) Two fragments each containing an aromatic ring

The only general synthesis in this category is that due to Ullmann, in which 2-chloro-5-nitrobenzophenone reacts with arylamines at 150–200 °C to give acridines (**552**) or benzacridines (**553**) and (**554**) ⟨06CB298⟩. The reaction can be done in two stages, heating first with potassium hydroxide to give the 2-arylamino-5-nitrobenzophenone, with subsequent cyclization by acid.



(**552**) R = H, 40%

(**553**) 50%

(**554**) 95%

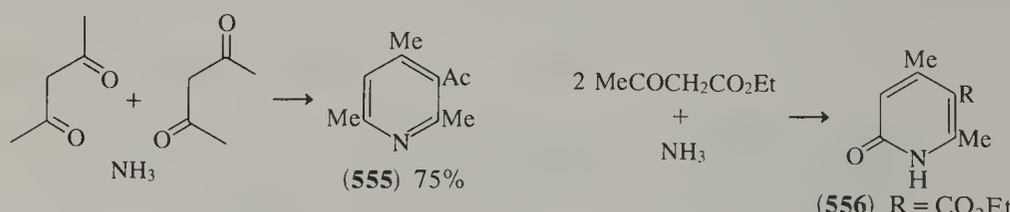
i, α-naphthylamine; ii, β-naphthylamine, $PhNO_2$, 205 °C

2.08.2.3 Formation of Three Bonds

2.08.2.3.1 From fragments containing one, two, and three atoms

(i) Syntheses using ammonia or simple amines to produce pyridines

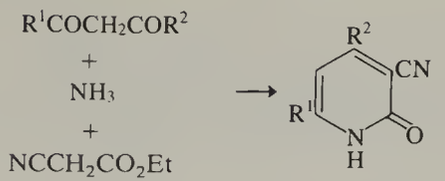
The syntheses in this section are often variations on the Hantzsch synthesis (Section 2.08.2.4.2.i), many of the early examples being due to Guareschi. Many examples are given in reviews, one being especially detailed ⟨60HC(14-1)355⟩; there is another general review ⟨72CR1⟩, and one concerned with calcium antagonists which are 1,4-dihydropyridines ⟨81AG(E)762⟩. The simplest cases are those in which there is only one component other than ammonia; thus, pentane-2,4-dione acts as a β-diketone and as a simple ketone in the synthesis of the acetyltrimethylpyridine (**555**) ⟨47CB502⟩. Similarly, ethyl acetoacetate and ammonia gave 4,6-dimethylpyrid-2-one, presumably *via* the intermediate (**556**) ⟨02JCS100⟩.



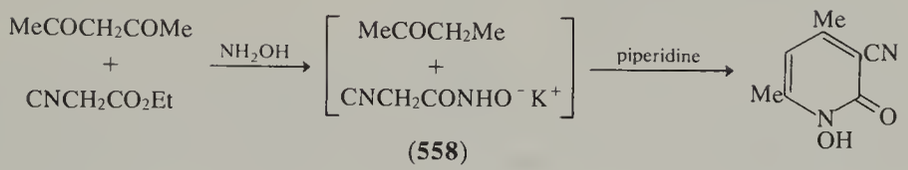
(**555**) 75%

(**556**) R = CO_2Et

A number of variations are possible in which 1,3-diketones condense with a second component which has an active methylene group, the ring being completed by ammonia. In one of the simpler versions, 1,3-diketones and ethyl cyanoacetate give excellent yields of 3-cyanopyrid-2-ones (**557**) under mild conditions ⟨1898MI20800, 55AP174⟩. Hydroxylamine has been used to give 3-cyano-1-hydroxypyrid-2-ones (**559**); the reaction can be done directly ⟨71JCS(C)2044⟩ but the yield is better if the intermediate (**558**) is isolated ⟨74JCS(P1)327⟩. Replacement of ethyl cyanoacetate by malononitrile can give 2-amino-3-cyanopyridines; the two routes are illustrated by the synthesis of the tetrahydroquinolines (**560**) and (**561**) ⟨55AP174⟩. A unique synthesis is that of the 3-hydroxypyrid-2-one (**562**) from chloroacetone, diethyl ketosuccinate, and ammonia in ether ⟨02CB1545⟩.

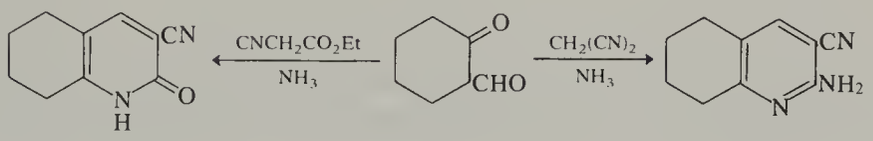


(**557**) $R^1 = R^2 = Me$, 85–90%
$R^1 = Ph$, $R^2 = Me$

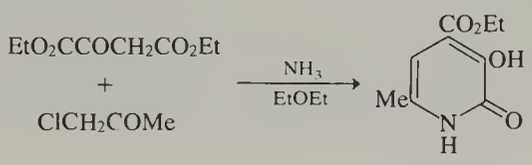


(**558**)

(**559**)



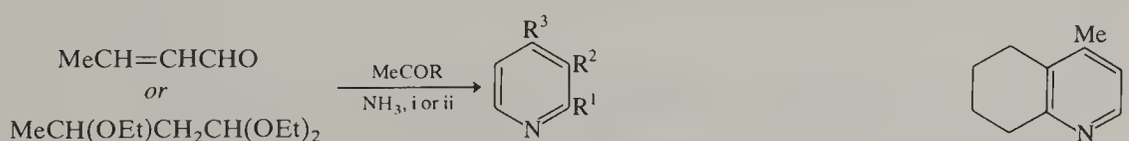
(**560**) (**561**)



(**562**)

There are a very large number of patented processes for the synthesis of pyridines, often in very small yields, from ketones and ammonia. Most of the syntheses must involve the condensation of two molecules of the carbonyl compound to give an α,β-unsaturated aldehyde or ketone, and such unsaturated compounds can be used directly. The early work on the vapour-phase catalytic processes dates from the 1920s and a series of papers by Chichibabin. In one of these ⟨24JPR(107)154⟩ he records the use of acrolein, acetaldehyde, and ammonia over an alumina catalyst at 370–380 °C to give a poor yield of pyridine and a very poor yield of 3-methylpyridine. The major problems are to separate the mixtures of products from the considerable amount of tarry material. Many catalysts and many mixtures of ketones have since been used; a few of the better yields are reported here.

Crotonaldehyde and acetaldehyde with ammonia over a silica–alumina catalyst at 400 °C are reported to give mainly 3,4-dimethylpyridine (**563**) ⟨62BRP898869⟩, while formaldehyde and acrolein produce up to 67% of pyridine ⟨66BRP1038537⟩. Strictly speaking this should be classified as the sole representative of the [4 + 1 + 1] type of cyclization. The protected crotonaldehyde (**564**) with acetone and ammonia over cadmium phosphate give 2,4-dimethylpyridine (**565**) ⟨60YZ784⟩. By a similar process, the tetrahydroquinoline (**566**) is obtained from cyclohexanone ⟨60YZ784⟩. Phenylacetaldehyde, acrolein and ammonia, at 460 °C over a fluidized bed of mixed catalyst, are reported to give 65% of 3-phenylpyridine (**567**) ⟨79BRP2020270⟩. Ishiguro and his coworkers have used mixtures of allyl alcohol, ketones and ammonia, mainly on cadmium phosphate catalysts, to give mixtures of 2,3-disubstituted pyridines (**568**) ⟨55YZ1496, 58YZ216, 60JAP6006382⟩. Pentan-3-one and ammonia are reported to react over a platinum–silica catalyst to give 2,6-diethyl-3-methylpyridine (**569**) in 90% yield; the intermediate pent-1-en-3-one is formed by dehydrogenation ⟨76CC1038⟩. Acrolein, acetylene and ammonia are also reported to give pyridine, although pyridine was still formed when acrolein was omitted ⟨54YZ1009⟩.

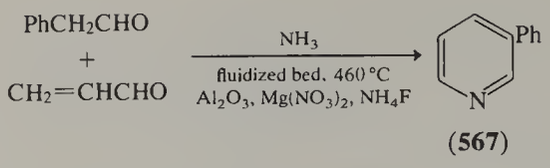


(**564**)

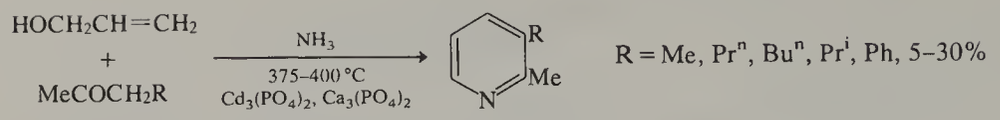
i, silica-alumina, 400 °C;
ii, $Cd_3(PO_4)_2$, 350–400 °C

(**563**) $R^1 = H$, $R^2 = R^3 = Me$
(**565**) $R^1 = R^3 = Me$, $R^2 = H$, 42%
$R^1 = R^2 = Me$, $R^3 = H$, 35%
$R^1 = Ph$, $R^2 = H$, $R^3 = Me$, 31%

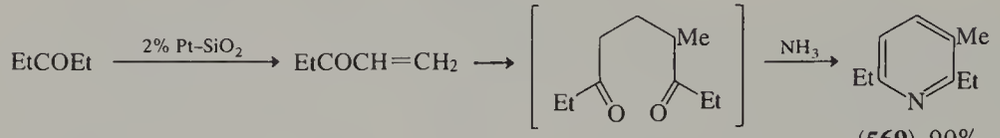
(**566**)



(**567**)

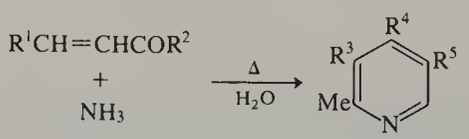


(**568**)

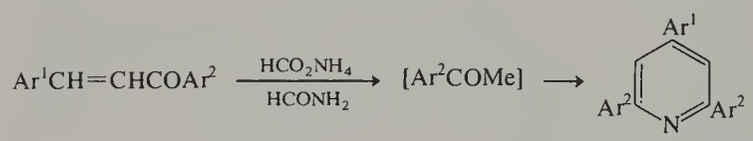


(**569**) 90%

In contrast to these vapour-phase reactions, it has been reported that ketones and aqueous ammonia (or ammonium acetate) in an autoclave give less complex mixtures of pyridines. Crotonaldehyde gives 5-ethyl-2-methylpyridine (**570**) in up to 59% yield, methyl vinyl ketone gives 2,3,4-trimethylpyridine (**571**) rather than 2,3,6-trimethylpyridine; 1,3,3-trimethoxybutane has been used in place of methyl vinyl ketone ⟨49JA2629⟩. In some cases reverse aldol reactions occur (for example with benzalacetophenone) giving unwanted products. A similar reverse aldol is responsible for the production of triarylpyridines (**572**) when benzalacetophenones are treated with formamide and ammonium formate ⟨73JA4891⟩.

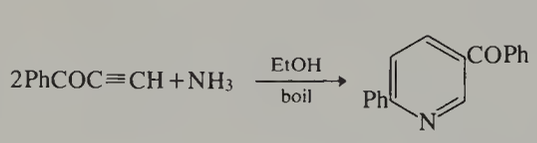


(**570**) $R^3 = R^4 = H$, $R^5 = Et$, 59%
(**571**) $R^3 = R^4 = Me$, $R^5 = H$

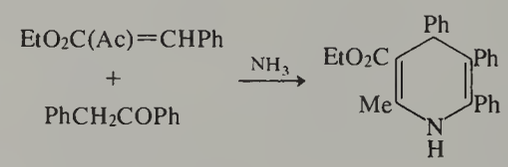


(**572**) Ar^1 = Ph, 4-$MeOC_6H_4$, Ar^2 = 4-$MeOC_6H_4$, Ph, 30–33%

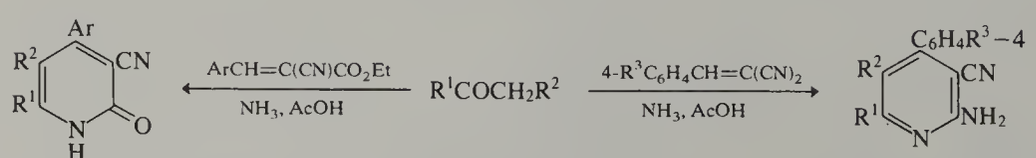
With more reactive unsaturated ketones better yields can be obtained in liquid phase reactions. Benzoylacetylene reacts with ammonium carbonate in aqueous alcohol to give, in good yield, 5-benzoyl-2-phenylpyridine (**573**) ⟨46JCS953⟩. Simple ketones react with α,β-unsaturated ketones to give 1,4-dihydropyridines (**574**) ⟨1894LA(281)25⟩, with arylidene cyanoacetates to give pyrid-2-ones (**575**) ⟨77S841⟩, and with arylidenemalononitriles to give 2-amino-3-cyanopyridines (**576**) ⟨80S366⟩; in the latter two cases ammonium acetate was used. A very detailed review is available ⟨76S1⟩ of the process in which a pyridinium ketone reacts with an α,β-unsaturated ketone and ammonium acetate to give 2,4,6-trisubstituted pyridines as in equation (66). The synthesis can be modified to give 2-carboxypyridines or pyrid-2-ones by using arylidene crotonates or pyridinium acetates respectively.



(**573**) 58%

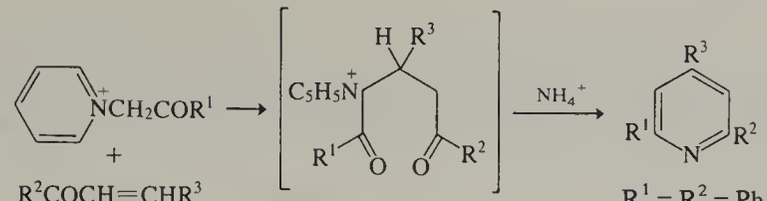


(**574**)



(**575**) R^1 = Me, 4-$MeOC_6H_4$;
R^2 = H, Me;
R^3 = various 3- or 4-C_6H_4; 21–53%

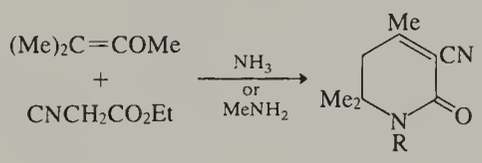
(**576**) R^1 = Me, Bu^i, Ph;
R^2 = H, Me;
R^3 = H, Me, MeO; 39–74%



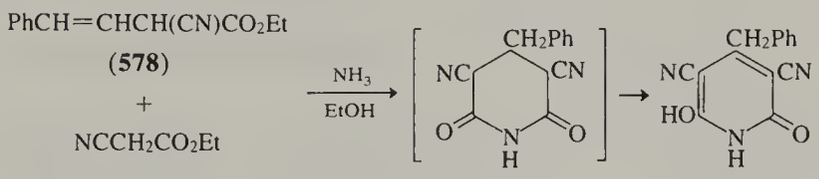
(66)

$R^1 = R^2 = Ph$, $R^3 = H$, 82%
$R^1 = R^2 = R^3 = Ph$, 92%
$R^1 = Me$, $R^3 = 2$-furyl, $R^2 = CO_2H$, 53%

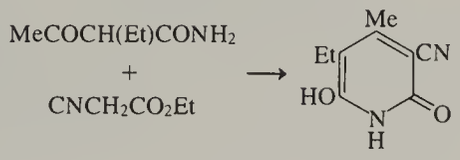
Guareschi reported the formation of 5,6-dihydropyrid-2-ones (**577**) from mesityl oxide, ethyl cyanoacetate, and ammonia (or methylamine) ⟨1893MI20800⟩. The double bond can be in the β,γ-position in the starting material if sufficient activation is available to allow the equilibration; ethyl cyanoacetate, ammonia and the cyanoacetate (**578**) gave a highly substituted pyrid-2-one ⟨26JCS2735⟩. The synthesis of 6-hydroxypyrid-2-one (**579**) was reported by Guareschi, using an acetoacetamide, cyanoacetate and ammonia ⟨1896MI20800⟩. Hurd and Kelson report that acetoacetyl chloride reacts with aniline at room temperature to give 2,6-dimethyl-4-oxo-1-phenylpyridine-3-carboxylic acid (**580**) ⟨40JA1548⟩; it seems very likely that this product is derived from dehydroacetic acid, known to be formed from acetoacetyl chloride on standing.



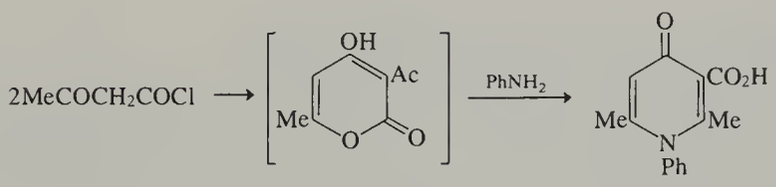
(**577**) R = H, Me



55%



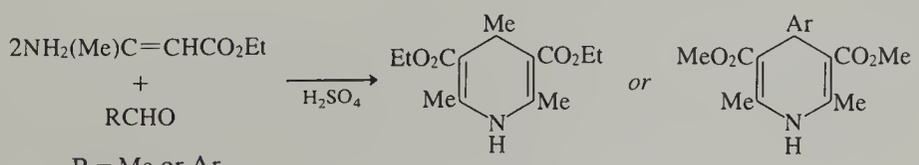
(**579**)



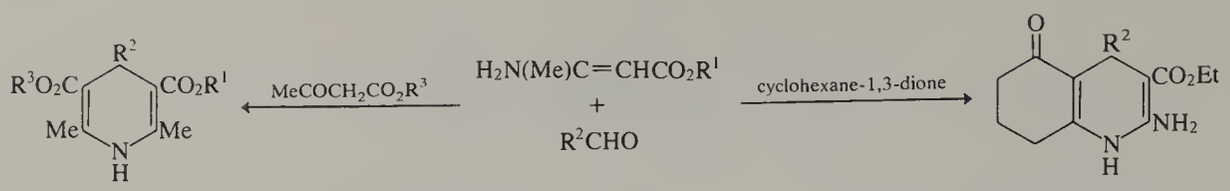
(**580**)

(ii) Syntheses using enamines or amidines as the source of nitrogen

Aldehydes condense with β-aminocrotonates to give 1,4-dihydropyridines. Collie used sulfuric acid as the condensing agent with paraldehyde to give compound (**581**) ⟨1884LA(226)294⟩, but the reaction will occur in boiling aqueous methanol with *o*-nitrobenzaldehyde to give compound (**582**) ⟨80JAP(K)8002652⟩. It is possible to use acetoacetate and aminocrotonate to condense with aldehydes, forming the unsymmetrical 1,4-dihydropyridines (**583**), without much contamination from the symmetrical products of type (**582**) ⟨72GEP2117573⟩; similarly cyclohexanedione gives tetrahydroquinolin-5-ones (**584**) ⟨76USP3946026⟩.



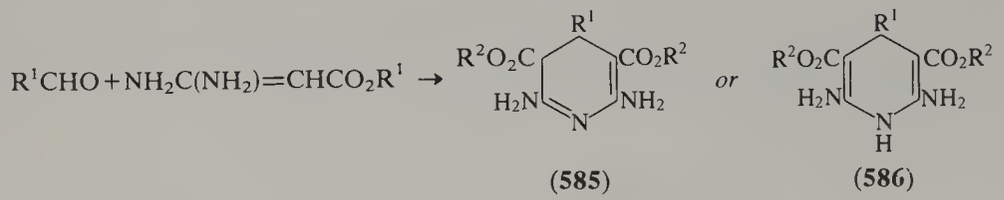
(**581**) (**582**) 85%, Ar = 2-$O_2NC_6H_4$



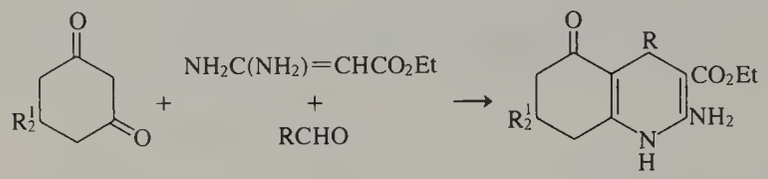
(**583**) 42–75%

(**584**) R^2 = 4-quinolyl, 2-pyridyl, *etc.*

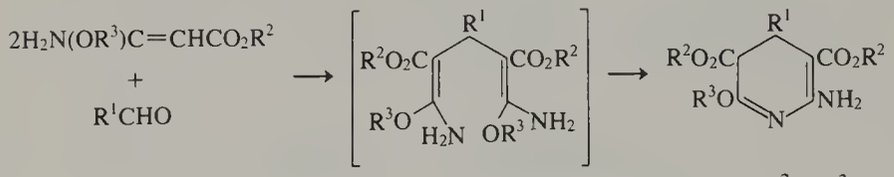
Amidines condense with aldehydes to give 3,4-dihydro- (**585**) and/or 1,4-dihydropyridines (**586**) ⟨78LA1483⟩. The formation of 3,4-dihydropyridines is thought to be due to steric interactions, the 4-(*o*-nitro) derivative being entirely in the form (**585**; R^1 = *o*-$O_2NC_6H_4$). When an *N*,*N*-dimethylamidine is used a 6-amino-2-dimethylamino-4,5-dihydropyridine is obtained, but the yields are poor. Cyclohexane-1,3-diones react with amidines to give 1,4,7,8-tetrahydroquinolin-5(6*H*)-ones (**587**) ⟨77LA1895⟩. Imino ethers condense with aldehydes to give 2-alkoxy-6-amino-3,4-dihydropyridines (**588**) ⟨76LA1762⟩.



(**585**) (**586**)



(**587**) R^1 = H, R = 2-pyridyl, 93%



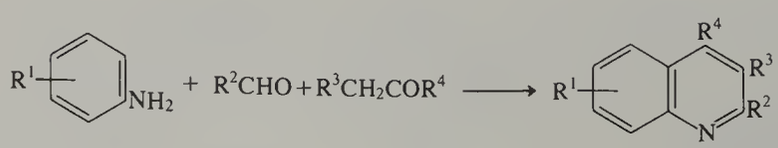
(**588**) $R^2 = R^3$ = Et

R^1	Me	Ph	2-py	4-py	various
%	44	51	46	45	26–56

(iii) Syntheses using arylamines and two acyclic fragments

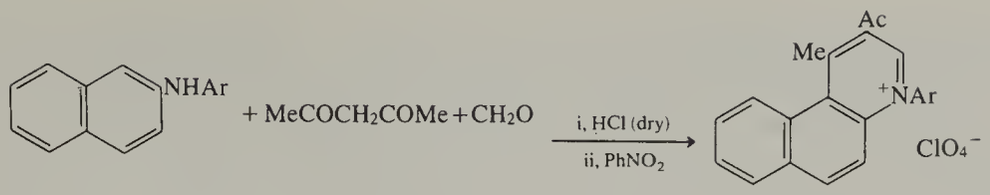
In the original Doebner–von Miller synthesis of quinolines an arylamine condenses with two molecules of an aldehyde; most of the variants have been dealt with in Section 2.08.2.2.3.ii since the intermediate (often used directly) is an α,β-unsaturated aldehyde. Two further major variations, the Beyer modification and the Doebner cinchoninic acid synthesis, will be dealt with here, since intermediates are rarely isolated.

Beyer discovered that a mixture of an aldehyde and a ketone could be used to give 2,4-di- or 2,3,4-tri-substituted quinolines, if the difference in reactivity was sufficient ⟨1886JPR(33)393⟩. The commonest carbonyl compounds used are acetone or acetophenone (both unambiguous), and formaldehyde is particularly useful, giving quinolines with no substituent in position 2. The general reaction is given in equation (67). The usual procedure is to allow the aldehyde and ketone to stand with dry hydrogen chloride (presumably to form the α,β-unsaturated ketone) and then to add amine, concentrated hydrochloric acid, and, possibly, an oxidizing agent such as nitrobenzene. Secondary aromatic amines give quaternary quinolinium salts ⟨62MIP148412⟩; naphthylamines give benzoquinolinium salts (**589**) ⟨72ZOB420⟩.



(67)

R^2 = H, alkyl, aryl; R^3 = H, alkyl; R^4 = alkyl, aryl



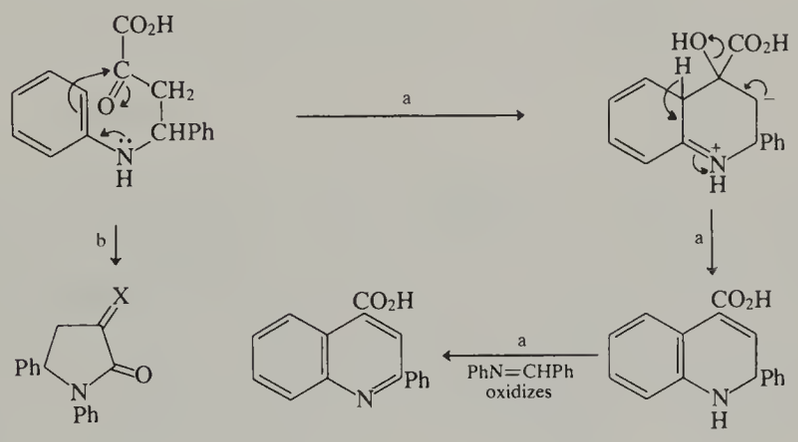
(**589**) Ar = Ph, 4-RC_6H_4

The cinchoninic acid synthesis, originally discovered by Böttinger ⟨1883CB2357⟩ but fully developed by Doebner ⟨1887CB277⟩, comes from the discovery that pyruvic acid and aniline condenses to give 2-methylcinchoninic (2-methylquinoline-4-carboxylic) acid. Doebner's deduction that some pyruvic acid decarboxylated to give acetaldehyde led to the generalization in which an aldehyde, pyruvic acid and an aromatic amine boiled in alcoholic solution give 2-substituted quinoline-4-carboxylic acids (which can readily be decarboxylated). The reaction has been reviewed ⟨77HC(32-1)125⟩, so an outline will suffice. The synthesis is particularly suitable for the production of 2-arylquinoline-4-carboxylic acids, and the accepted mechanism is given in the Scheme 7. Significant contributions to the establishment of the mechanism were made by Garzarolli-Thurnlakh, ⟨1899CB2274⟩ by Bodforss ⟨27LA(455)41⟩ and by Bücherer and Russischwili ⟨30JPR(128)29⟩. A major byproduct can be the dioxopyrrolidone (**590**) or its anil (**591**), and it can be seen that intermediate (**592**) can cyclize in either of two ways (*a* or *b*) to give the two major products. Quinoline formation is maximized in alcohol, dioxopyrrolidine formation in ether, or in the presence of mineral acids. Very reactive amines give quinolines under all conditions, very unreactive amines (nitroanilines) always give dioxopyrrolidines.

$$PhNH_2 + PhCHO \rightarrow PhN{=}CHPh$$

$$PhN{=}CHPh + MeCOCO_2H \rightarrow PhCH(NHPh)CH_2COCO_2H$$

(**592**)

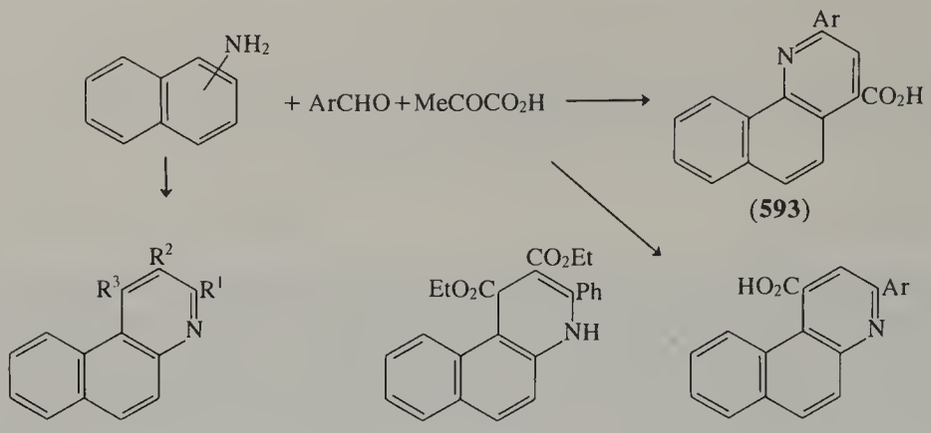


(**590**) X = O
(**591**) X = NPh

Scheme 7

The various modifications of the synthesis are illustrated here by the synthesis of benzoquinolines, since these are not dealt with in the quoted review. With aromatic aldehydes and pyruvic acid, 1- and 2-naphthylamine give respectively benzo[*h*]- (**593**) and benzo[*f*]- (**594**) quinolinecarboxylic acids ⟨1894CB352, 04CB1742⟩. Glyoxylic acid, pyruvic acid and 2-naphthylamine give the dicarboxylic acid (**595**) ⟨01LA(317)147⟩, and substituted pyruvic acids give 2-substituted benzo[*f*]quinoline-1-carboxylic acids (**596**) ⟨09CB4072⟩. Oxaloacetate, benzaldehyde and 2-naphthylamine give benzo[*f*]quinoline-1,2-dicarboxylate (**597**), with some of the dihydro derivative (**598**), presumed to be the normal intermediate ⟨08MI20800⟩. When oxaloacetic acid is used some decarboxylation occurs from position 2. Substituted pyruvic acids usually give much reduced yields with aniline. In all these reactions the exclusive formation of angular benzoquinolines from 2-naphthylamine should be noted.

There are a few routes to quinolines which can be viewed as modified Doebner–von Miller syntheses. When 4-alkoxydiphenylamines are treated with enol ethers or esters it is reported that *N*-(4-alkoxyphenyl)-2-methylquinolinium salts (**599**) are obtained ⟨79ZOR1299⟩; the alkoxy group must have an adverse effect on the cyclization. Arylamines

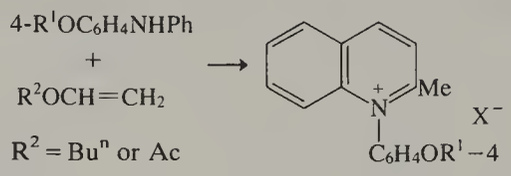


(**595**) $R^1 = R^3 = CO_2H$; $R^2 = H$
(**596**) R^1 = H, aryl; R^2 = aryl, benzyl; $R^3 = CO_2H$
(**597**) R^1 = Ph; $R^2 = R^3 = CO_2Et$

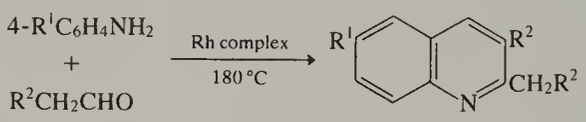
(**598**)

(**594**) Ar = Ph, 4-$Me_2NC_6H_4$

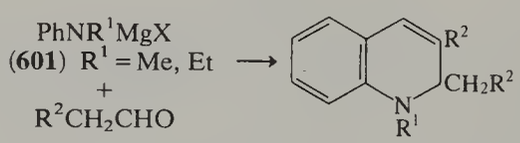
are also reported to react with aliphatic aldehydes at 180 °C in the presence of a rhodium complex to give 2,3,6-trisubstituted quinolines (**600**) ⟨79CL1025⟩. Two syntheses involve the anion of an aromatic amine. The anilinomagnesium halides (**601**) react with aldehydes of general structure RCH_2CHO to give 1,2,3-trisubstituted 1,2-dihydroquinolines (**602**) ⟨74T2695⟩. Solutions of these dihydroquinolines can be oxidized by oxygen to give quinolinium salts, but on heating with oxygen they give mixtures of 2- and 4-quinolones. When treated with tin(IV) chloride in boiling toluene, and then with phenylacetylene, lithium anilides give 2-methyl-2,4-diphenyl-1,2-dihydroquinolines (**605**) ⟨81S975⟩. The mechanism is thought to involve the metal complexes (**603**) and (**604**); only phenylacetylene could be used.



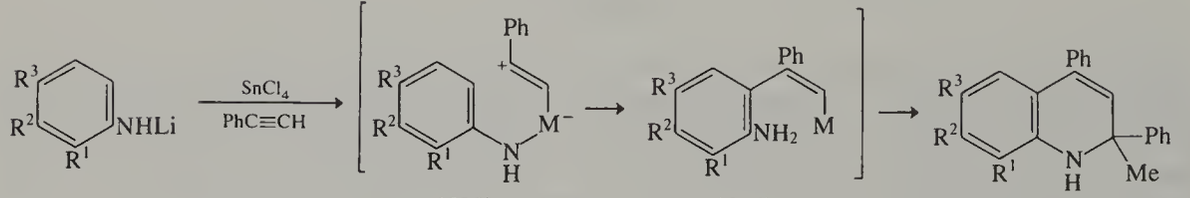
(**599**) R^1 = Me, Et, Pr^n, Pr^i, Bu^n



(**600**) R^1 = H, MeO; R^2 = H, Me, Et; 30–82%



(**602**) *e.g.* $R^1 = R^2$ = Me, 62%

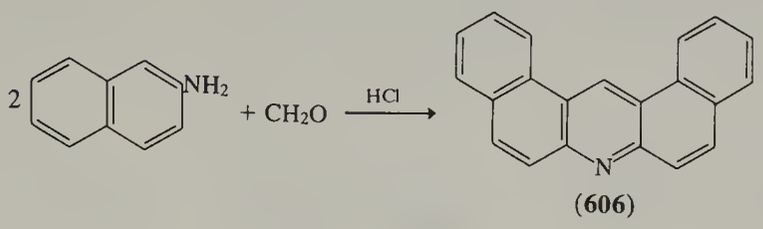


(**605**) $R^1 = R^2 = R^3$ = H, 40%; others, 30–50%

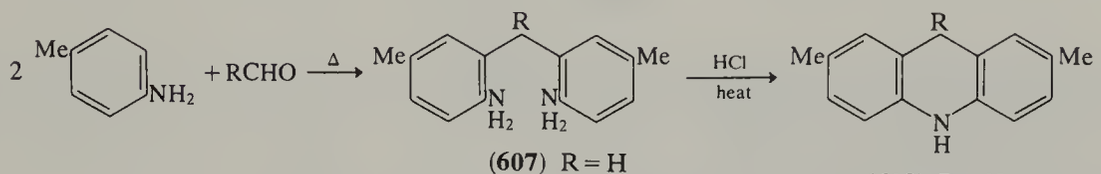
(iv) Syntheses using two aromatic and one acyclic fragment

A very important group of syntheses which produce acridines (or acridans), and benzologues of acridine are of this general type. One aromatic fragment is always an arylamine, the acyclic fragment can be an aldehyde or ketone, a carboxylic acid, or a dihalomethane. Morgan, in 1898, reported that 2-naphthylamine, paraformaldehyde, and hydrochloric acid, heated in a sealed tube, gave a dibenzacridine ⟨1898JCS536⟩. The structure of the product, dibenz[*a*,*h*]acridine (**606**), was established later ⟨02CB4164⟩, and Ullmann showed that *p*-toluidine hydrochloride and formaldehyde at 200 °C gave 2,2′-diaminodiphenylmethane

(**607**) which could be cyclized by acid to the acridan (**608**) ⟨03CB1017⟩; the acridan was oxidized by iron(III) chloride to the acridine. Ullmann also used benzaldehyde, with a mixture of *p*-toluidine and its hydrochloride, to give a mixture of acridan (**609**) and acridine (**610**) (35:65).Ullmann also established that the acridan can be obtained by heating an anil with the aromatic amine and its hydrochloride. The formation of the diphenylmethane is reversible, so that the product (**611**) from 2,4-diaminotoluene can be converted into the unsymmetrical acridan (**612**) by heating it with *p*-toluidine and *p*-toluidine hydrochloride ⟨03CB1017⟩.

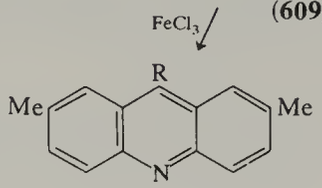


(**606**)

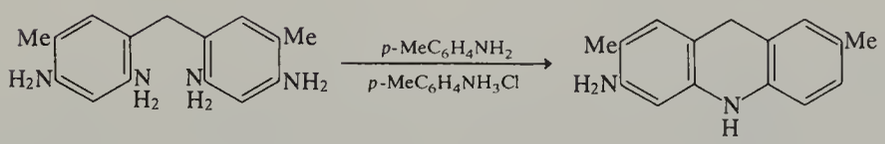


(**607**) R = H

(**608**) R = H
(**609**) R = Ph

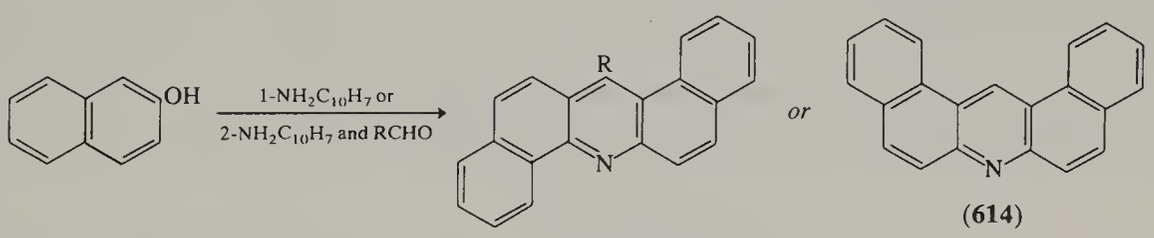


(**610**) R = Ph



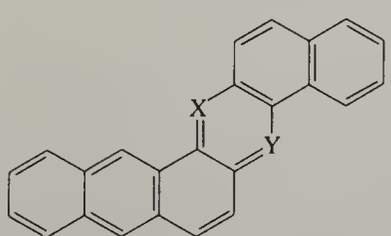
(**611**) (**612**)

Ullmann and Fetvadjian reported the modification which made the synthesis more generally useful, when they heated together equimolar amounts of an aromatic amine and a phenol with paraformaldehyde or with benzaldehyde, thus making it possible to obtain unsymmetrical acridines ⟨03CB1027⟩. Thus, from 2-naphthol and 1-naphthylamine they obtained dibenzo[*c*,*j*]acridine (**613**), and from 2-naphthol and 2-naphthylamine dibenzo[*c*,*h*]acridine (**614**). In a similar manner, from 1-aminoacridine and the two naphthols are obtained the benzo[*a*]- and benzo[*c*]-naphtho[2,3-*h*]acridines (**615**) and (**616**), and from 2-aminoacridine and the naphthols the benzo[*a*]- and benzo[*c*]-naphtho[2,3-*j*]acridines (**617**) and (**618**) ⟨69JCS(C)1337⟩. The isomeric benzo[*a*]- and benzo[*c*]-

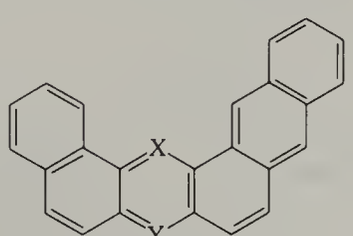


(**613**) R = H or Ph

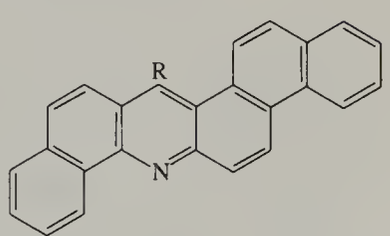
(**614**)



(**616**) X = N, Y = CH
(**617**) X = CH, Y = N

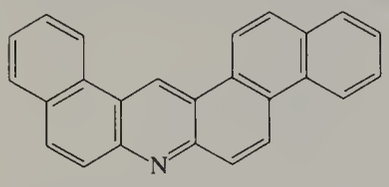


(**615**) X = N, Y = CH
(**618**) X = CH, Y = N

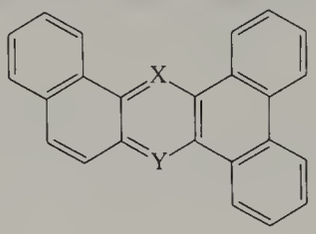


(**619**) R = H, Me

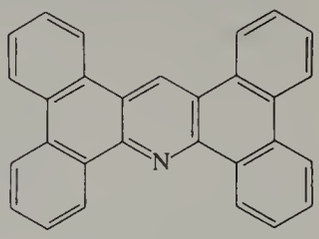
naphtho[1,2-*j*]acridines (**619**) and (**620**) were obtained from 2-aminophenanthrene, and the tribenzacridines (**621**) and (**622**) from 9-aminophenanthrene. It is noteworthy that in the latter two cases the major product was tetrabenzo[*a*,*c*,*h*,*j*]acridine (**623**), from two molecules of 9-phenanthrylamine ⟨67JCS(C)665⟩. In all cases where an amino polycycle could give two isomers, only the angular fusion is found. If the conjugation of the polycycle is interrupted, as in aminofluorene, a mixture of isomers can be obtained ⟨70JHC155⟩.



(**620**)

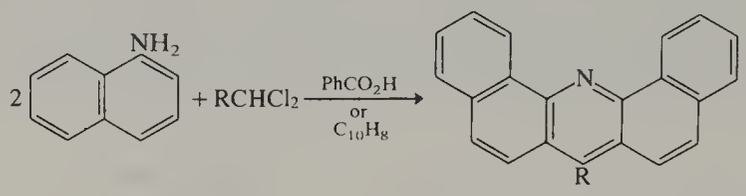


(**621**) X = N, Y = CH
(**622**) X = CH, Y = N



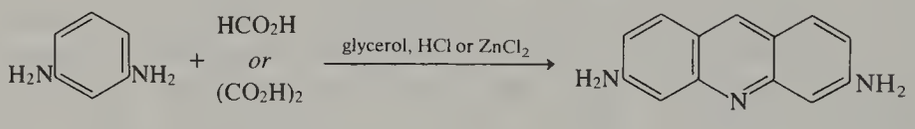
(**623**)

The methine bridge in acridines can be derived from dihalomethanes. Originally sodium carbonate was used, with dichloro- or diiodo-methane, to prepare dibenzacridine (**624**) from 2-naphthylamine ⟨02JCS280⟩. Subsequently, better yields were obtained when dichloromethane, 1,1-dichloroethane or benzal chloride, 1-naphthylamine, and a solvent were heated, the products being dibenz[*c*,*h*]acridines (**624**) ⟨06JCS1387⟩.



(**624**) R = H, Me, Ph

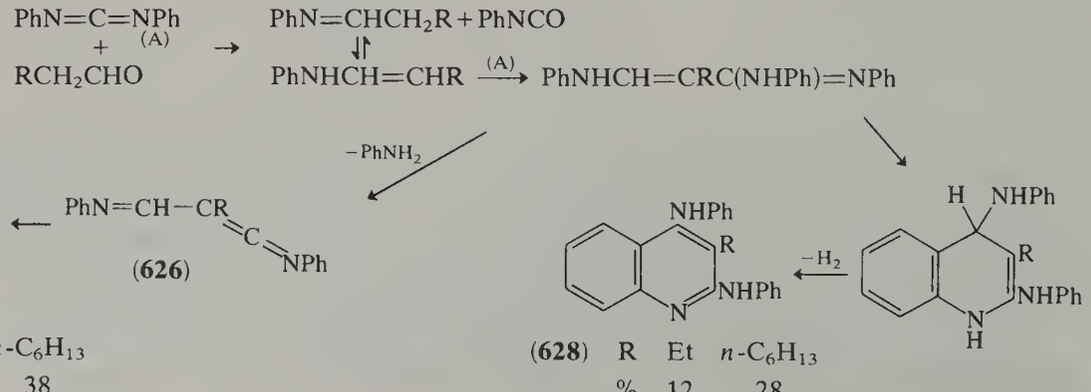
With *m*-phenylenediamines, a mixture of oxalic acid, glycerol and zinc chloride ⟨41JCS121⟩, or of formic acid, hydrochloric acid and glycerol ⟨41JCS484⟩, will give good yields of derivatives of proflavine (3,6-diaminoacridine) (**625**). The mechanism has been investigated, and the bis(3,5-diaminophenyl)methanol or its anhydride is thought to be an intermediate.



(**625**)

(*v*) *Miscellaneous syntheses*

There are two reactions in which an aliphatic aldehyde provides the two-carbon fragment while a benzene derivative provides both three-atom and one-atom fragments. In the first, diphenylcarbodiimide reacts with an aldehyde to give a 3-substituted 4-anilinoquinoline (**627**) and a 3-substituted 2,4-dianilinoquinoline (**628**) ⟨74JOC3516⟩, by the mechanism shown. In the second, phenyl isocyanate and an aldehyde react in benzene at 200 °C to give the same product (**627**) together with a uracil and *sym*-diphenylurea ⟨76JCS(P1)1597⟩; the intermediate (**626**) has been invoked in this reaction also.



R	Me	Et	*n*-C_6H_{13}
%	34	30	38

(**628**)

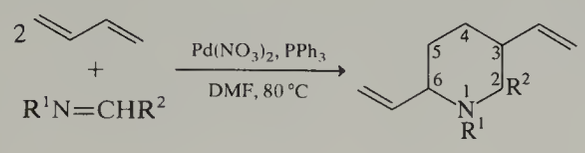
R	Et	*n*-C_6H_{13}
%	12	28

2.08.2.3.2 From three two-atom fragments

The number of syntheses of this type is limited, and are best summarized as catalytic or non-catalytic.

(i) Metal-catalyzed cyclizations

Piperidines (**629**) can be made from butadienes and benzaldimines, by use of palladium(II) nitrate and triphenylphosphine in DMF; for the case where $R^1 = Me$, $R^2 = Ph$, four stereoisomers were isolated by GLC and the structures determined by NMR, the major products being (2r,3-*trans*-6-*cis*) (45% of total isomers), and (2r,3-*cis*-6-*cis*) (40%) ⟨74CC506⟩.



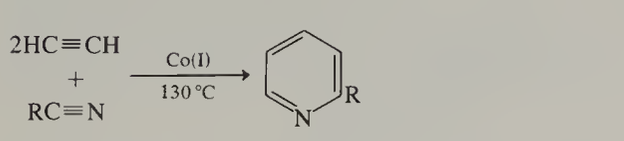
(**629**)

R^1 = Me, Et, allyl; R^2 = Ph
R^1 = Me, R^2 = Ph, 73%

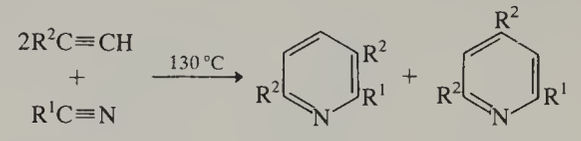
Configuration relative to R^2

3	6	%
trans	*cis*	45
cis	*cis*	40
trans	*trans*	9
cis	*trans*	6

Much work has been done on the cobalt(I)-catalyzed cooligomerization of nitriles and alkynes; there is a detailed review ⟨78AG(E)505⟩. The synthesis is most successful when unambiguous; if acetylene and a nitrile are used a 2-substituted pyridine is obtained. The major competing reaction is the formation of benzene, and this can be minimized by using an excess of nitrile and keeping the concentration of acetylene low. Thus 2-substituted pyridines (**630**) are obtained in yields of 90–97% (based on the nitrile) ⟨60BCJ425⟩. Cobalt(I) catalysts can be prepared *in situ*, and such catalysts have been used with substituted alkynes to give mixtures of 2,3,6- (**631**) and 2,4,6- (**632**) trisubstituted pyridines in a one-pot reaction ⟨74S575⟩. If mixtures of acetylene and a substituted alkyne are used still more isomers are produced, as, for example, 2,3-, 2,4-, and 2,6-dimethylpyridines from acetylene, methylacetylene, and acetonitrile. A mechanism for the production of 2-substituted pyridines is shown in Scheme 8. In a similar reaction, alkynes react with isocyanates to give pyrid-2-ones (**633**) and (**634**), and with diphenylcarbodiimide to give 2-phenyliminopyridines (**635**) and (**636**) ⟨77TL1333⟩.

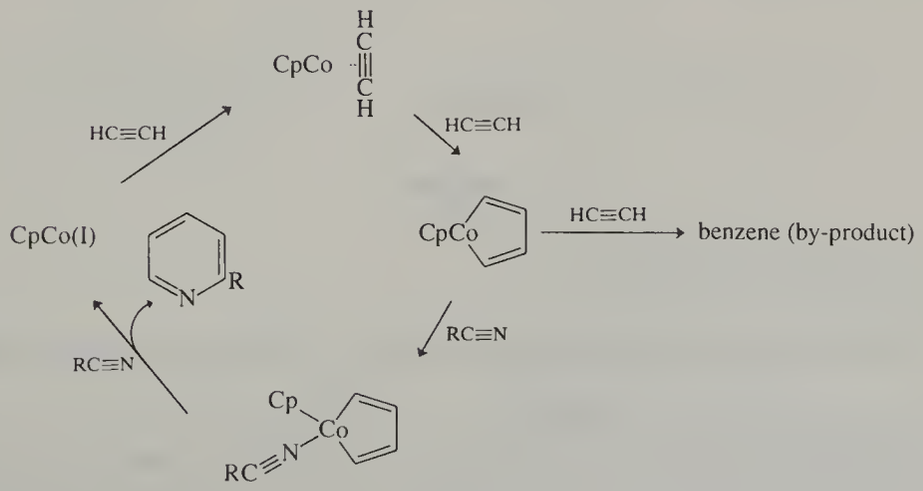


(**630**) R = alkyl, CH=CH$_2$, Ph

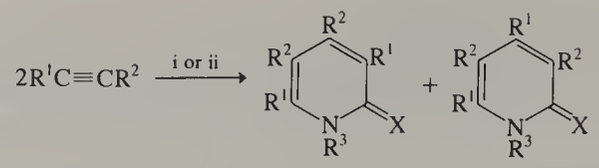


(**631**) (**632**)

R^1	R^2	% (**632**)	% (**631**)
Me	Me	30	40
Me	C_5H_{11}	20	38
Ph	Me	17	37



Scheme 8

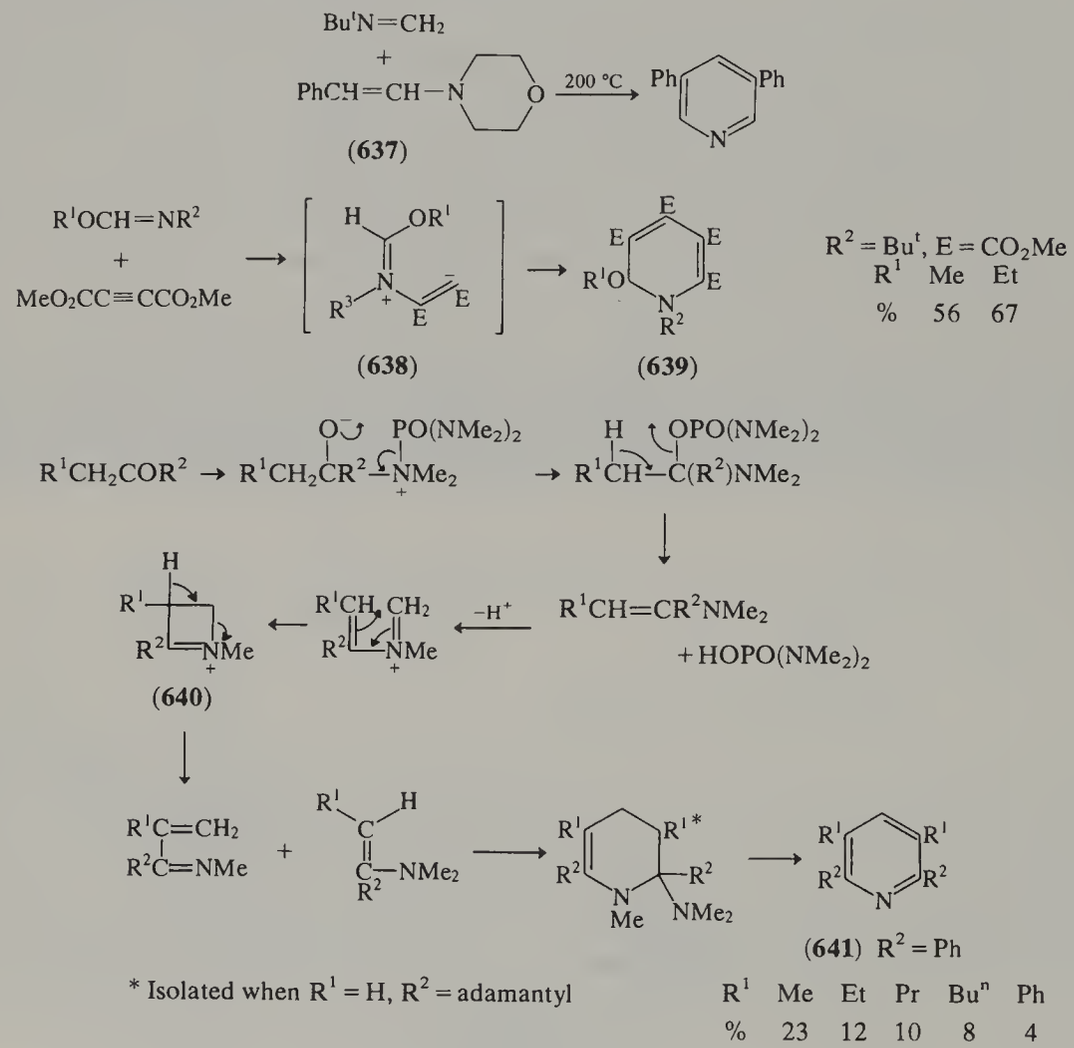


(**633**) X = O (**634**) X = O
R^1 = Ph, R^2 = CO_2Me, 40% and 26%
(**635**) X = NPh (**636**) X = NPh

i, R^3NCO, Co catalyst; ii, PhN=C=NPh, Co catalyst

(ii) Uncatalyzed condensations

The enamine (**637**) reacts with *t*-butylazomethine in benzene at 200 °C to give 3,5-diphenylpyridine ⟨76TL4589⟩. Imino ethers react with dimethyl acetylenedicarboxylate in boiling dioxan to give 2-alkoxy-1,2-dihydropyridines (**639**), presumably *via* the intermediate ylide (**638**) ⟨75JOC2360⟩. A reaction in which alkyl aryl ketones combine with hexamethylphosphoric triamide (HMPT) to give symmetrically-substituted pyridines (**641**) at first sight belongs to the category [2+2+1+1], but the mechanism shown in Scheme 9 invokes a dihydroazete (**640**) as an intermediate ⟨75T1145⟩. A variant of the reaction converts benzils into 2,3,5,6-tetraarylpyridines in low yield ⟨75JOC1672⟩.



R^2 = Bu^t, E = CO_2Me

R^1	Me	Et
%	56	67

(**638**) (**639**)

(**640**)

(**641**) R^2 = Ph

* Isolated when R^1 = H, R^2 = adamantyl

R^1	Me	Et	Pr	Bu^n	Ph
%	23	12	10	8	4

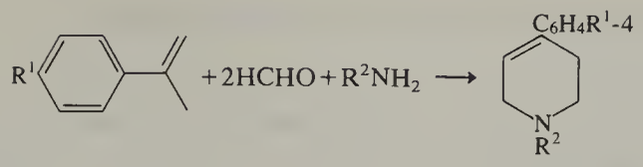
Scheme 9

2.08.2.4 Formation of Four Bonds

2.08.2.4.1 From a fragment containing three atoms, and three one-atom fragments

(i) An alkene as the three-atom fragment

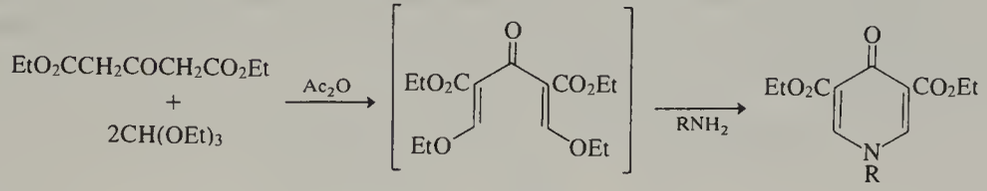
In the only example of this type of synthesis a number of α-methylstyrenes react with formaldehyde and ammonia (or a primary amine) to give 1,2,5,6-tetrahydropyridines (**642**) ⟨56JA425; 56JOC1194, 56JOC1195⟩.



(**642**) $R^1 = R^2 = Me$, 61%
$R^1 = Me$, $R^2 = Pr^i$, 39%

(ii) A ketone as the three-atom fragment

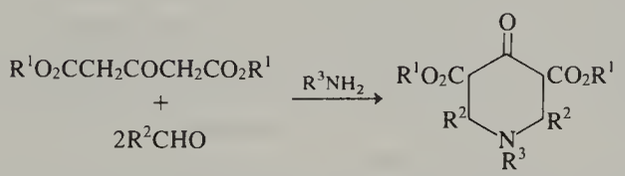
All the syntheses of this type give piperid-4-ones or pyrid-4-ones. Errera reported that diethyl acetonedicarboxylate condensed with triethyl orthoformate in hot acetic anhydride, and that treatment of the product with ammonia gave a poor yield of the pyrid-4-one (**644**) ⟨1898CB1682⟩. It is certain that the intermediate is the di(ethoxyvinyl) ketone (**643**), so that this is perhaps better classified as a [5+1] synthesis, but most developments from this beginning do not involve isolation of intermediates. An arylamine has been used to obtain an *N*-arylpyrid-4-one (**645**) ⟨46JA1253⟩.



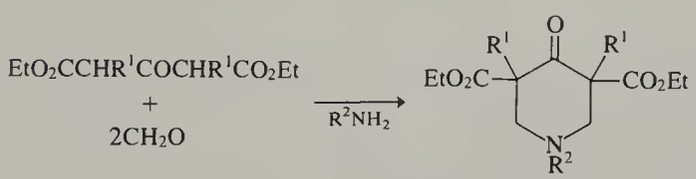
(**643**)

(**644**) R = H, poor yield
(**645**) R = 3-ClC_6H_4, 17%

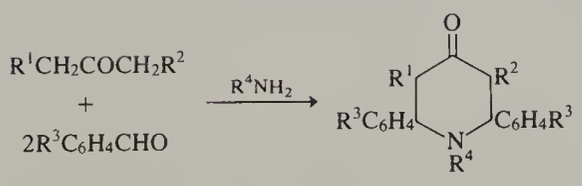
The most important development of this route was the discovery that aldehydes could be used in place of ethyl orthoformate to give piperid-4-ones of general type (**646**). In most syntheses aromatic aldehydes were used ⟨06CB1358, 09CB3683, 30CB608⟩. Formaldehyde seems to be too reactive, but can be condensed with methylamine and a diethyl 2,4-dialkyl-3-ketoglutarate to give a tetrasubstituted piperid-4-one (**647**) ⟨36CB2299⟩. Ethyl acetoacetate is reported to condense with aromatic aldehydes and ammonium acetate in acetic acid to give piperid-4-one-3-carboxylates (**648**), although formaldehyde gave the normal Hantzsch product ⟨54JIC832⟩. The lowest degree of activation in the three-carbon fragment is shown in the use of dialkyl ketones to give 3,5-dialkylpiperid-4-ones (**649**); a number of arylcarbaldehydes can be used ⟨48JA3853; 54MI20801⟩. Laevulinic acid and its ethyl ester both react with arylcarbaldehydes and ammonium acetate to give piperidin-4-on-3-ylacetic acids and ethyl esters (**650**) and (**651**) ⟨54MI20800⟩.



(**646**) *e.g.* $R^1 = R^3 = Me$, $R^2 = Ph$, 65%



(**647**) R = Et, 40%; R = allyl, 50%



(**648**) $R^1 = R^4 = H$, $R^2 = CO_2Et$

R^3	H	4-MeO	2-MeO	3-NO_2	4-Cl
%	47	51	38	15	14

(**649**) $R^1 = R^2 = R^3 = R^4 = H$
$R^1 = R^2 = Me$, $R^3 = R^4 = H$, 57%

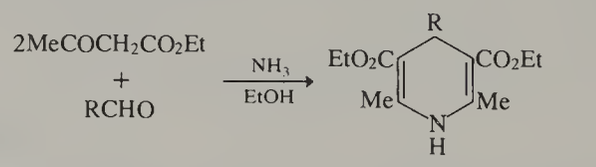
(**650**) $R^1 = R^3 = R^4 = H$, $R^2 = CH_2CO_2H$
$R^1 = R^4 = H$, $R^2 = CH_2CO_2H$, $R^3 = OMe$

(**651**) $R^1 = R^3 = R^4 = H$, $R^2 = CH_2CO_2Et$, 56%
$R^1 = R^4 = H$, $R^3 = OMe$, $R^2 = CH_2CO_2Et$, 50%

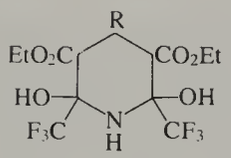
2.08.2.4.2 From two two-atom fragments and two one-atom fragments

(i) Hantzsch and related syntheses

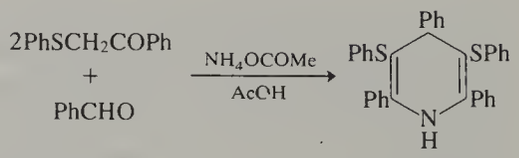
The most famous synthesis of pyridines is undoubtedly due to Hantzsch ⟨1882LA(215)1⟩, who used ethyl acetoacetate, an aldehyde and ammonia (or an aldehyde ammonia) to obtain 1,4-dihydropyridines as outlined in equation (68). The conditions are mild (warming in alcohol) and the yields are often excellent. The dihydropyridines can be easily oxidized (nitrous fumes and nitric acid are commonly used) to the corresponding pyridines. The scope of the synthesis is indicated in tables in a review ⟨60HC(14-1)510⟩; another review deals with a number of syntheses of 1,4-dihydropyridines, including the Hantzsch method ⟨72CRV16⟩. The synthesis is assumed to proceed through aminocrotonate and an α,β-unsaturated ketone, or from a 1,5-diketone and the ammonia or amine; when ethyl trifluoroacetoacetate is used the presumed general intermediate (**652**) is isolated, rather than the dihydropyridine ⟨80JHC1109⟩. A considerable degree of activation is required in the methylene group of the two carbon fragment, unless high temperatures are to be used, and most of the early examples use β-keto esters or 1,3-diketones, the latter giving 3,5-diacetyl-1,4-dihydropyridines. With ammonium acetate in hot acetic acid as the nitrogen source a lower degree of activation can be used, as shown in the synthesis of the 3,5-di(phenylthio)-1,4-dihydropyridine (**653**) ⟨61CB707⟩.



(68)

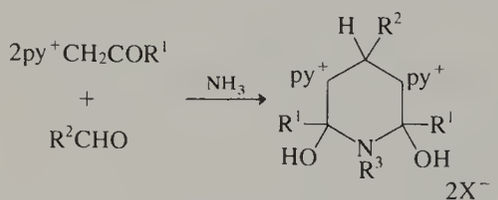


(**652**) R = 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-pyridyl, 3-pyridyl

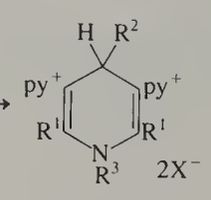


(**653**)

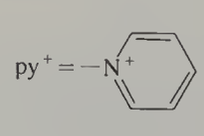
An interesting variant uses acyl- or aroyl-methylpyridinium salts with ammonia or an amine to produce dipyridiniumdihydropyridine salts (**655**). With aromatic aldehydes the dihydropyridines are produced directly or the intermediate (**654**) can be isolated and subsequently treated with perchloric acid ⟨75LA849⟩. With formaldehyde (giving dihydropyridines without a substituent in position 4), the 1,5-diketone can be isolated and cyclized by ammonia ⟨75LA864⟩. The dipyridinium salts (**655**) undergo some useful transformations; they can be oxidized to pyridines (**656**), and these dipyridinium pyridine salts give 3,5-diaminopyridines when heated with piperidine. The amino groups are formed *via* the glutaconic aldehyde derivative. The products (**655**) from formaldehyde lose one pyridinium residue when heated with ammonium acetate in the absence of oxygen, while undergoing normal aromatization if oxygen is present. When cyclohexane-1,3-dione is used hexahydroacridine-1,8-diones (**657**) are formed ⟨63JCS4877⟩. In a modification which allows the preparation of 1,4-dihydropyridines (**658**) without substituents in positions 2 and 6, methyl propiolate provides the two two-carbon framents ⟨74JHC819, 75JCS(P1)926⟩.

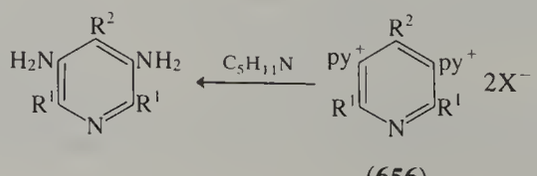


(**654**)

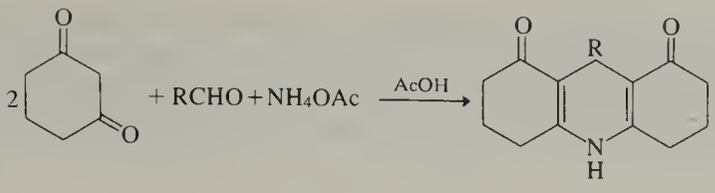


(**655**) R^1 = Me, Ph
R^2 = H, Ph, 4-MeC_6H_4
R^3 = H, Me

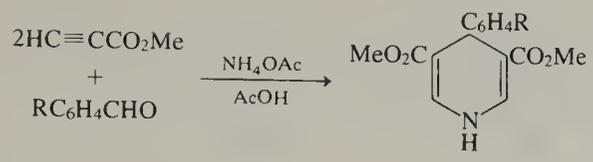




(**656**)



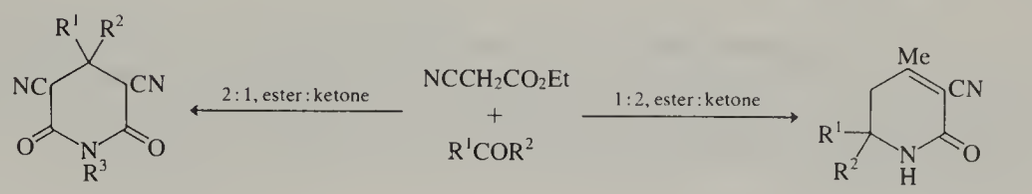
(**657**) R = 4-$O_2NC_6H_4$, 4-$Me_2NC_6H_4$



R	H	2-Cl	3-O_2N	4-Me	4-Cl	4-MeO
%	79	72	57	76	72	68

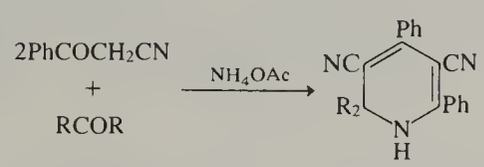
(**658**)

If the active methylene component is ethyl cyanoacetate a dicyanopiperidine-2,6-dione (**659**) is formed ⟨03MI20800⟩; ketones can be used to give 4,4-disubstituted derivatives ⟨00MI20800⟩. An alternative mode of cyclization between two moles of ketone and one of cyanoacetate gives the dihydropyrid-2-one (**660**) ⟨1893MI20800⟩. Other products are often obtained when cyanoacetate condenses with aldehydes and ammonia; the mixtures are generally worse when cyanoacetamide is used. Ketones react with benzoylacetonitrile and ammonium acetate to give 2,2-dialkyl (or spirocycloalkyl) 1,2-dihydropyridines (**661**) ⟨69BCJ220⟩. Ketones are reported to condense with malononitrile, an aromatic aldehyde and ammonium acetate to give acceptable yields of 2-amino-3-cyanopyridines (**662**) ⟨80S366⟩.

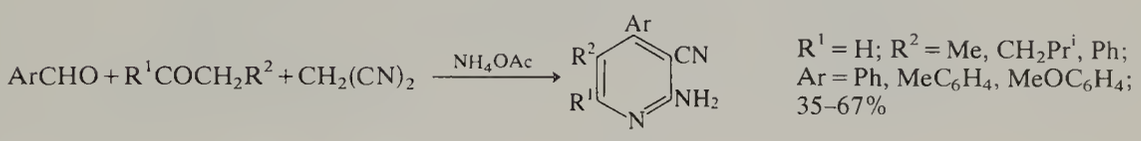


(**659**) *e.g.* $R^1 = H$, $R^2 = Me$
$R^1 = R^2 = Me$

(**660**) $R^1 = R^2 = Me$

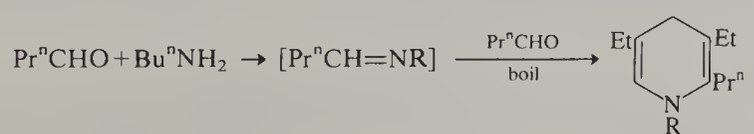


(**661**) R = Me, R,R = $(CH_2)_4$; R,R = $(CH_2)_5$



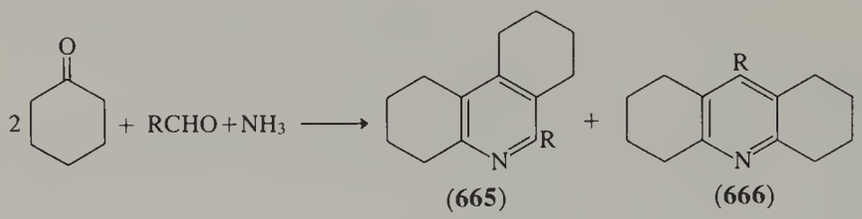
(**662**)

The synthesis of pyridines from α,β-unsaturated aldehydes or ketones and ammonia is discussed in Section 2.08.2.3.1.i. Many technical processes start from aldehydes and ammonia, often producing mixtures of pyridines. The most thoroughly studied reaction is probably that between acetaldehyde and ammonia which can give very high yields of 2-methyl-5-ethylpyridine. A mixture of aqueous ammonia and an ammonium salt is often used, and a discussion of the optimization of the ratios of reagents has been presented ⟨46JA1368⟩. Many other aldehydes, ketones, and mixtures of the two have been used; only a few examples where reasonable yields are obtained can be quoted here. Butanal and *n*-butylamine give up to 70% of the dihydropyridine (**663**), but the imine is formed first and treated with further butanal to obtain optimum yields ⟨55USP2704759⟩. At 100 °C butanal and aniline in acetic acid give the 1,4-dihydropyridine (**664**), but at the boiling point the



(**663**) R = Bu^n, 70%
(**664**) R = Ph

pyridine is obtained ⟨50USP2479815⟩. Cyclohexanone, ammonia, and aldehydes give mixtures of octahydrophenanthridines (**665**) and octahydroacridines (**666**) ⟨39BSF522⟩. An excellent yield of 2-methyl-5-ethylpyridine has been obtained from a mixture of acetylene and aqueous ammonia containing cobalt chloride; it is possible that acetaldehyde is an intermediate ⟨52GEP858399⟩.



(665) (666)

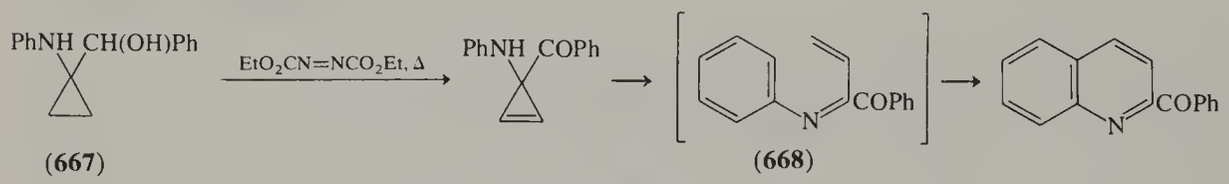
2.08.3 SYNTHESES FROM OTHER RING SYSTEMS

A two-volume work contains many examples of ring transformations ⟨B-73MI20800, B-73MI20801⟩.

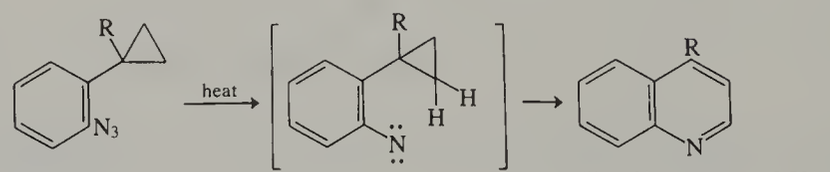
2.08.3.1 From Three-membered Rings

2.08.3.1.1 Cyclopropanes

The arylaminocyclopropane (**667**), when treated with diethyl azodicarboxylate in boiling benzene, gives 2-benzoylquinoline ⟨76H(4)1905⟩. The reaction is assumed to proceed by dehydrogenation, the cyclopropene so formed opening to the intermediate (**668**). Thermolysis of *o*-azidocyclopropylbenzenes (**669**) gives poor yields of quinolines *via* a nitrene intermediate ⟨79ZOR1425⟩.



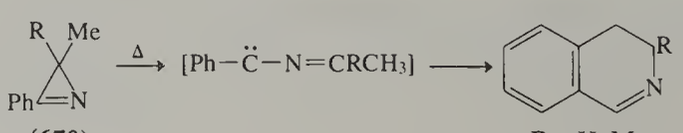
(667) (668)



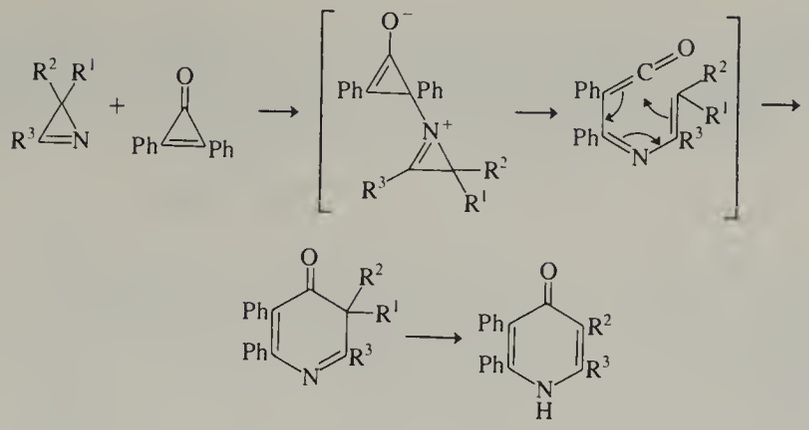
(669) R = H, Me R = H, 9%; R = Me, 25%

2.08.3.1.2 Azirines

In the simplest example of this type, pyrolysis of the azirine (**670**) gives a carbene, which by C—H insertion produces 3,4-dihydroisoquinoline ⟨76JOC831⟩. Azirines can react with diphenylcyclopropenone in two modes. When the azirine has no quaternary carbon atom, the sequence shown in equation (69) leads to a pyrid-4(1*H*)-one (**672**) ⟨72JOC2325⟩. When a quaternary carbon is present the pyrid-4(3*H*)-one (**671**) is produced ⟨78C468⟩. Padwa and his coworkers have reported the conversion into pyridines of a number of azirines carrying unsaturated side chains at position 3. The double bond can be next to the azirine ring as shown in equations (70) ⟨76JOC543⟩ or (71) ⟨78TL433⟩, allylic as in equation (72) ⟨78JOC2029⟩, or more distant as in equation (73) ⟨75CC789⟩. Nitrene intermediates are invoked, and the reactions proceed by thermolysis or photolysis.



(670) R = H, Me

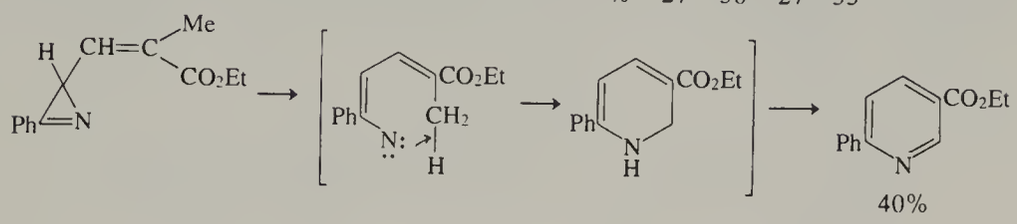


(69)

(**671**) $R^1 = R^2 = Me$, $R^3 = NMe_2$, 70%

(**672**)

R^2	H	Me	Ph	Et
R^3	Ph	Ph	Ph	Et
%	27	50	27	33



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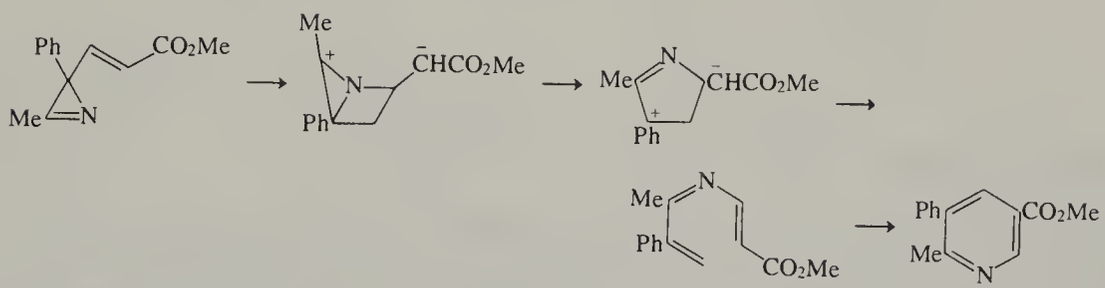
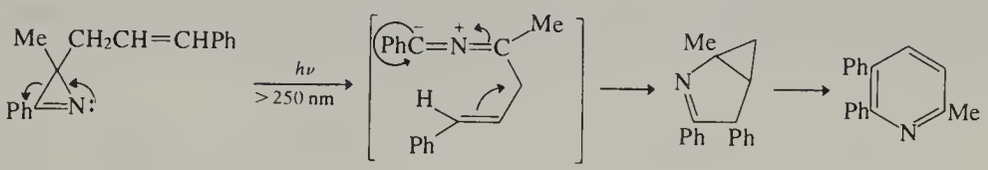


(71)



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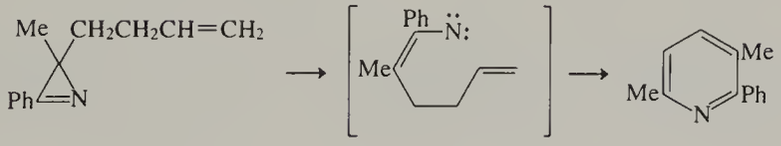
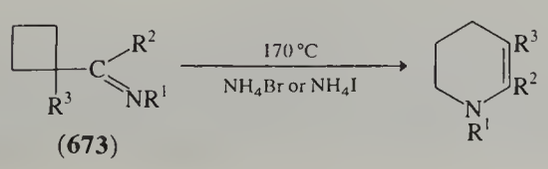


(73)

2.08.3.2 From Four-membered Rings

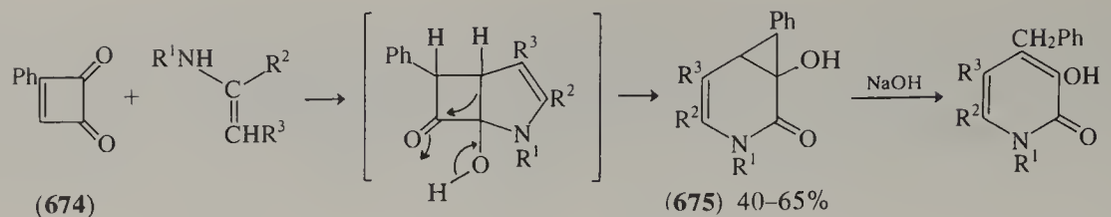
2.08.3.2.1 Carbocyclic rings

Mild acid treatment of the cyclobutyl ketimines (**673**) gives tetrahydropyridines ⟨75CC682⟩. The cyclobutenedione (**674**) reacts with an enamine to give a cyclopropanopyridone (**675**) which can be treated with base to give a 3-hydroxypyrid-2-one ⟨72LA(762)1⟩. Even more reactive are the stabilized cyclobutadienes (**676**) and (**678**). The former reacts at −70 °C with phenylisothiocyanate to give the highly substituted pyridine-2-thione (**677**) ⟨75AG711⟩, and the latter with ethyl cyanoformate to give the picolinate (**679**), possibly *via* a 'Dewar pyridine' ⟨76TL2263⟩. A similar species is intermediate in the interconversion of the stable 1,2-dihydropyridine (**680**) into the much less accessible compounds (**681**) ⟨76JA2344⟩.

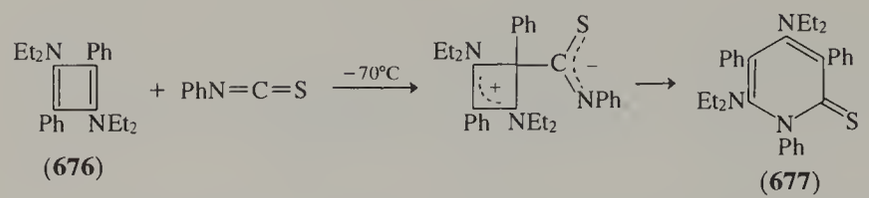


(**673**)

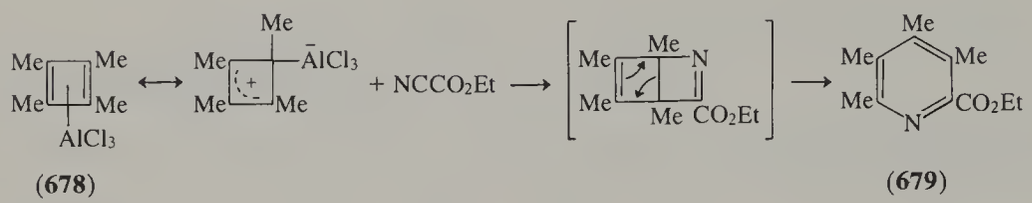
R^1	Me	CH_2Ph
R^2	H	H
R^3	CO_2Et	CO_2Et
%	66	61



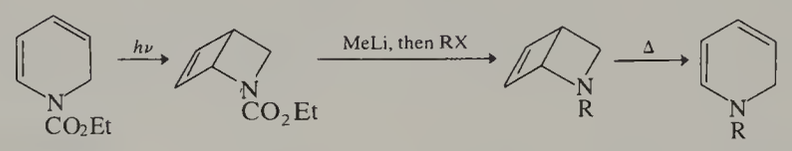
(674) (675) 40–65%



(676) (677)



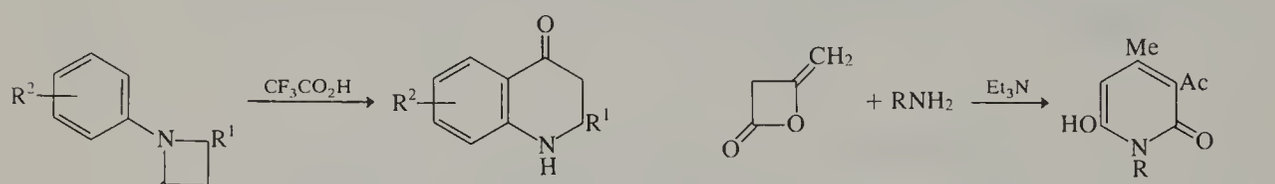
(678) (679)



(680) (681) R = alkyl, 40–60%

2.08.3.2.2 Heterocyclic rings

Azetidinones (**682**) can be converted by treatment with trifluoroacetic acid into dihydroquinol-4-ones; should the *N*-aryl group carry a *meta*-substituent mixtures of 5- or 7-substituted dihydroquinolones are obtained ⟨76H(4)1649, 80JCS(P1)2105⟩. Diketene, with hydroxylamines, gives 3-acetyl-6-hydroxy-1-oxypyrid-2-ones (**683**) ⟨71YZ772, 72CPB1368⟩.

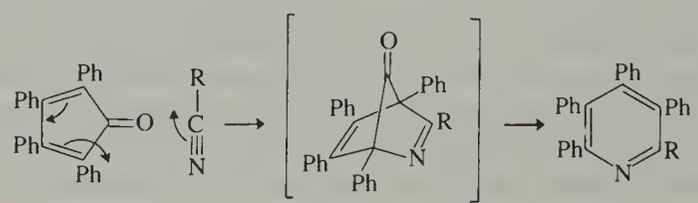


(682) *e.g.* R^2 = 6-MeO, R^1 = Me or Ph, 100% (683) R = OH or OR^1

2.08.3.3 From Five-membered Rings

2.08.3.3.1 Carbocyclic rings

Cycloaddition of nitriles to tetraphenylcyclopentadienone gives an intermediate which by loss of carbon monoxide gives a pyridine, as shown in equation (74) ⟨35CB1159, 52MI20802⟩.

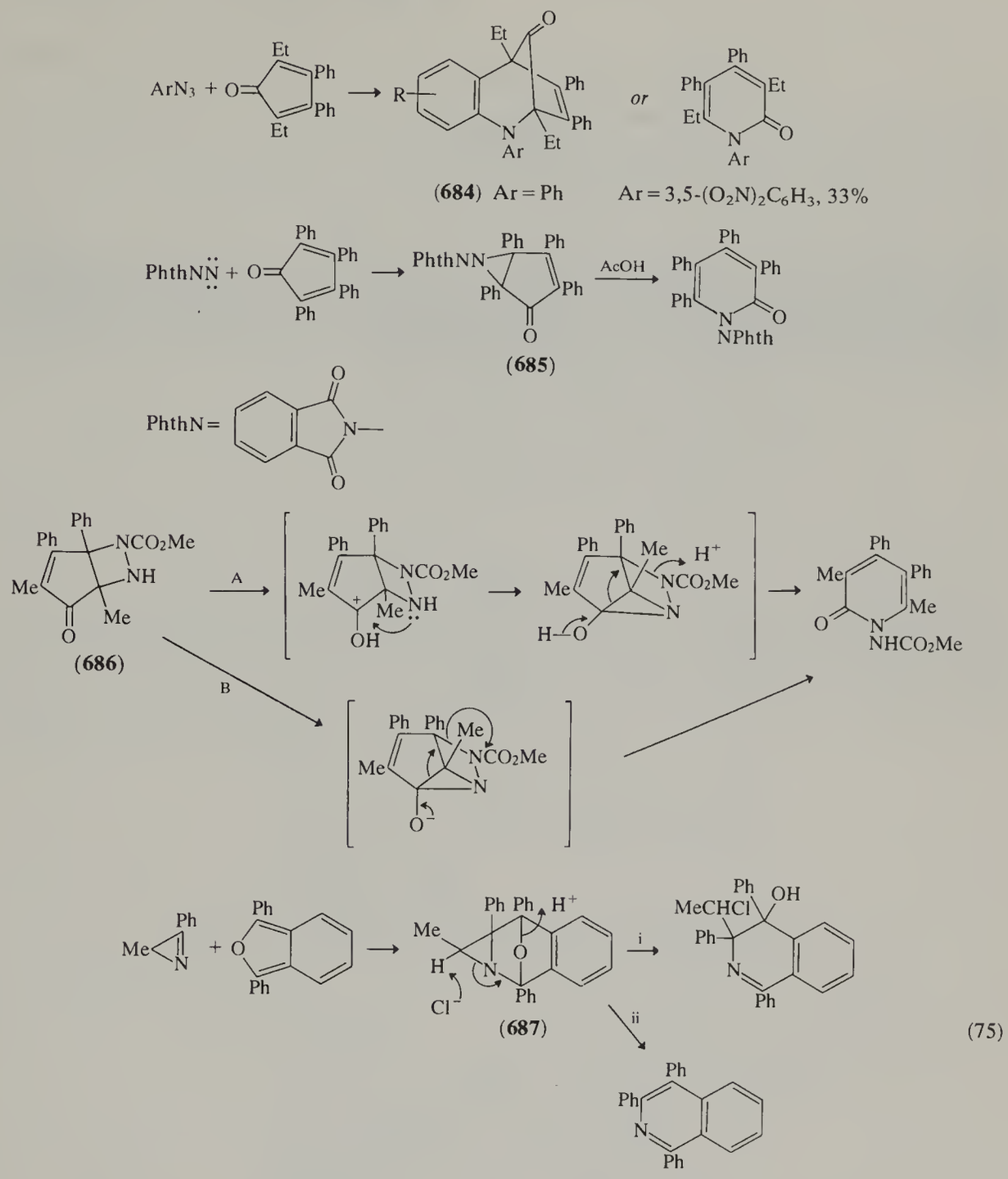


(74)

R = aryl, 50–86%; R = PhCO, 62%

Diethyldiphenylcyclopentadienone reacts with 3,5-dinitrophenyl azide on heating to give a pyrid-2-one; in a similar reaction with phenyl azide, also suggested to proceed *via* the nitrene, a bridged intermediate (**684**) is formed ⟨77TL2463⟩. A different adduct (**685**) was isolated from the reaction between phthalimidonitrene and tetracyclone; when treated with

acetic acid this adduct also gives a pyrid-2-one ⟨75C531⟩. An adduct (**686**) from 2,5-dimethyl-3,4-diphenylcyclopentadienone and azodicarboxylate can be converted by acid (route A) or base (route B) into a derivative of 1-aminopyrid-2-one ⟨75CJC1973⟩. 1,3-Diphenylisobenzofuran reacts with the azirine (**687**) as shown in equation (75) to give an isoquinoline ⟨72JOC2508⟩.

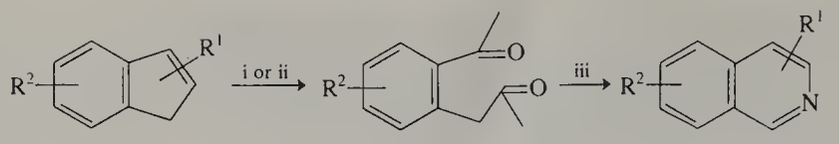


(75)

i, anhydrous HCl, cold; ii, anhydrous HCl, boiling C_6H_6

There are two syntheses of isoquinolines from indenes by oxidation and subsequent addition of ammonia or ammonium salts, differing only in oxidizing medium. Both are summarized in equation (76); in the first, ozonolysis with a reductive work-up is used ⟨80JOC5312⟩, in the second, periodate and catalytic amounts of osmium tetroxide ⟨81JOC4999⟩. The yields can be very good.

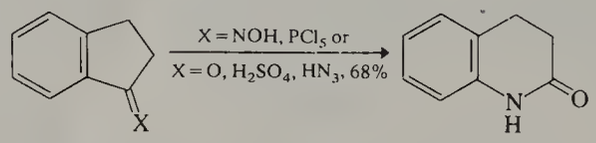
The Beckmann rearrangement of the oximes of cyclic ketones can lead to ring expansion. The reaction has been reviewed ⟨60OR(11)1⟩ and only a few examples will be quoted. Cyclopentanone oxime can give 2-ketopiperidine in over 90% yield ⟨54BRP719109⟩. Unsymmetrical ketones can give two ring-expanded products, although indanone oxime is reported to give only dihydroquinol-2-one (**688**) ⟨1894JCS490⟩. Much better yields are obtained of phenanthridone (**689**) from fluorenone oxime ⟨52JA5153⟩. The varying effects of substituents in the fluorenone on the direction of the ring expansion have been discussed in a review



(76)

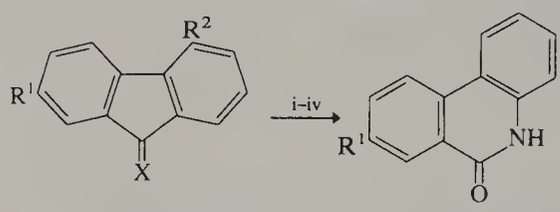
$R^1 = R^2 = H$, 73%
$R^2 = H$, R^1 = 1-Me, 3-Me or 4-Me, 70–96%
$R^1 = H$, R^2 = various, 58–83%

i, O_3, then Me_2S or Raney Ni; ii, $NaIO_4$, OsO_4; iii, NH_3 or NH_4X



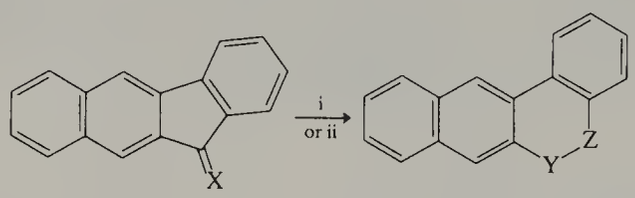
(**688**)

⟨71AHC(13)315⟩, but 2-nitrofluorenone oxime is reported to give 8-nitrophenanthridinone (**690**) in 90% yield ⟨27JA2618⟩. Benzo[*b*]fluorenone oxime gives both possible benzophenanthridinones (**691**) and (**692**) ⟨65JHC15⟩. The dibenzophenanthridinone (**693**) can be prepared unambiguously by a Beckmann rearrangement ⟨64TL2109⟩.



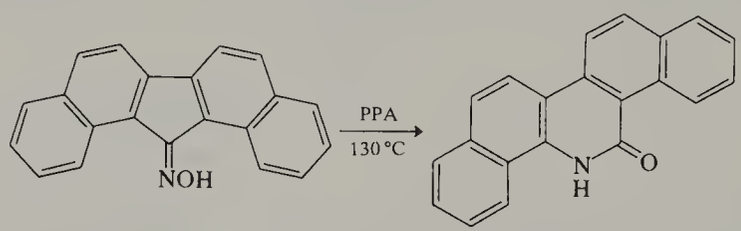
(**689**) $R^1 = H$, >90%
(**690**) $R^1 = NO_2$, 90%; PCl_5, X = NOH

i, X = NOH, $R^1 = R^2 = H$, PPA; ii, X = O, H_2SO_4, HN_3; iii, X = O, $MeNO_2$, PPA; iv, X = O, $R^1 = H$, $R^2 = NH_2$, NaOH



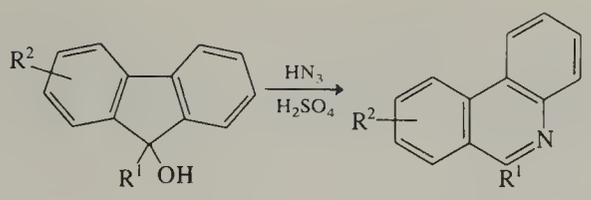
(**691**) Y = NH, Z = CO
(**692**) Y = CO, Z = NH

i, X = NOH, PPA; 21% total; ii, X = O, Cl_3CCO_2H, HN_3; 43% total



(**693**) 65%

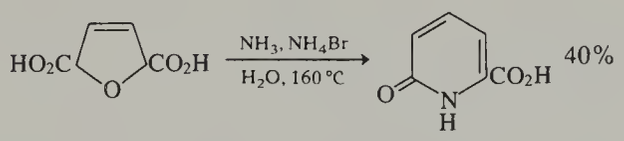
The Schmidt reaction (the reaction of hydrazoic acid on ketones) can often be used to give better yields of six-membered lactams than the Beckmann rearrangement. It has also been reviewed ⟨46OR(3)307⟩. Cyclopentanone gives piperid-2-one ⟨30CB502⟩, and indanone gives dihydroquinol-2-one (**688**) in good yield ⟨37JCS456⟩. Fluorenones also undergo the Schmidt reaction in good to excellent yield ⟨48JA320⟩; the varying effect of substituents in the fluorenones are discussed in a review on phenanthridines ⟨71AHC(13)315⟩. Benzo[*b*]- and benzo[*c*]-fluorenones give mixtures of benzophenanthridinones under Schmidt conditions, but benzo[*a*]fluorenone fails to react, possibly because of steric hindrance. A modified Schmidt reaction uses fluorenols or 9-alkylfluorenols as shown in equation (77) ⟨53JCS178, 55JCS1634⟩ to produce phenanthridines. The migrating ring is that with greater electron release at C-9. Phenanthridinone is also obtained by fusion of 4-aminofluorenone with sodium hydroxide ⟨1895LA(284)312⟩, and from fluorenone, nitromethane and polyphosphoric acid ⟨57CJC180⟩.



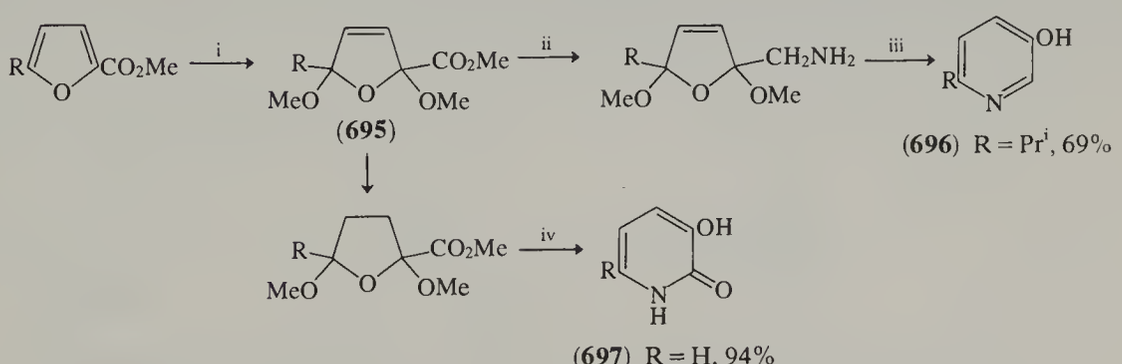
(77)

2.08.3.3.2 Furans

The synthesis of pyridines from furan derivatives has been reviewed ⟨60HC(14-1)154, 74HC(14-1)226⟩, with many tables of examples. Furan itself obviously needs an extra carbon atom as well as a nitrogen atom; tetrahydrofuran reacts with hydrogen cyanide in the vapour phase to give pyridine ⟨43GEP743468⟩. The tetrahydrofuran probably dehydrates to give butadiene, which is known to react with nitriles to give pyridines. More commonly, the additional carbon atom is provided by a substituent on the furan. Furfuryl alcohol and ammonia over ammonium molybdate give pyridine ⟨51USP2543424⟩. Dihydrofurans such as the dicarboxylic acid (**694**) give pyridones on treatment with ammonia and ammonium salts under pressure ⟨50BJ(46)506⟩. An ingenious sequence in which furans are converted into pyridines starts with electrolytic methoxylation to give 2,5-dimethoxy-2,5-dihydrofurans (**695**). The dihydrofurans (**695**) can, after suitable modification of the substituent at position 2, be directly converted into 3-hydroxypyridines such as compound (**696**). Reduction to the tetrahydrofuran then treatment with ammonia and subsequent acid-catalyzed ring opening gives 3-hydroxypyrid-2-ones (**697**) ⟨55ACS14⟩. Furans can be converted into pyridines, the nitrogen atom being supplied either by a substituent group or by the reagent. Furamide heated with ammonia and ammonium salts gives 2-amino-3-hydroxypyridine (**698**) ⟨77JHC203⟩, while 2-aminomethyl-5-hydroxymethylfuran when treated with acid gives a very good yield of 3-hydroxy-6-methylpyridine ⟨56ACS1603⟩. There are many examples of the conversion of 2-acylfurans into pyridines ⟨60HC(14-1)168, 74HC(14-1)231⟩; in the example given the products are 2-substituted 3-hydroxypyridines (**699**), and the substituent can be an alkyl or an aryl group ⟨53CB123⟩. Already quoted in Section 2.08.2.1.1 is the reaction between furfural and an aromatic amine to give a hydroxyglutaconic dianil, which can be cyclized to give a 3-hydroxypyridinium salt.



(**694**) 40%

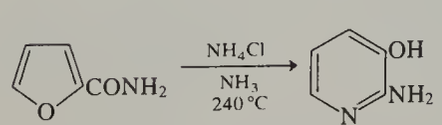


(**695**)

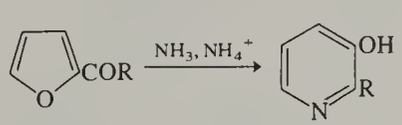
(**696**) R = Pr^i, 69%

(**697**) R = H, 94%

i, electrolytic methoxylation; ii, NH_3, then $LiAlH_4$; iii, acid; iv, NH_3, then acid

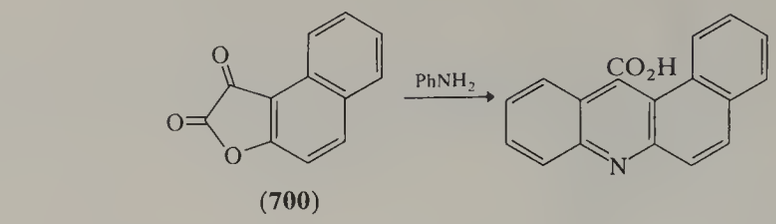


(**698**) 55%

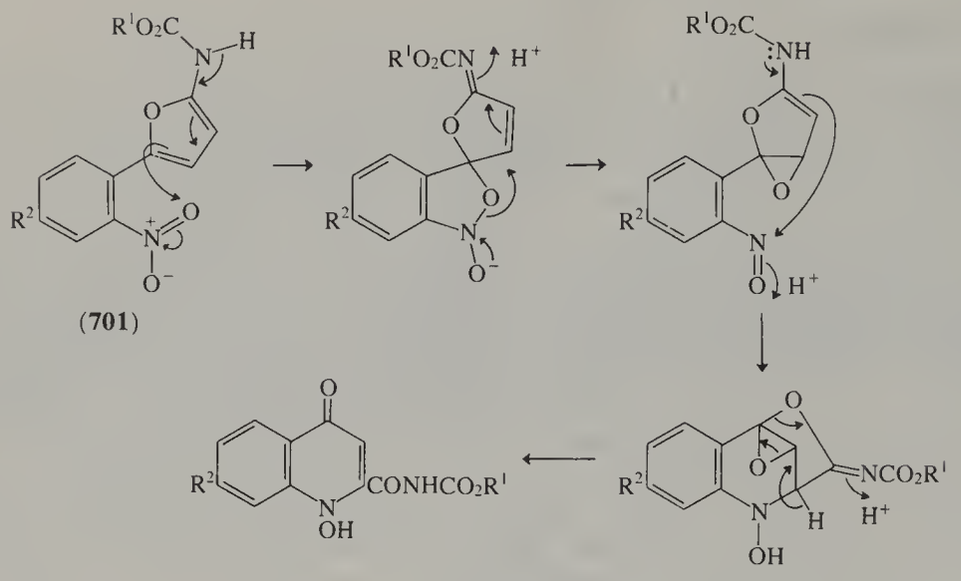


(**699**) *e.g.* R = Bu^n, 52%

Treatment of the naphthofurandione (**700**) with aniline gives a benz[*a*]acridine ⟨25CB1958, 64JCS5622⟩. An *N*-hydroxyquinolone is obtained when a solution of the furyl carbamate (**701**) is exposed to daylight for seven days; the suggested mechanism is shown (equation 78) ⟨81H(16)751⟩. Some carbohydrates possessing furanose rings can give pyridines when heated with ammonium salts ⟨60HC(14-1)172⟩.



(700)

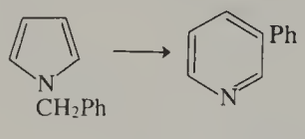


(701)

(78)

2.08.3.3.3 Pyrroles, indoles and carbazoles

Pyrolysis of alkylpyrroles gives pyridines. Pictet obtained 3-phenylpyridine (**702**) from *N*-benzylpyrrole, quinoline from 2-methylindole (**703**), isoquinoline from *N*-methylisoindolin-1-one (**704**), and phenanthridine (**705**) from *N*-methylcarbazole ⟨05CB1946⟩. Flash vacuum pyrolysis of the oxindoles (**706**) gives quinol-2-ones; the mechanism suggested involves homolytic cleavage ⟨73AJC369⟩. Radicals are also thought to be involved in the pyrolytic conversion of methyl- and benzyl-indoles to quinolines ⟨75JOC1511⟩. More generally useful are the reactions of pyrroles or of indoles with carbenes to give pyridines or quinolines. The mechanism of addition of dichlorocarbene is illustrated in the formation of the pyridines (**707**). References to earlier work on additions to pyrroles are given in a paper that illustrates the greatly improved yields of 3-chloropyridines (**707**; equation 78a) that can be obtained if neutral (thermal decomposition of trichloroacetate) rather than strongly basic conditions are used for the dichlorocarbene generation ⟨69JCS(C)2249⟩.



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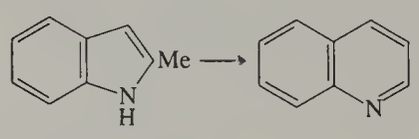

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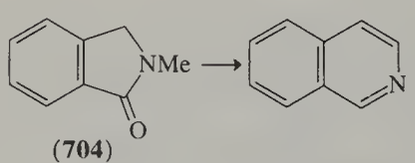
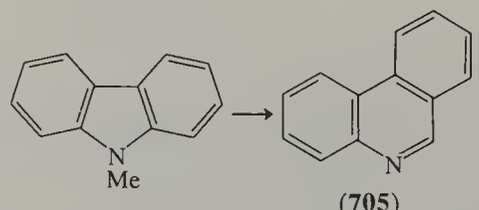
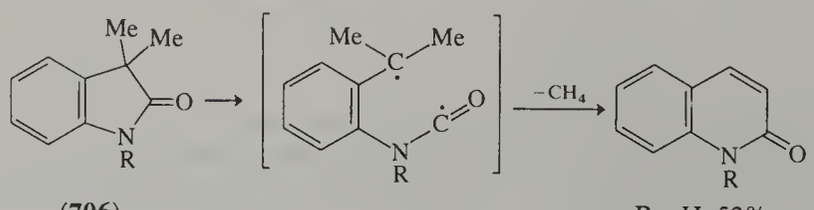


(704)

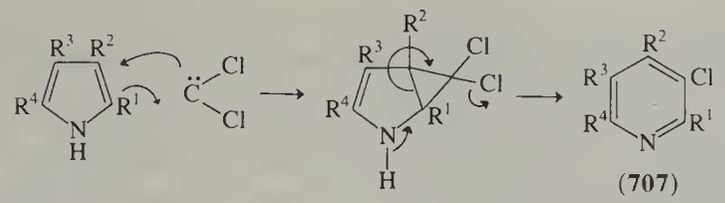


(705)



(706)

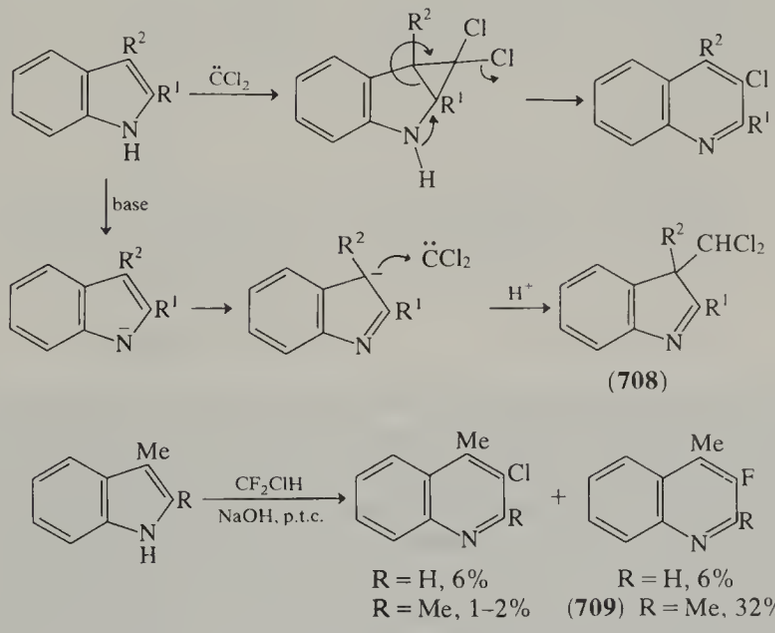
R = H, 52%
R = Me, 30%



(78a)

(707)

The mechanism of formation of quinolines from indoles is similar (equation 79) ⟨64JCS938⟩. The byproduct is an indolenine (**708**), thought to arise by reaction between the indolyl anion and dichlorocarbene. The phase transfer catalyzed procedure for generating carbenes can be applied to the reaction with pyrroles ⟨76S798⟩ and to indoles ⟨76S249, 76S798⟩. The reaction has been performed with chloroform and with bromoform (to give 3-bromoquinolines); chlorodifluoromethane gives mixtures of 3-chloro- and of 3-fluoro-quinolines although in reasonable yield only for the synthesis of compound (**709**) ⟨79LA1456⟩. A review lists other carbenes which have been used in attempted quinoline syntheses ⟨77HC(32-1)232⟩; monohalocarbenes obviously give quinolines without a 3-substituent. There is one example of the use of 18-crown-6 in the carbene preparation with an increase in yield over the phase transfer catalyst ⟨76S249⟩; in other cases there was no advantage.



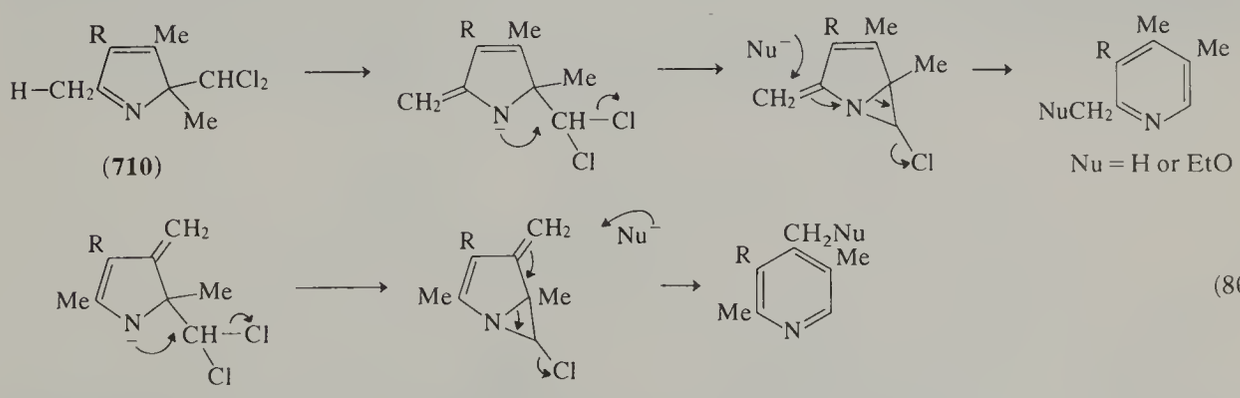
(79)

(708)

R = H, 6%
R = Me, 1–2%

R = H, 6%
(**709**) R = Me, 32%

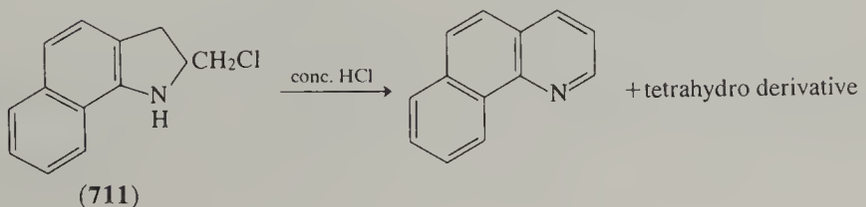
The 2-dichloromethylpyrrolenines (**710**) can be converted into pyridines by strong bases ⟨69JCS(C)2555⟩. The mechanism shown in equation (80) allows formation of 2- or of 4-ethoxymethylpyridines if a methyl group is available in position 2 or 4 of the pyrrole. The benzindoline (**711**) gives a mixture of benzo[*h*]quinoline and its tetrahydro derivative when heated in concentrated hydrochloric acid, presumably *via* the carbenium ion and a dihydrobenzoquinoline ⟨72KGS1121⟩.



(710)

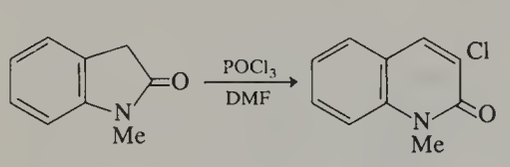
Nu = H or EtO

(80)

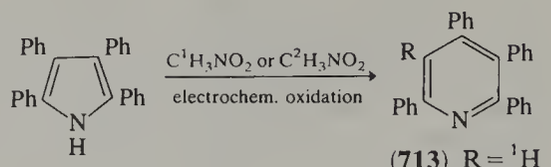


(711)

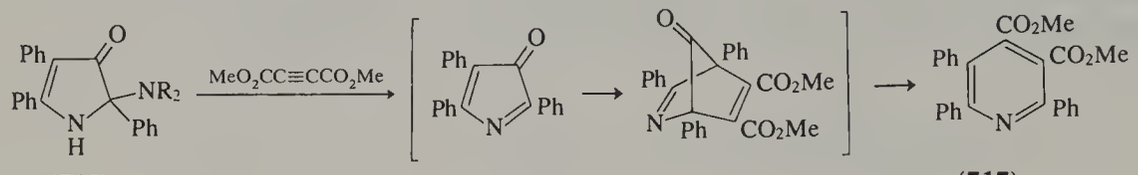
Another electrophilic ring expansion is the formation of 3-chloro-*N*-methylquinol-2-one (**712**) when *N*-methyloxindole is treated with the Vilsmeier reagent ⟨76MI20802⟩. Electrochemical oxidation of tetraphenylpyrrole in nitromethane gives the tetraphenylpyridine (**713**); with trideuterionitromethane the deuteriopyridine (**714**) is obtained ⟨72BSF3639⟩. Cycloaddition reactions are reported to occur with 1,2-dihydro-3*H*-pyrrol-3-one (**715**) ⟨75TL3915⟩ and with the *N*-oxide (**716**) ⟨80JOC4898⟩. The same pyridine diester (**717**) is obtained from both reactions; in the latter case a second product (**718**) was isolated, not an intermediate in the formation of the main product, but convertible into it by heat or irradiation.



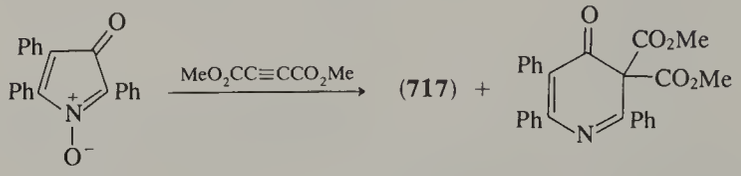
(**712**) 79%



(**713**) R = ^{1}H
(**714**) R = ^{2}H

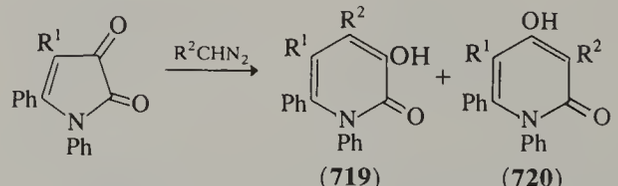


(**715**) (**717**)



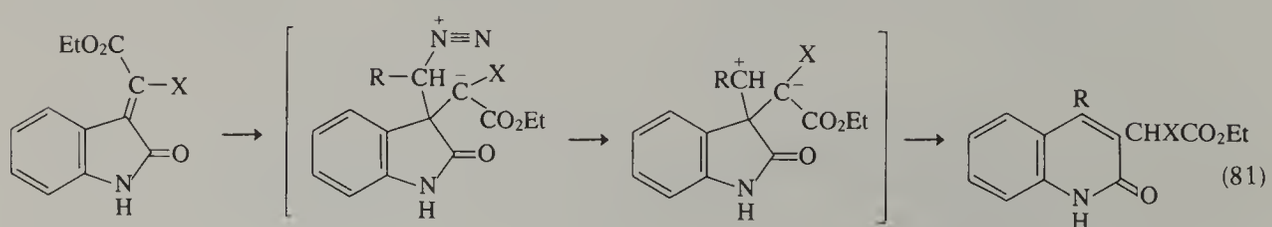
(**716**) (**718**)

Ring expansion by diazoalkanes could involve carbene intermediates, but most mechanisms involve addition of the intact diazoalkane. The substrates are pyrrolones, indolones, isatins, or closely related species. The reactions can give mixtures, as in the reaction of pyrrole-2,3-diones where 3-hydroxypyrid-2-ones (**719**) and 4-hydroxypyrid-2-ones (**720**) are obtained ⟨76LA1023⟩. A number of examples of quinoline synthesis by diazoalkane ring expansion are given in a review ⟨77HC(32-1)230⟩; the suggested mechanism for expansion of oxindolylidene cyanoacetate is given in equation (81) ⟨78JOC4383⟩. Isatins can also give mixtures; 1-acetoxyisatin gives 3-hydroxyquinol-2-ones (**721**) with diazomethane or diazoethane, but a 4-hydroxyquinol-2-one (**722**) with diazopropane ⟨69LA(725)37⟩. Isatins react with enamino esters by the mechanism shown in equation (82) to give derivatives (**723**) of quinoline-3,4-dicarboxylic acid ⟨71CB3341⟩. The condensation products (**724**) from isatin and active methylene derivatives, react with alcohols in an acid- or base-catalyzed reaction, giving 3-cyanoquinoline-4-carboxylates (**725**) ⟨76YZ33, 76CB723⟩. The Pfitzinger synthesis (Section 2.08.2.2.2) is also relevant here, since isatins can be used to generate isatoic acids *in situ*.



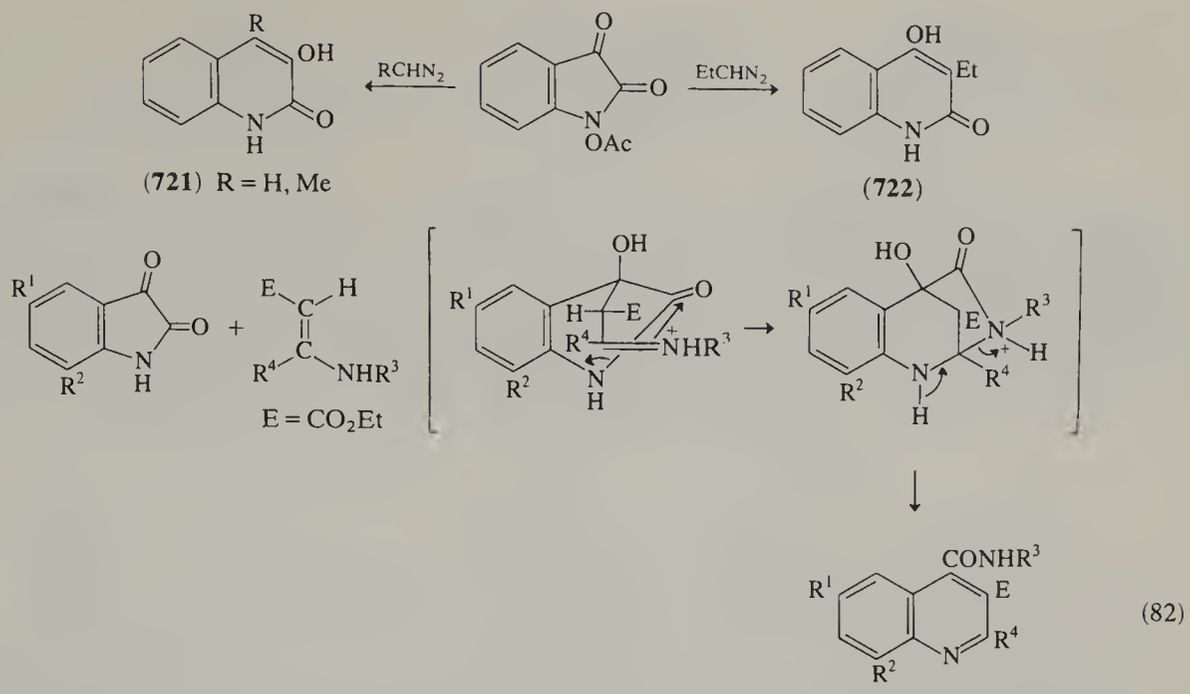
(**719**) (**720**)

R^1 = H, Me, Et, Ph; R^2 = Me



(81)

R = H, X = CN, 92%
R = Ph, X = CN, 42%

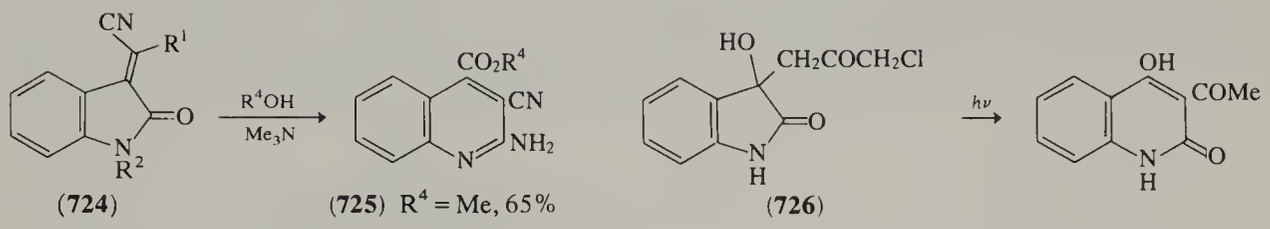


(721) R = H, Me

(722)

(723) Yields mainly 50–70%

(82)

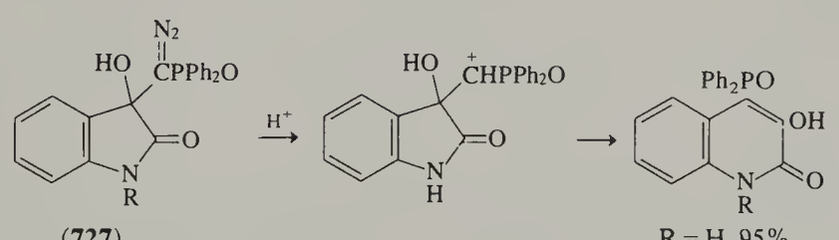


(724)

(725) R^4 = Me, 65%

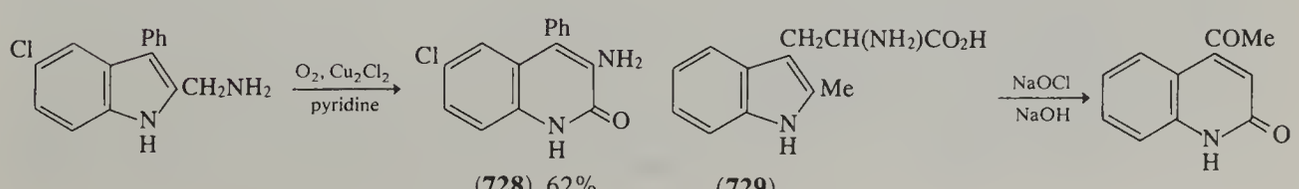
(726)

Some oxygenated indoles, and other indoles by oxidative procedures, can be transformed into quinolones. The hydroxyoxindole (**726**) is photochemically transformed into a 4-hydroxyquinol-2-one ⟨70TL3163⟩; a homolytic ring cleavage and recyclization is invoked. In the compounds (**727**) a carbenium ion site is generated by loss of nitrogen, then ring expansion gives the quinolylphosphine oxide ⟨76LA225⟩. From a 3-hydroxyindolin-2-one a 4-phosphoryl-3-hydroxypyrid-2-one is obtained in a similar reaction. A number of reactions are known in which an indole ring is oxidatively cleaved, then recyclized to a quinolone. Many of these reactions involve compounds with additional fused heterocyclic rings; the production of the 3-aminoquinol-2-one (**728**) provides a less complex example ⟨79CPB551⟩. Hypochlorite converts the tryptophan derivative (**729**) into 4-acetylquinol-2-one ⟨67T687⟩. When the dihydroxyindoline (**730**) is reduced a quinol-4-one is formed, *via* a spiro intermediate (**731**) ⟨72BCJ2590⟩. Treatment of the hydroxyisoindolones (**732**) with a diamine gives a 1-oxo-isoquinolin-3-carboxamide which can further cyclize to give an imidazoline or tetrahydropyrimidine substituent ⟨71USP3594380⟩. Isatins with imino ethers give 2-methoxyquinoline-4-carboxamides (**733**) as shown in equation (83), while amidines give 2-amino-4-carboxamides (**734**) ⟨67LA(707)242⟩. Isatogens react with phenylacetylenes to give quinol-4-ones, as shown in equation (84) ⟨69JCS(C)2453⟩.



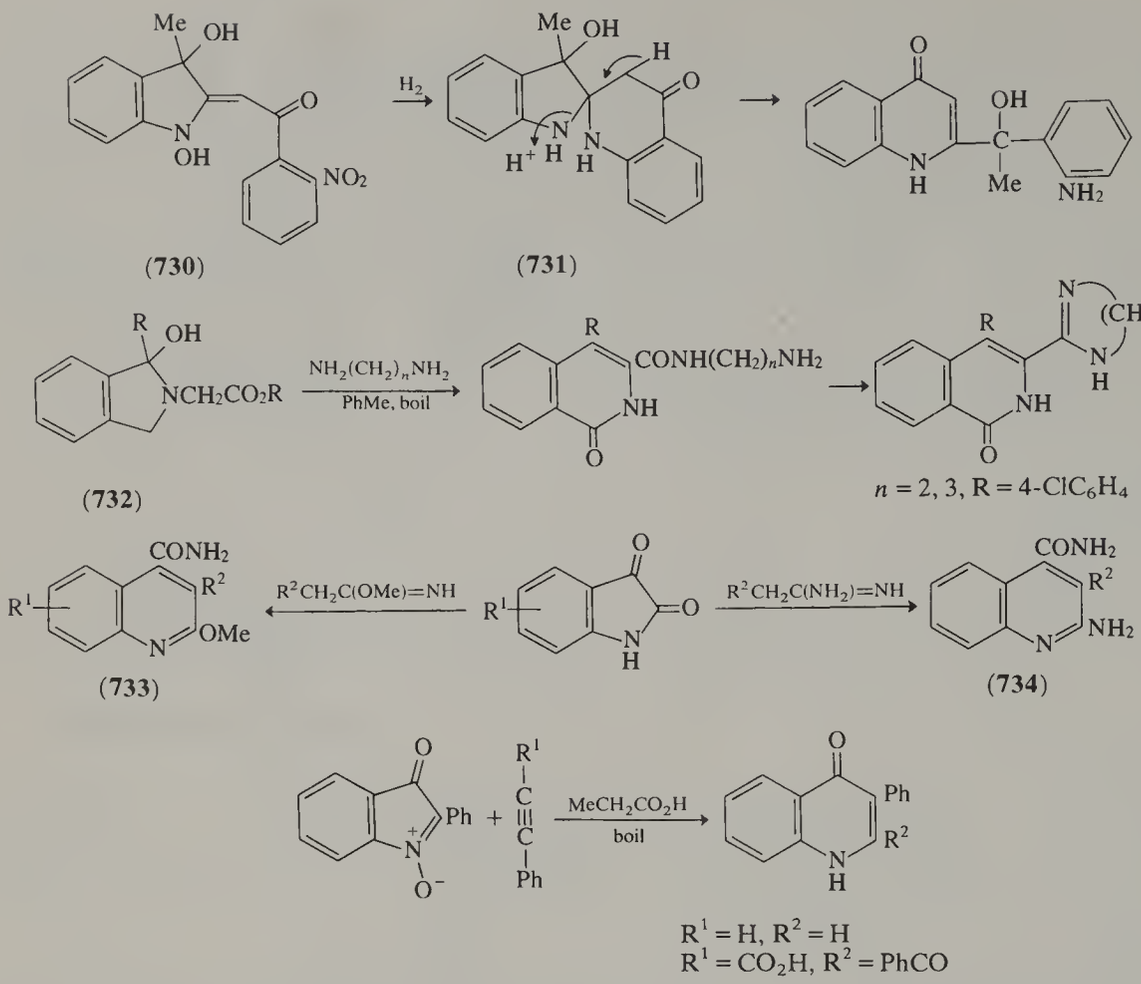
(727)

R = H, 95%



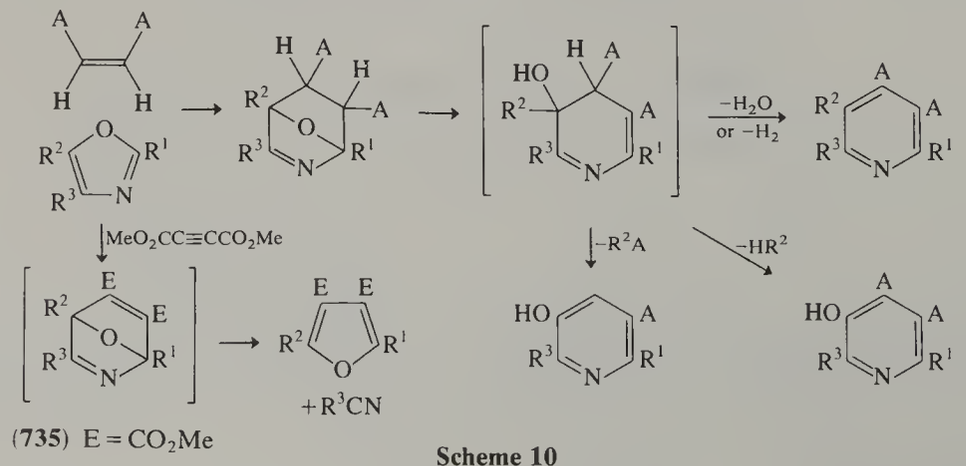
(728) 62%

(729)

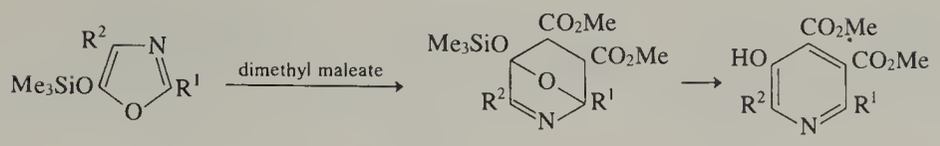


2.08.3.3.4 Oxazoles, thiazoles and isoxazoles, and their benzologues

Some oxazoles react as azadienes to give adducts with dienophiles. These adducts can be converted into pyridines by a number of different elimination reactions. The reaction was investigated in detail in the course of research directed towards the synthesis of pyridoxin (vitamin B_6). It was well summarized in two reviews, the first in 1969 ⟨69RCR540⟩ and the second in 1974 ⟨74AHC(17)99⟩, the latter including a full discussion of the mechanism. Salient points are shown in Scheme 10. The nature of HX, eliminated in the final stage, depends on the substituents but loss of ethanol is common because 5-ethoxyoxazoles are activated towards addition. The general order of activation by substituents is alkoxy > alkyl > 4-phenyl > acetyl > ethoxycarbonyl ≫ 2- or 5-phenyl. The other important points to note are that the addition is regioselective, so that acrylates or acrylonitriles eventually lead to 4-substituted pyridines, and that alkynes cannot normally be used since the intermediate (**735**) readily loses cyanide to give a furan ⟨70JCS(C)552⟩. In a recent example the activation is provided by a trimethylsilyloxy group; yields of pyridine diesters (**736**) are high ⟨79CL183⟩. The products (**736**) can easily be converted into pyridoxin analogues.

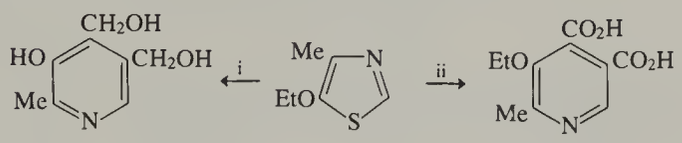


Scheme 10



(**736**)

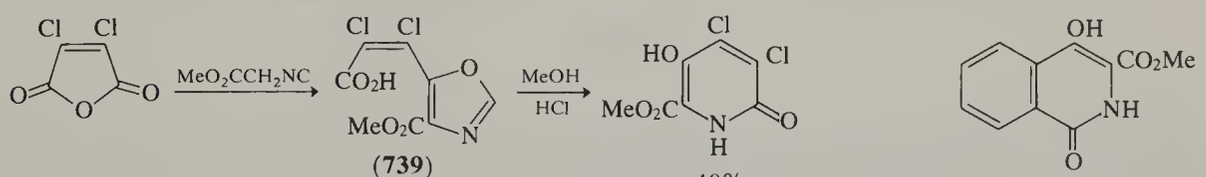
Thiazoles also undergo Diels–Alder additions, but have been used less. In the examples shown, 5-ethoxy-4-methylthiazole is converted into the pyridinedicarboxylic acid (**738**), and into pyridoxine (**737**) ⟨65FRP1400843⟩. The mechanism must be similar to that proposed for the oxazole additions. In both cases the initial adducts are treated with hydrochloric acid; sulfur dioxide is said to be given off in the first case, hydrogen sulfide in the second, the latter providing an analogy with the oxazole mechanism.



(**737**) (**738**) 63%

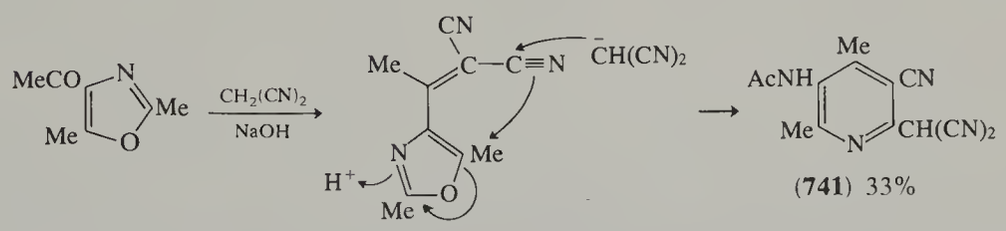
i, $HOCH_2C{\equiv}CCH_2OH$, $PhNO_2$, $AlCl_3$, 100 °C, then HCl, H_2O; ii, dimethyl maleate, 200 °C, then HCl, H_2O

A number of other reactions use ring opening of oxazoles to provide sections of a pyridine ring. Treatment of the oxazole (**739**) with acid opens the oxazole ring, releasing an amino group for cyclization to a pyridone ⟨78S461⟩. The oxazoles are made from maleic anhydrides and an isocyanoacetate; substitution of phthalic anhydrides in the first stage allows the preparation of isoquinolin-1-ones (**740**).

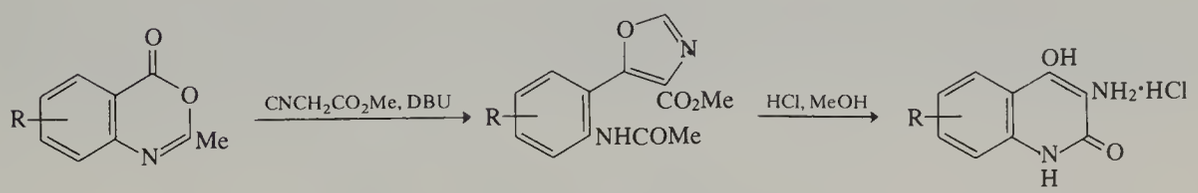


(**739**) 40% (**740**) 95%

There are two superficially similar reactions in which the oxazole ring provides a substituent nitrogen atom on the pyridine ring rather than the ring nitrogen. In one, 4-acetyl-2,5-dimethyloxazole reacts with malononitrile to give the highly substituted pyridine (**741**) ⟨72JOC1047⟩, and in the second, acetanthranils react with cyanoacetate and DBU to give an aryloxazole, which is converted with acid into 3-amino-4-hydroxyquinol-2-one (**742**) in very high yield ⟨76S805⟩.

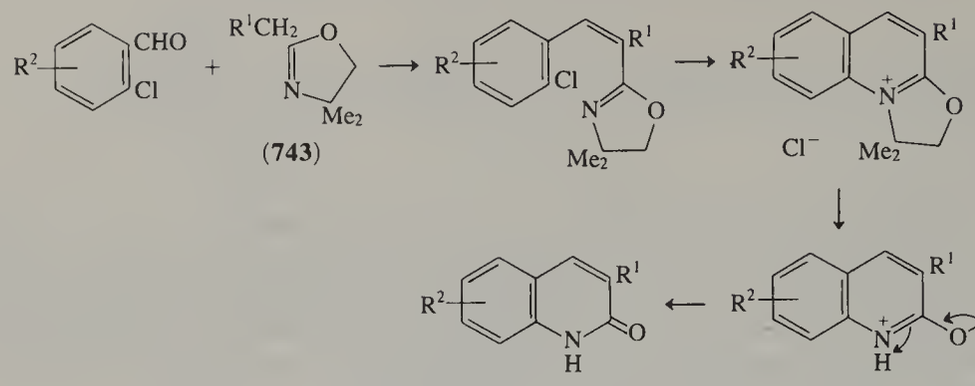


(**741**) 33%



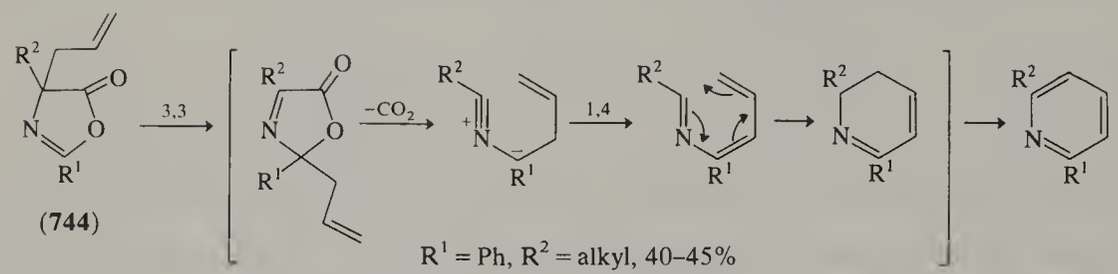
(**742**) 85–98%

The oxazolines (**743**) undergo acid-catalyzed condensation with *o*-chlorobenzaldehydes to give 3-substituted quinol-2-ones, as shown in equation (85) ⟨76JHC61⟩. When heated, the oxazolinones (**744**) undergo successively a 3,3-sigmatropic shift, loss of carbon dioxide, 1,4-hydrogen shift, and a 6π-electrocyclization, to give 2,6-disubstituted pyridines ⟨76CB2331⟩. In one case ($R^2 = CH_2CO_2Me$, $R^1 = Ph$) the methoxycarbonylmethyl group is lost and 2-phenylpyridine is produced. Treatment of 5-methylisoxazole with LDA at −10 °C in the presence of aromatic nitriles gives moderate to good yields of 2-aminopyrid-4-ones (**746**), *via* the dianion (**745**) ⟨78TL4221⟩.

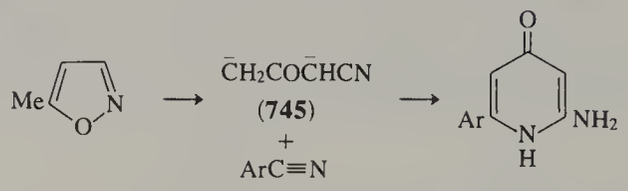


(85)

R^1 = Ph, R^2 = 6-O_2N, 95%

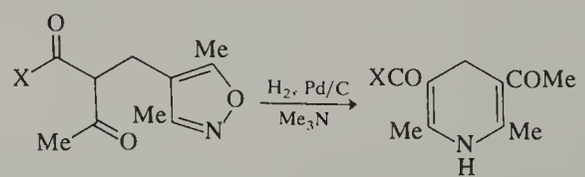


R^1 = Ph, R^2 = alkyl, 40–45%

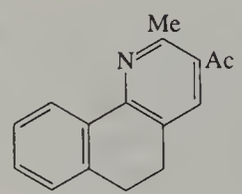


(746) 48–67%

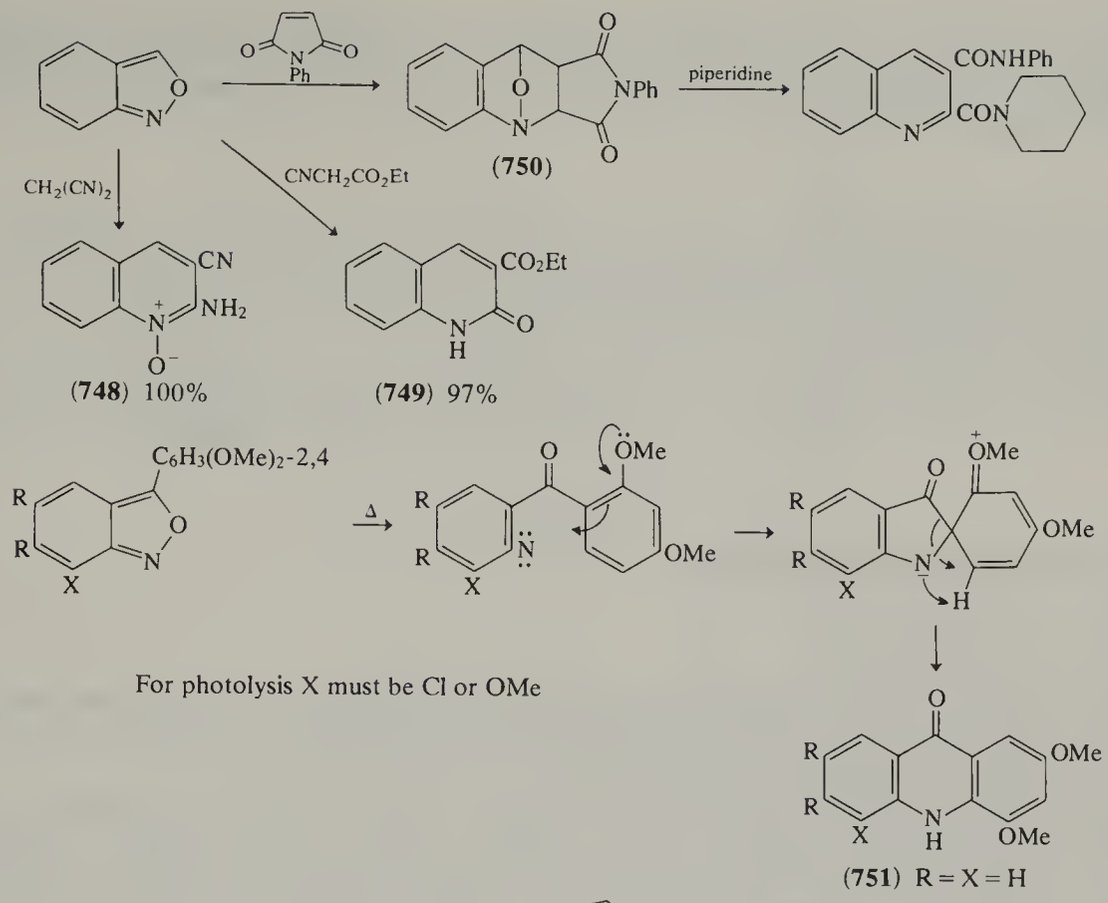
Reduction of isoxazoles can give enamino ketones; if a suitably placed carbonyl group is available a dihydropyridine is formed. The sequence is shown in equation (86) for the production of 1,4-dihydropyridines ⟨71JOC2784⟩. The benzoquinoline (**747**) has been similarly obtained, but in poorer yield, starting from a 1-tetralone. Much more variation is possible with benz[*c*]isoxazole (anthranil) which reacts with malononitrile to give the aminoquinoline *N*-oxide (**748**) and with cyanoacetate to give the 1-hydroxyquinol-2-one (**749**) ⟨67TL2337⟩. Cycloaddition occurs with *N*-phenylmaleimide to give an adduct (**750**) but this can be converted by piperidine into a quinolinediamide ⟨67JOC1899⟩. Benzyne and anthranil give acridine (not acridine *N*-oxide), although it has been suggested ⟨69JCS(C)748⟩ that the reaction goes *via* a dipolar intermediate. Cyclohexanone reacts with anthranil to give 1,2,3,4-tetrahydroacridine ⟨66LA(698)149⟩. Pyrolysis or photolysis of 3-arylanthranils gives acridones (**751**); in both cases a nitrene intermediate was suggested ⟨63JOC2880, 69T5205⟩. In the pyrolysis the position of substituents was not that expected from direct insertion, leading to the suggestion of a spiro intermediate ⟨63JOC2880⟩. A synthesis of acridones in which *o*-nitrobenzaldehyde is treated with concentrated sulfuric acid and sodium nitrite in an aromatic hydrocarbon solvent proceeds *via* an anthranil (**752**) which can be isolated and subsequently treated with the nitrosating mixture ⟨32CB834⟩. The isoxazoline (**753**) is converted by heat into 2,4,6-triphenylpyridine ⟨75T3069⟩, but the reaction almost certainly occurs by cleavage to acetophenone and benzonitrile with recombination of these fragments.

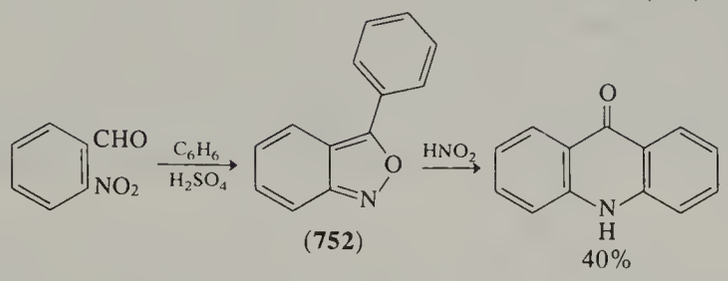


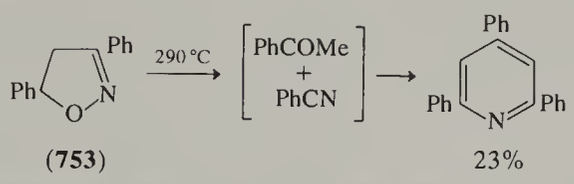
(86)



(747)

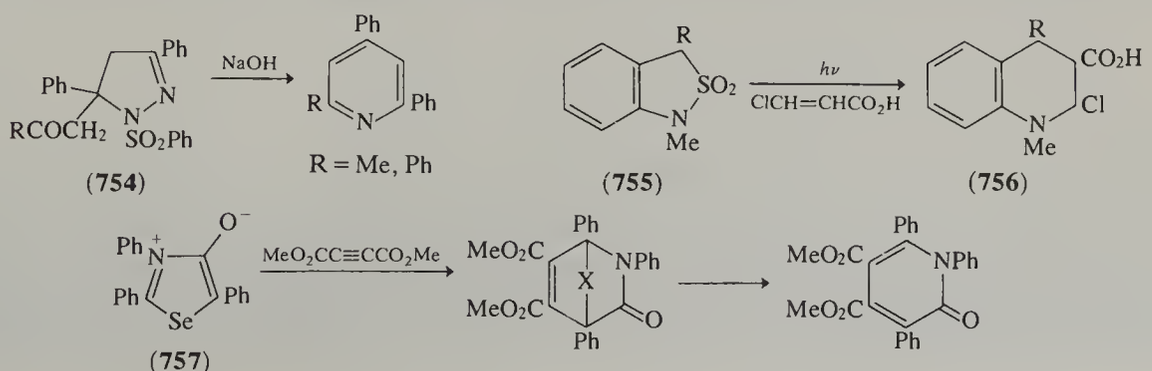




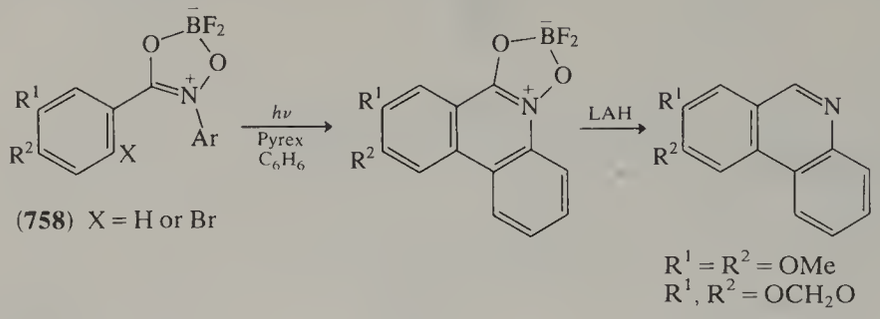


2.08.3.3.5 Miscellaneous five-membered heterocycles

The pyrazoline (**754**) when treated with base gives 2,4,6-triphenylpyridine ⟨75T1667⟩. Photolysis of the benzisothiazoline dioxide (**755**) with β-chloroacrylic acid gives the tetrahydroquinoline (**756**) ⟨80CC471⟩. The mesoionic compound (**757**), on standing for one week with acetylenedicarboxylate, gives an adduct which loses selenium to give a pyrid-2-one ⟨75CC617⟩. If the bridge is a sulfur atom, an alternative pathway for the elimination (loss of phenyl isocyanate) gives a thiophene.



The cyclic borates (**758**) are useful alternatives to benzanilides in the photochemical synthesis of phenanthridines. Irradiation, followed by reduction with lithium aluminum hydride, gives phenanthridines in good yield, the borate ring maintaining the correct stereochemistry ⟨78CC884⟩.



(**758**) X = H or Br

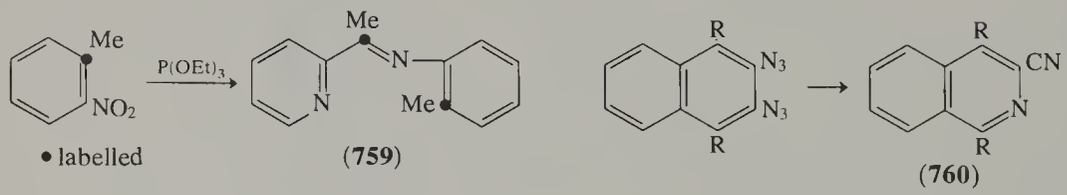
$R^1 = R^2 = OMe$
$R^1, R^2 = OCH_2O$

2.08.3.4 From Six-membered Rings

2.08.3.4.1 Carbocyclic rings

Some cyclohexane derivatives can give pyridines when heated with ammonia and zinc chloride; a number of cases where cyclohexanones react with ammonia under pressure to give poor yields of pyridines are also mentioned in a review ⟨60HC(14-1)152⟩.

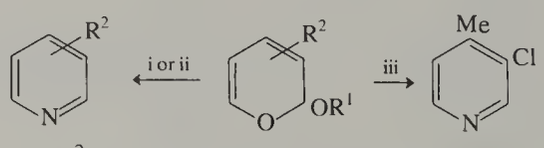
A very reactive nitrogen atom is required to convert benzenes or naphthalenes into pyridines, and there are a number of such reactions which involve nitrenes or nitrenoid species. A number of substituted benzenes have been treated with sulfonyl diazide or carbonyl diazide and moderate yields of pyridines recorded ⟨27CB1717⟩. Thus *p*-xylene gives 2,5-dimethylpyridine; there is no indication of the fate of the carbon atom which is lost. More controlled reaction is possible in intramolecular insertions. The examples in which *o*-nitrotoluene is converted into a derivative (**759**) of 2-acetylpyridine, and where 2,3-diazidonaphthalenes give 3-cyanoisoquinolines (**760**) are quoted in a review ⟨81AHC(28)231⟩.



• labelled (**759**) (**760**)

2.08.3.4.2 Pyrans, pyrones and pyrylium salts, and their benzologues

Routes from the corresponding six-membered oxygen heterocycles are very important but can only be summarized here. Tetrahydropyrans are converted into pyridines only with difficulty, but certain types of dihydropyran can give excellent yields of pyridines. In particular, 2-alkoxy-3,4-dihydropyrans, which are cyclic acetals of 1,5-dicarbonyl compounds, are converted by treatment with ammonia and steam over a catalyst into pyridines in high yields ⟨56USP2741618⟩; the same transformation has been effected in solution with ammonium salts ⟨55BRP726378⟩. Some modification to the pyran is possible before the ammonia treatment, as for example chlorination ⟨55BRP726378⟩. All these transformations are summarized in equation (87). Many other examples are given in a review ⟨60HC(14-1)175⟩.

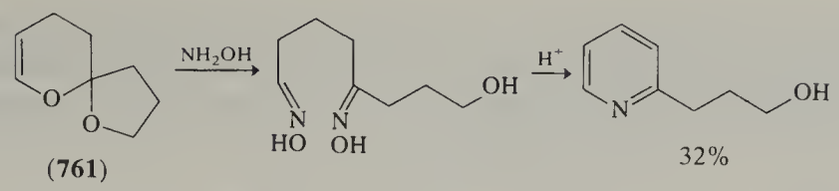


(87)

e.g. R^2 = 4-Me, 91% 52%

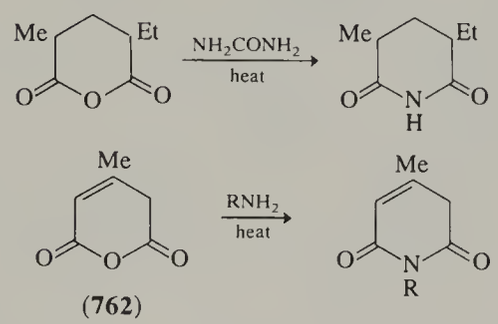
i, NH_3, steam Al_2O_3 + Cu, Cr salts; ii, $FeNH_4(SO_4)_2$, heat; iii, Cl_2, then aq. NH_4^+, $FeCl_3$

The probable course of another general reaction is indicated in the example of the spirocyclic ketal (**761**) with hydroxylamine. The isolated dioxime is subsequently cyclized by treatment with acid ⟨54BSF1139⟩.



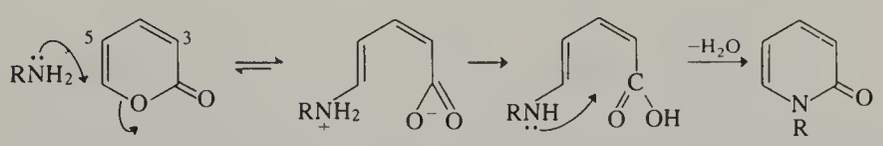
(761)

Treatment of cyclic lactones with ammonia gives pyrid-2-ones. One of the easier routes to 2,6-dioxopiperidines, shown in equation (88), is by treatment of glutaric anhydrides with ammonia, an amine, or urea ⟨52JA700⟩. By using glutaconic anhydrides (**762**), the pyridine-2,6-diones can be obtained ⟨56JA4683⟩. Many α-pyrones have been converted into pyrid-2-ones, and many γ-pyrones into pyrid-4-ones, as shown in equations (89) and (90). There are tables of examples in a review ⟨60HC(14-1)189, 60HC(14-1)195⟩. The reaction proceeds in both cases by addition of the amine, ring opening, and recyclization.

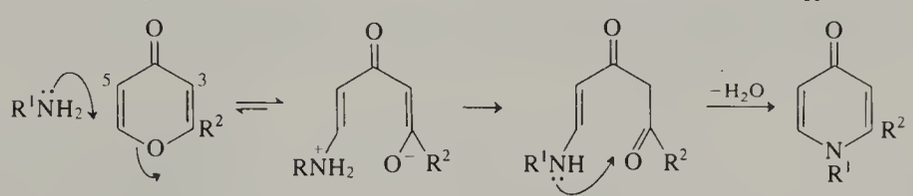


(88)

(762)

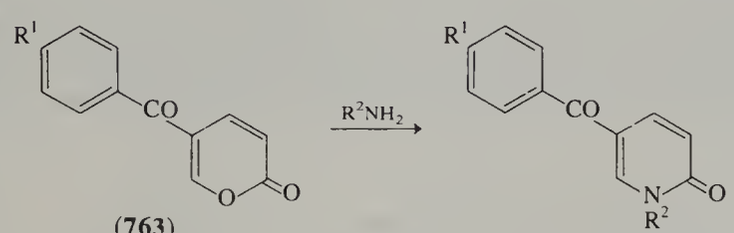


(89)



(90)

It is well established that electron-withdrawing groups in position 3 or position 5 of an α-pyrone leads to enhanced reactivity, an effect which is obviously stronger at position 6 than position 2. As an example, the 5-aroyl-2-pyrones (**763**) give high yields of pyridones when treated with hot aqueous ammonia; amines give generally lower yields ⟨56JA2393⟩. In the case of the γ-pyrones there seems no doubt that attack by ammonia or amines occurs at position 2 or 6. Electron withdrawing groups can activate the γ-pyrone best if placed in position 3 or 5; groups at positions 2 or 6 can inhibit attack, by steric obstruction. Best results are obtained in both series by using stronger bases (ammonia, aliphatic amines, hydrazines, hydroxylamine, and the aromatic amines which do not carry electron-withdrawing substituents). The acyclic intermediate may be able to recyclize in two directions (if for example a carboxylic acid derivative is available in position 3 of the original pyrone), and the use of hydrazine on α-pyrones can give pyrazoles or diazepines as well as pyridines. The use of pyranthiones seems to have no particular merit.

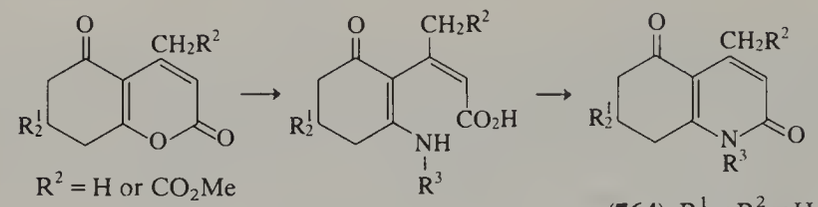


(763)

$R^2 = H$					
$R^1 = H$	Me	Et	Br	Cl	
% 88	86	79	86	80	
$R^1 = H$					
$R^2 = Me$	$PhCH_2$		$PhCH_2CH_2$		
% 60	35		65		

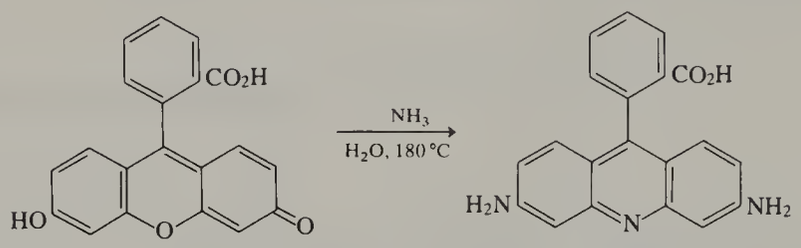
Isocoumarins react with ammonia to give isoquinolin-1-ones. A bicyclic example illustrates the possibility of interconversion (side chain group becoming ring carbon and *vice versa*) during the synthesis of a quinolinedione (**764**) ⟨77JOC889⟩, and fluorescein is reported to give a proflavine (**765**) when treated with aqueous ammonia at 180 °C ⟨1888CB3376⟩. One of the variants of the pyrone synthesis uses 4-*exo*-methylenepyrans which are easily made, for example by condensing 4-pyrones with malononitrile. An example which illustrates the delicate balance in the reaction between such pyrans and amines is provided by the

malononitriles (**766**). Methylamine reacts normally to give the pyridine (**767**), but more hindered amines find it easier to recyclize *via* the malononitrile residue, giving the aminopyridines (**768**) ⟨71JHC367⟩. Somewhat similar is the production of aroylpyridin-2-ones (**770**) from the benzpyranone (**769**) ⟨74TL1183⟩.

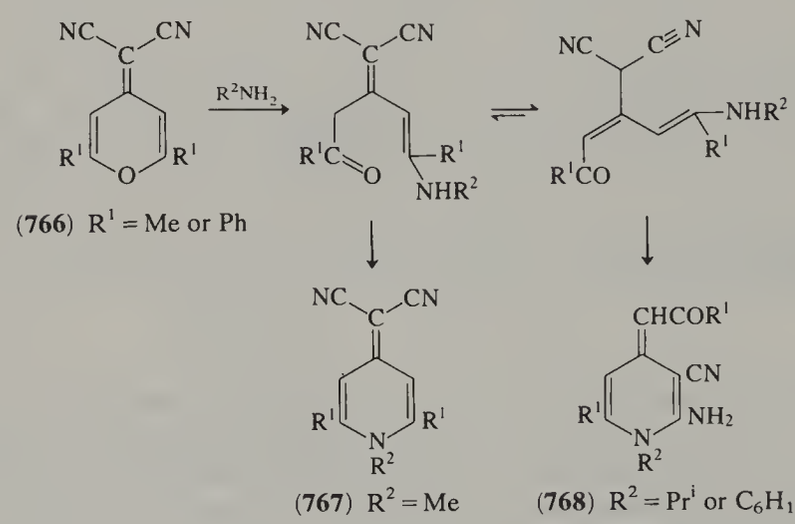


R^2 = H or CO_2Me

(**764**) $R^1 = R^2 = H$, $R^3 = CH_2Ph$, 74%
$R^1 = R^3 = H$, $R^2 = CO_2H$, 90%
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = CH_2Ph$, 80%



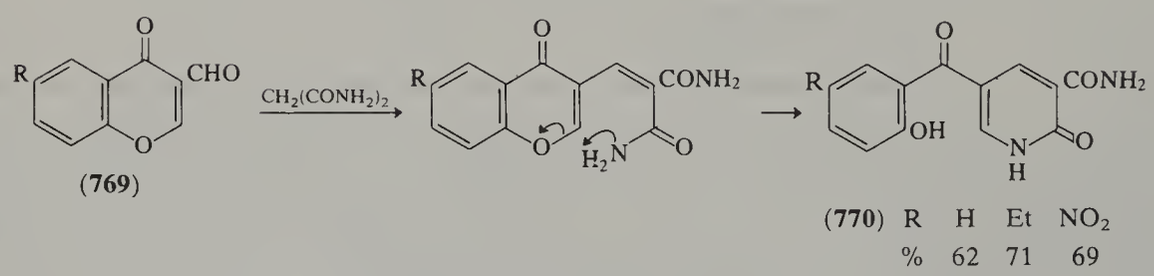
(**765**)



(**766**) R^1 = Me or Ph

(**767**) R^2 = Me

(**768**) R^2 = Pr^i or C_6H_{11}

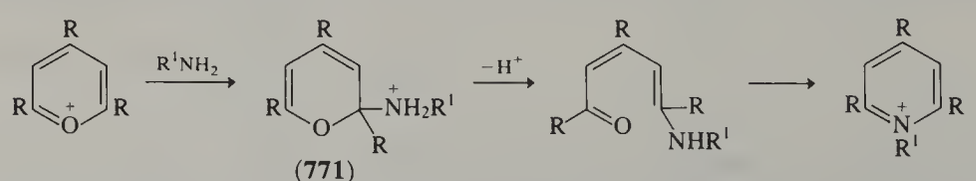


(**769**)

(**770**)

R	H	Et	NO_2
%	62	71	69

The other major group of oxygen heterocycles which can give pyridines are the pyrylium salts. With ammonia or ammonium salts the products are pyridines, while with primary amines the products are pyridinium salts, as shown in equation (91). The simplified mechanism shows the important stages; it is notable that a second molar equivalent of base (which

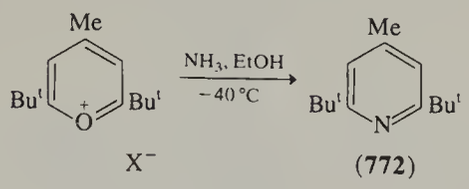


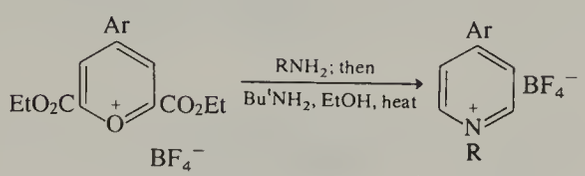
(**771**)

(91)

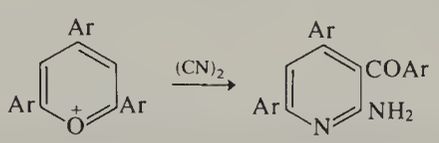
can be triethylamine) is needed to deprotonate the adduct (**771**). Evidence for the mechanism has been advanced in a review ⟨80T679⟩, and there are tables with many examples in other reviews ⟨60HC(14-1)214, 74HC(14-1)236, B-73MI20800, B-73MI20801⟩. Most of the examples reported have three substituents (at positions 2, 4, and 6) on the pyrylium salt; the route has been particularly useful for preparing hindered pyridines such as compound (**772**)

⟨76JOC3034⟩. A recent route to 4-substituted pyridinium salts (**773**) promises to make these much more readily available ⟨81S959⟩. Certain substituent groups can be replaced by nucleophilic amines, so that a 4-alkoxy- or 4-methylthio-pyrylium salt can give a 4-aminopyridinium salt. One unusual reaction is that between triarylpyrylium salts and cyanogen to give 2-amino-3-aroylpyridines (**774**) ⟨71JCS(C)3873⟩.





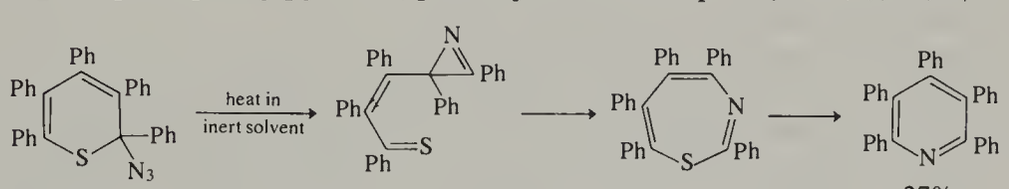
(**773**) Ar = Ph, *p*-MeC_6H_4



(**774**)

2.08.3.4.3 Thiopyrans

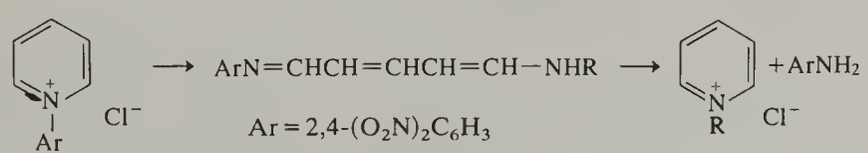
Syntheses of pyridines from thiopyrans are unimportant. The azidothiopyran (**775**) on thermolysis gives pentaphenylpyridine, possibly *via* a thiazepine ⟨75CR(C)(280)37⟩.



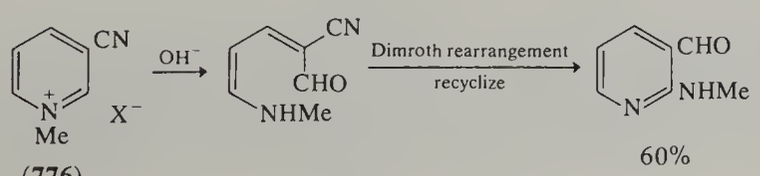
(**775**) 37%

2.08.3.4.4 Other pyridines, isoquinolines and quinolizinium salts

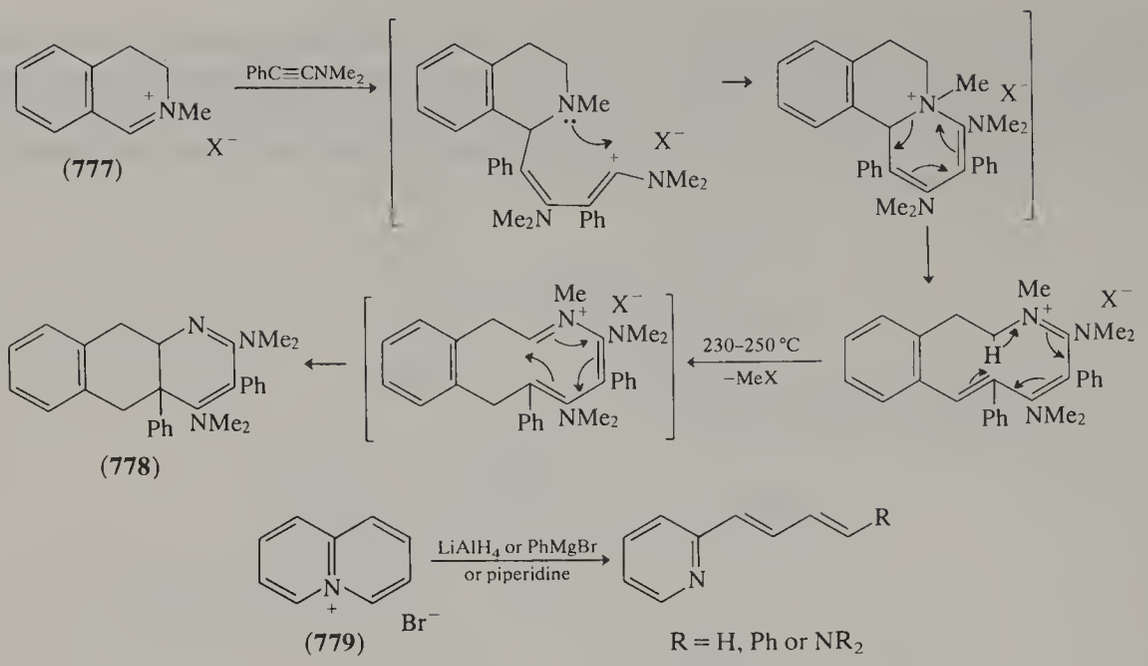
There are few interconversions which belong in this chapter. It is easy to prepare 2,4-dinitrophenylpyridinium chloride and Zincke found that the pyridine ring is easily opened by bases to give the famous Zincke salts. If the pyridinium chloride is treated with a primary amine a mixed dianil is obtained; if the added amine is a stronger base than 2,4-dinitroaniline, recyclization gives a new quaternary pyridinium salt ⟨04LA(333)296⟩. The sequence is shown in equation (92), and there are specific examples in the review ⟨60HC(14-1)313⟩. Two more instances of the conversion of quaternary salts into new six-membered ring heterocycles are the conversion of salt (**776**) into 2-methylaminopyridine-3-carbaldehyde ⟨71JCS(C)1892⟩ and the reaction between dihydroisoquinolinium salt (**777**) and an ynamine to give compound (**778**) ⟨76BSB892⟩. Quinolizinium salts (**779**) react with hydrides, with Grignard reagents, or with amines to give pyridylbutadienes ⟨69T397, 64CPB1344, 71LA(744)65⟩.



(92)

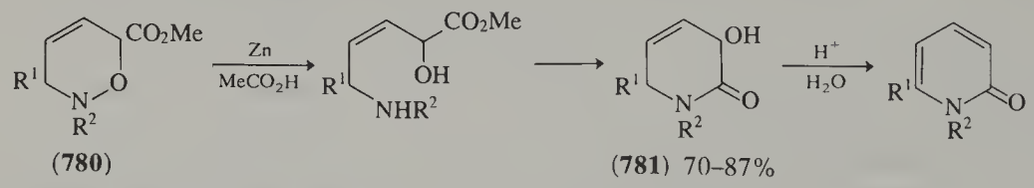


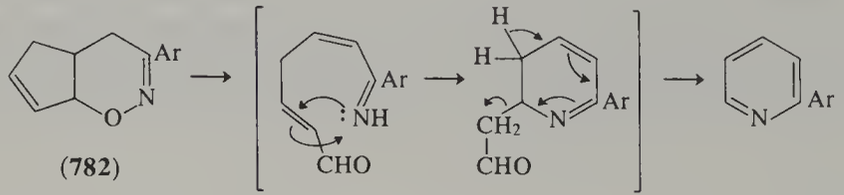
(**776**) 60%



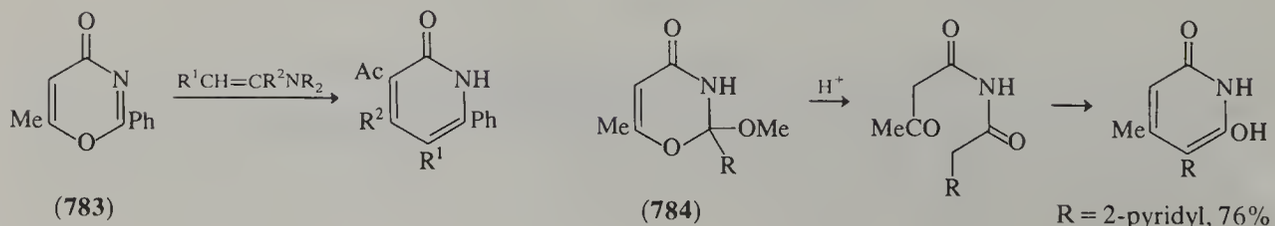
2.08.3.4.5 Oxazines, thiazines and diazines, and their benzologues

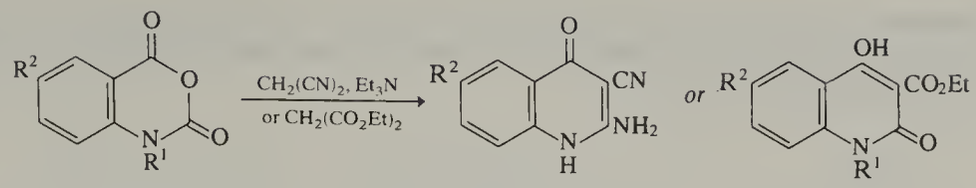
The dihydro-1,2-oxazines undergo ready ring contraction to pyrrolines or pyrroles, but in one or two cases can give pyridines. The monocyclic oxazines (**780**), reduced by zinc and acetic acid, give 3-hydroxy-3,6-dihydropyrid-2-ones (**781**), which are converted by acid into pyrid-2-ones ⟨66CB3695⟩. The bicyclic oxazine (**782**), prepared from cyclopentadiene and an unsaturated nitroso compound, fragments and recyclizes on heating to give 2-arylpyridines ⟨77CC252⟩. There are a few more syntheses of pyridines from 1,3-oxazines. The oxazinone (**783**) reacts with enamines to give pyrid-2-ones ⟨75H(3)293⟩, while its close relative (**784**) undergoes acid-catalyzed ring opening and recyclization to a 6-hydroxypyrid-2-one ⟨76CPB356⟩. Benzoxazinediones (isatoic anhydrides) (**785**) and (**786**) react with malononitrile and with diethyl malonate respectively to give, in the former case, a 2-aminoquinol-4-one ⟨77S500⟩ and in the latter a 4-hydroxyquinol-2-one ⟨75H(3)913⟩. Acetanthranils react with enamines to give diethylamine salts of quinoline-8-carboxylates (**787**) ⟨73AG505⟩, but with ynamines with retention of the diethylamino group, giving quinolines (**788**) ⟨72AG(E)720⟩. The dipolar thiazines (**789**) are converted by heat into quinol-4-ones by the route shown in equation (93) ⟨75JOC2596⟩. Azapyrylium salts (**790**) are attacked by malononitrile anion to give derivatives (**791**) of 2-aminopyridine ⟨69LA(723)111⟩; in the ring-opening stage both geometrical isomers of the butadiene are formed.





Ar	Ph	4-BrC$_6$H$_4$	2-Furyl
%	80	78	40

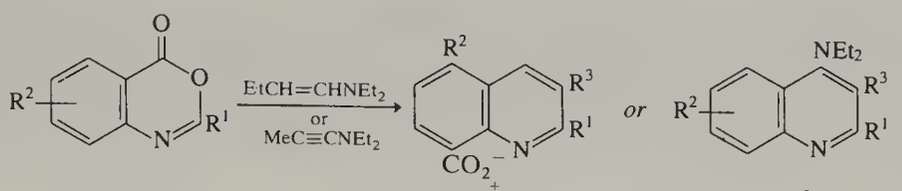




(**785**) R^1 = H, R^2 = various
(**786**) R^1 = Me, R^2 = H

from (**785**)

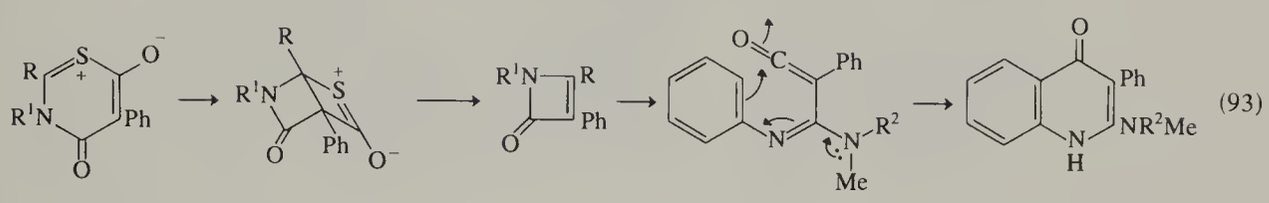
R	H	Cl	Me	MeO
%	86	86	73	69



(**787**) $R^1 = CF_3$, R^3 = Et

R^2	H	Cl	NO_2
%	65	48	67

(**788**) R^3 = Me

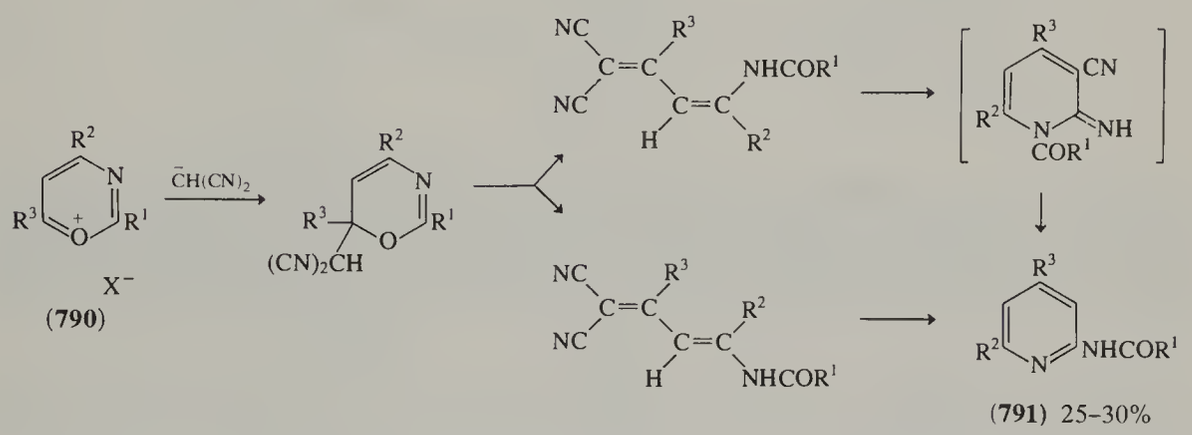


(93)

(**789**) R^1 = Ph

R^2 = Ph Me

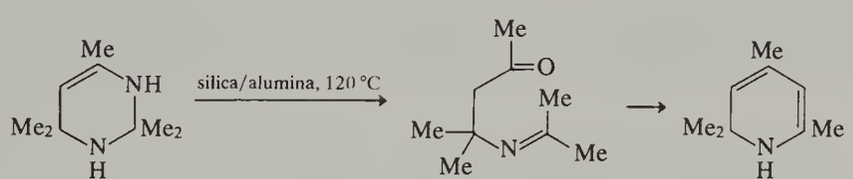
%	34	92



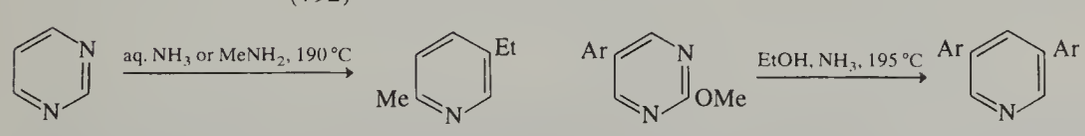
(**790**)

(**791**) 25–30%

There are now a reasonable number of reactions in which derivatives of pyrimidine are converted into pyridines. The tetrahydropyrimidine (**792**) is converted into a dihydropyridine by heating with silica and alumina ⟨48HCA612⟩. It was assumed that hydrolysis gave a ketoimine (also obtained directly from acetone and ammonia), which recyclized. Pyrimidine itself is converted by hot (190 °C) aqueous ammonia or methylamine into 2-methyl-5-ethylpyridine (**793**) ⟨71RTC1246⟩, while 2-methoxy-5-arylpyrimidines (**794**) with



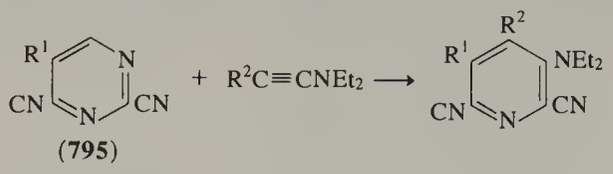
(**792**)



(**793**) 5–10% (**794**) Ar = Ph, 27%; *p*-$Me_2NC_6H_4$, 25%

alcoholic ammonia give 3,5-diarylpyridines. It seems very likely that both of these reactions involve cleavage to simple aldehydes or ethyleneimine followed by recyclization. The very electron-deficient pyrimidines (**795**) react with ynamines to give 3-diethylamino-2,6-

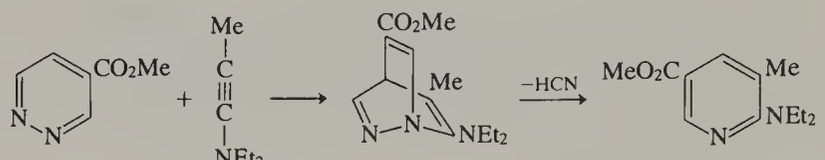
dicyanopyridines, by addition followed by expulsion of a cyanide ⟨80JHC1111, 74LA1190⟩. Similar cycloadditions occur between 5-nitropyrimidine and ketene-*N,N*- or -*O,O*-acetals, to give 3-nitropyridines ⟨82TL3965⟩.



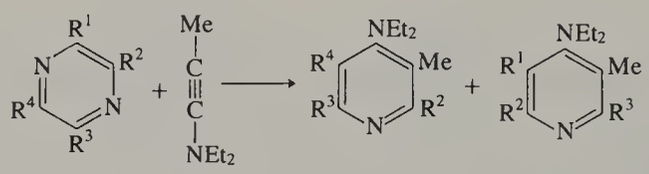
(795)

R^1	H	H	Me
R^2	Me	Ph	Me
%	97	20	36

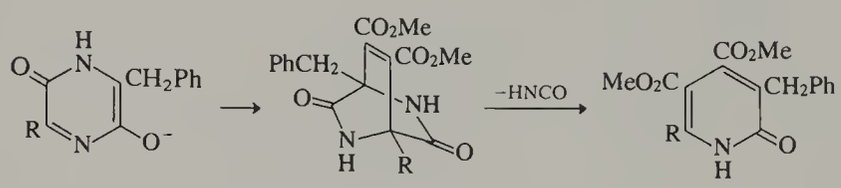
The other diazines can also undergo cycloaddition with ynamines; an example of a pyridazine addition is shown in equation (94) ⟨72TL1517⟩, and of an addition to a pyrazine in equation (95) ⟨72LA(761)39⟩. Pyrazinediones react with the electron-deficient acetylenedicarboxylic ester, with subsequent expulsion of isocyanic acid, as shown in equation (96) ⟨73JCS(P1)404⟩.



(94)



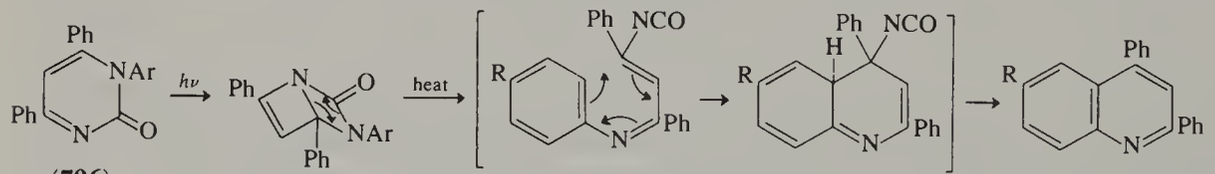
(95)



(96)

R = Me, CH_2Ph

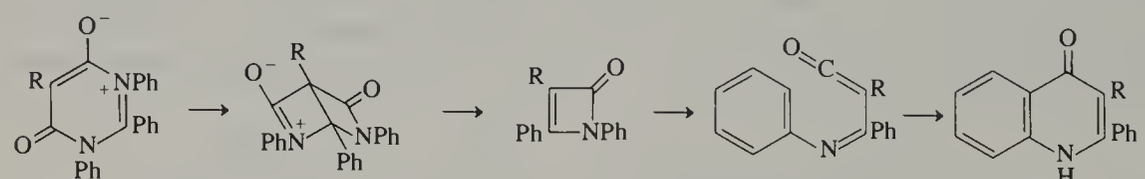
Photolysis of the pyrimid-2-one (**796**) gives a diazabicyclohexanone which can be thermolyzed as shown in equation (97) to give quinolines ⟨80TL2825⟩. Another diazabicyclohexanone is invoked as an intermediate in the conversion of the zwitterions (**797**) into quinol-4-ones ⟨75S247⟩; an alternative pathway can give 4-hydroxyquinol-2-ones ⟨79CB3424⟩.



(796)

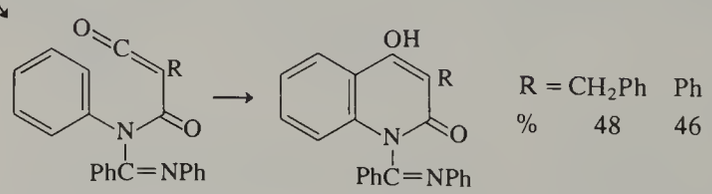
(97)

R	H	Me	MeO
%	100	100	100



(797)

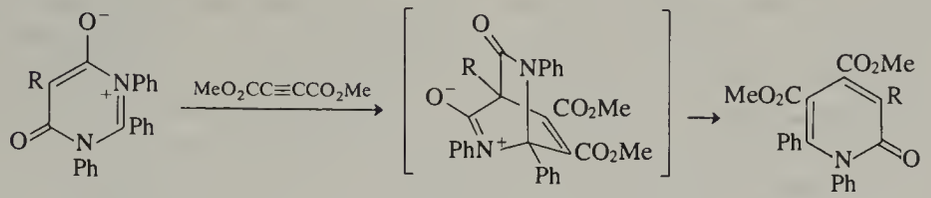
R =	CH_2Ph	Ph
%	70	60



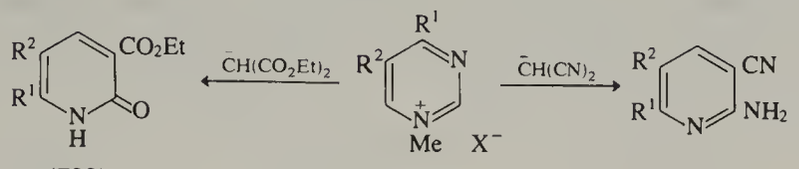
R =	CH_2Ph	Ph
%	48	46

The same zwitterions can give pyrid-2-ones (**798**) when treated with dimethyl acetylenedicarboxylate ⟨71AG(E)925⟩. Quaternary pyrimidinium salts are attacked by the anions from diethyl malonate or malononitrile to produce pyrid-2-ones (**799**) or 2-aminopyridines (**800**) respectively ⟨74RCT233⟩. Quinazoline *N*-oxide (**801**) reacts with ketones on heating to give quinolines; the reaction is assumed to be initiated by attack at C-4, with subsequent

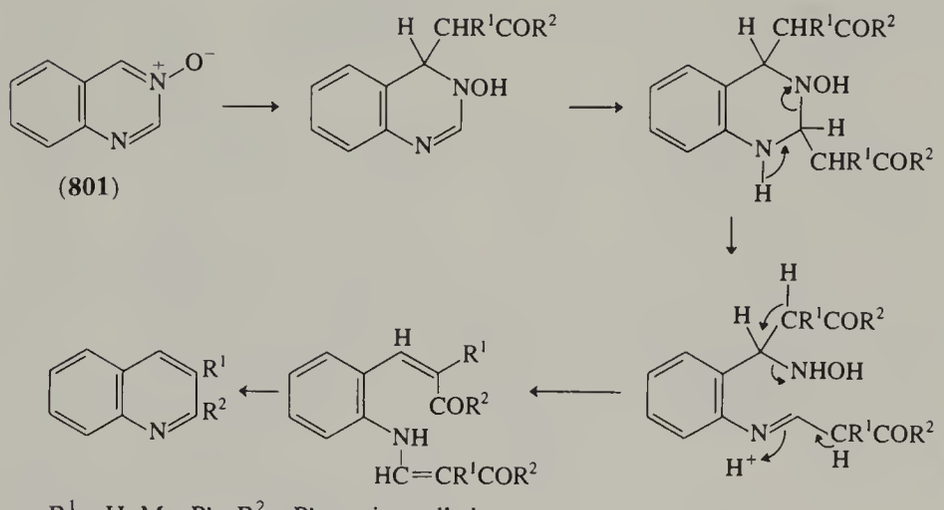
cleavage of the C(2)—C(3) bond and recyclization ⟨75CPB746⟩. The zwitterion (**802**) resembles the monocyclic system (**797**), and produces 4-hydroxyquinol-2-ones when thermolyzed ⟨79CB3424⟩.



(**798**)

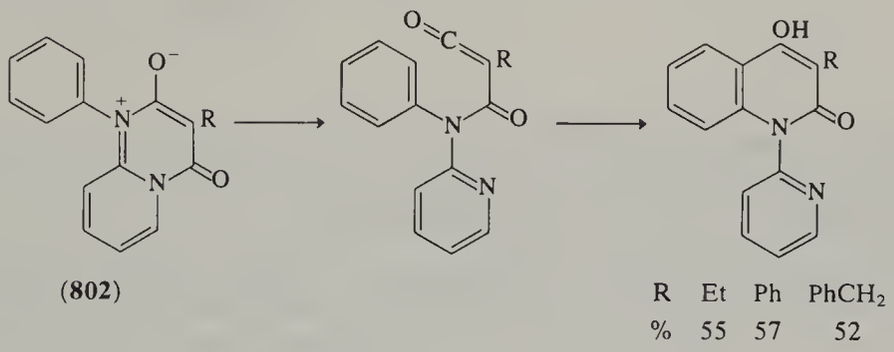


(**799**) (**800**)



(**801**)

R^1 = H, Me, Ph; R^2 = Ph, various alkyl

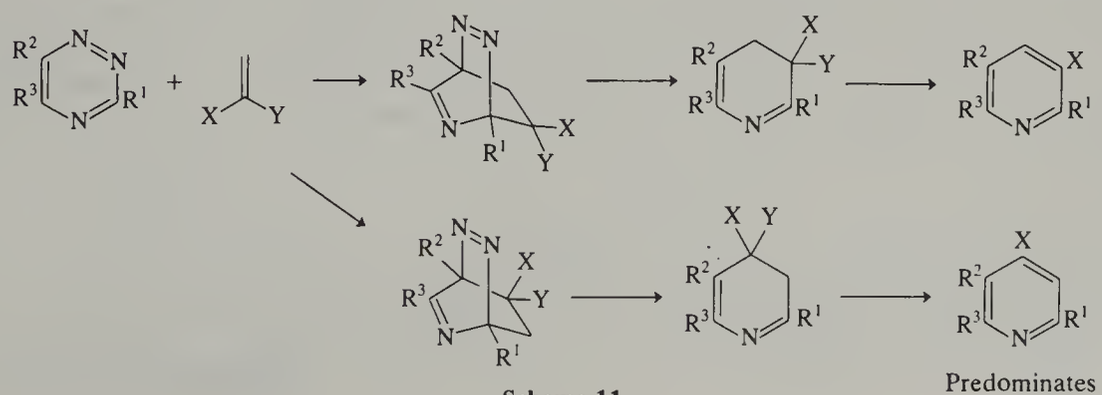


(**802**)

R	Et	Ph	$PhCH_2$
%	55	57	52

2.08.3.4.6 Triazines and benzotriazines

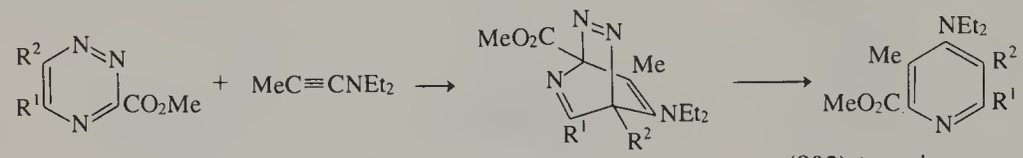
The Diels–Alder addition between 1,2,4-triazines and alkenes gives dihydropyridines or pyridines, provided that the alkene is electron-rich ⟨72LA(758)120⟩. Since most of the electron-rich alkenes are unsymmetrical some points of ambiguity arise, summarized in Scheme 11.

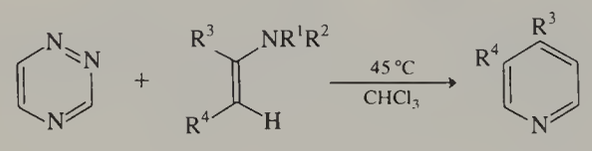


Predominates

Scheme 11

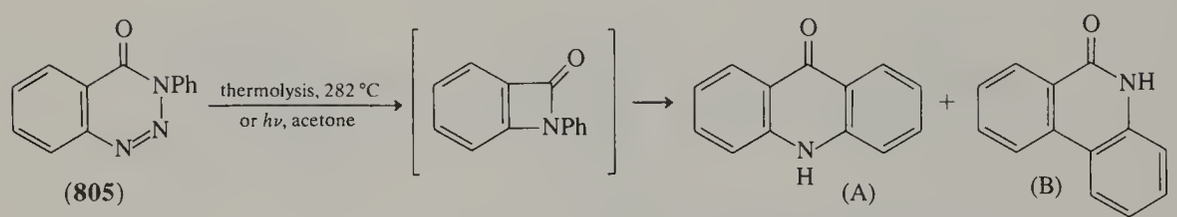
Mixtures can arise from lack of regioselectivity in the addition although the first examples showed a preference for group X to be in position 4. The second ambiguity (the nature of the fragment XH or YH which is eliminated) seems to be less critical because the relative ease of elimination can be assessed. It was at first reported that ynamines reacted with 1,2,4-triazines to give pyrimidines but there is at least one case ⟨75TL2901⟩ where the pyridine (**803**) or its regioisomer has been obtained. The addition of a wide selection of 1,1-disubstituted alkenes has been reported ⟨75TL2897⟩, and, more recently, the use of the parent triazine and enamines to give 3,4-disubstituted pyridines (**804**) in which the regiochemistry is controlled by the amino function which is placed at position 4 ⟨81JOC2179⟩. This paper contains an excellent list of references to cycloaddition routes to pyridines. The 1,2,3-benzotriazin-4-one (**805**) can be pyrolyzed or photolyzed to give acridone ⟨68JCS(C)1028, 68CB3079⟩. The mechanism suggested for the pyrolysis involves a ring contraction to a benzazetidinone.





R^3	Pr^n	Et	cyclohexyl
R^4	Et	Me	H
%	71	68	64

R^3,R^4 = $(CH_2)_n$, 22–78%

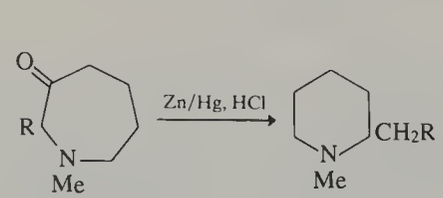


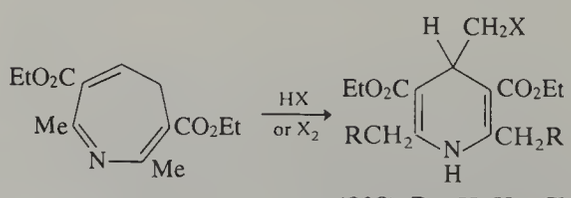
Thermolysis (A) 31% (B) 14%
Photolysis (A) 13% (B) 0%

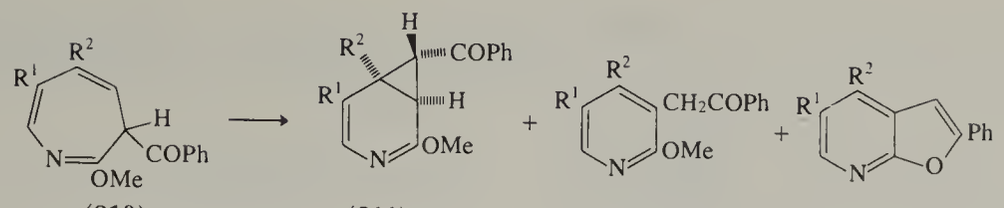
2.08.3.5 From Seven-membered Rings

2.08.3.5.1 Azepines, benzazepines and dibenzazepines

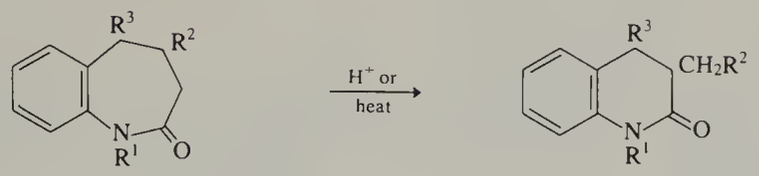
Clemmensen reduction of azepinone (**806**) produces a piperidine ⟨50JA3632⟩. Treatment of the azepine (**807**) with hydrochloric or hydrobromic acids gives dihydropyridines (**808**); a similar dihydropyridine (**809**) is obtained from the dihydroazepine with bromine in carbon tetrachloride ⟨65JCS2411⟩. Photolysis of the 3*H*-azepine (**810**) gives three related products (**811**)–(**813**) ⟨69T5217⟩. A number of similar ring contractions are known of dihydrobenzazepinones to dihydroquinol-2-ones. The ester (**814**) with acid gives the quinolone (**815**) ⟨55JA5932⟩, while the amide (**816**) is converted by heat into compound (**817**) (a mixture of *cis* and *trans* isomers) ⟨69HCA1929⟩. The dioxobenzazepine (**818**) similarly gives the 4-hydroxyquinol-2-one (**819**) ⟨59JOC41⟩. An attempt to introduce unsaturation into the tetrahydrobenzazepine (**820**) by heating it with lithium chloride in DMF produced a quinoline-4-carbaldehyde ⟨72JCS(P1)2012⟩. The benzazepinone (**821**) and the benzazepinedione (**823**) are converted by treatment with acid and with base respectively into the quinoline-4-carboxylic acid (**822**) ⟨69CJC1227⟩ and the 2-oxo-quinoline-4-carboxylic acid (**824**) ⟨62JCS3097⟩.





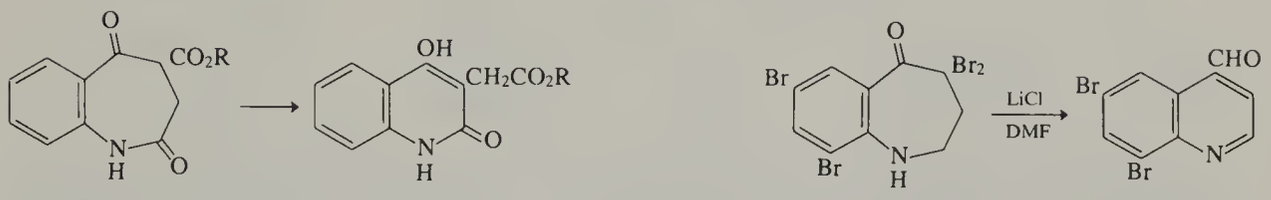


(**810**) (**811**) (**812**) (**813**)

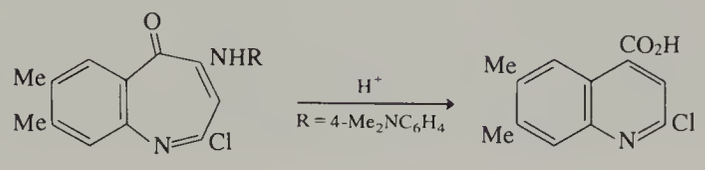


(**814**) $R^1 = R^3 = H$, $R^2 = CO_2Et$
(**816**) $R^1 = Me$, $R^2 = CONR_2$, $R^3 = Ph$

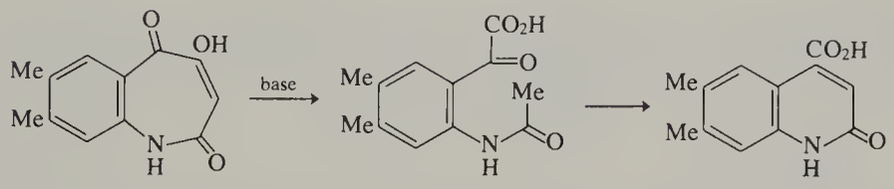
(**815**) $R^1 = R^3 = H$, $R^2 = CO_2Et$
(**817**) $R^1 = Me$, $R^2 = CONR_2$, $R^3 = Ph$
(*cis* and *trans*)



(**818**) (**819**) (**820**)

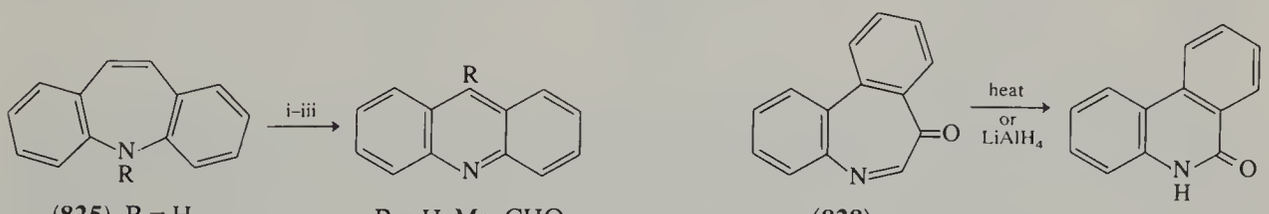


(**821**) (**822**)



(**823**) (**824**)

The dibenzazepines are also readily converted into acridines or phenanthridines. The parent dibenz[*b*,*f*]azepine (**825**) can give acridine or 9-methylacridine when treated with Fremy's salt or with acid ⟨68CC1412, 72AJC2451⟩, and the *N*-acetyl derivative (**826**) also gives 9-methylacridine with acid ⟨61HCA753⟩, but the *N*-nitroso derivative (**827**) gives with acid, or on thermolysis, acridine with a small amount of 9-formylacridine ⟨72AJC2451⟩. Benz[*b*,*d*]azepinone (**828**) can be converted into phenanthridinone by heat or by reduction with lithium aluminum hydride ⟨62JCS3468⟩.



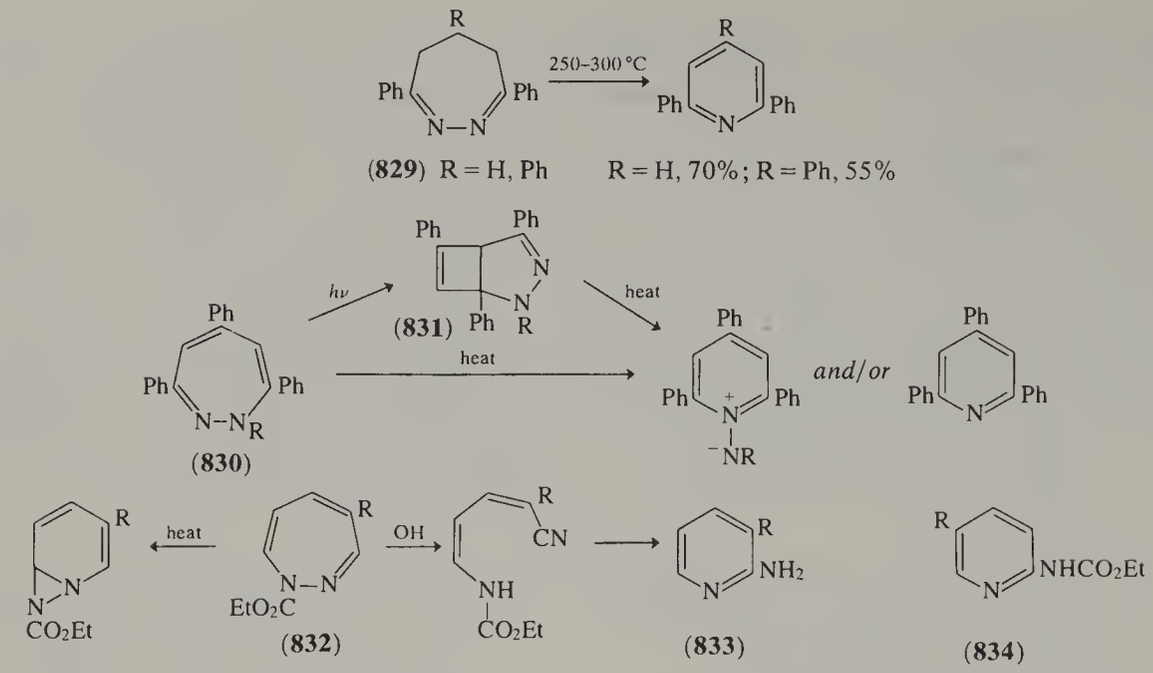
(**825**) R = H
(**826**) R = Ac
(**827**) R = NO

R = H, Me, CHO

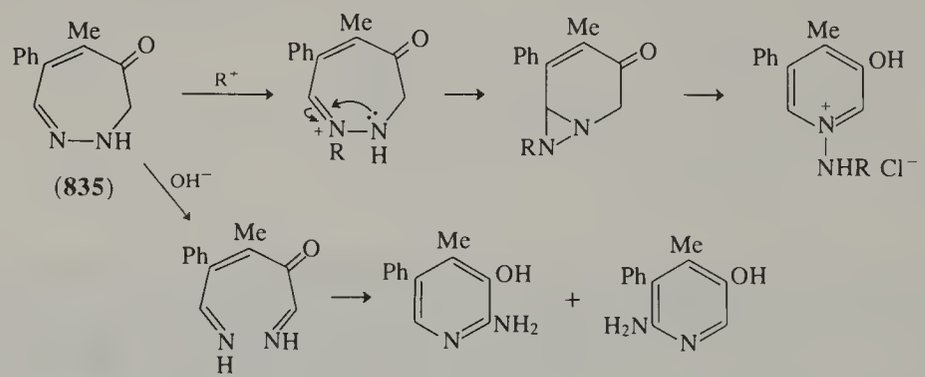
i, H^+; ii, Fremy's salt, iii, heat

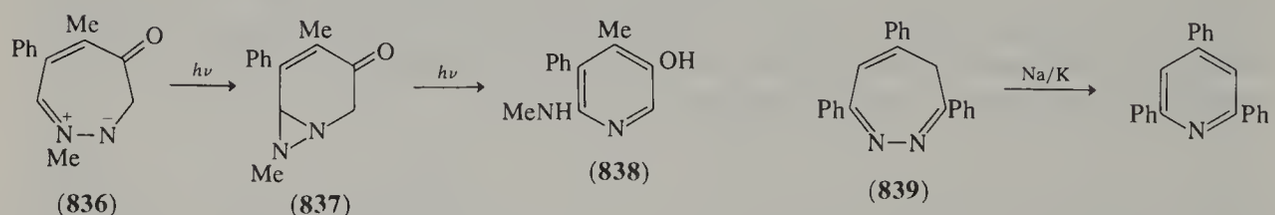
(**828**)

Diazepines of all types have been found to be very susceptible to ring contraction. The dihydro-1,2-diazepines (**829**) give pyridines on thermolysis ⟨71CI(L)1356⟩. Thermolysis of the 1*H*-1,2-diazepines (**830**) gives mixtures of pyridines and pyridinium ylides; the same products, though not in the same proportions, are formed by photolysis, with subsequent pyrolysis of the bicyclic intermediates (**831**) ⟨71CC1022⟩. It was later reported that the *N*-ethoxycarbonyl-1,2-diazepines (**832**) are converted by base into 2-aminopyridines (**833**), but that thermolysis takes a different route from that shown previously, to produce 2-pyridylcarbamates (**834**) ⟨73BSF635⟩.

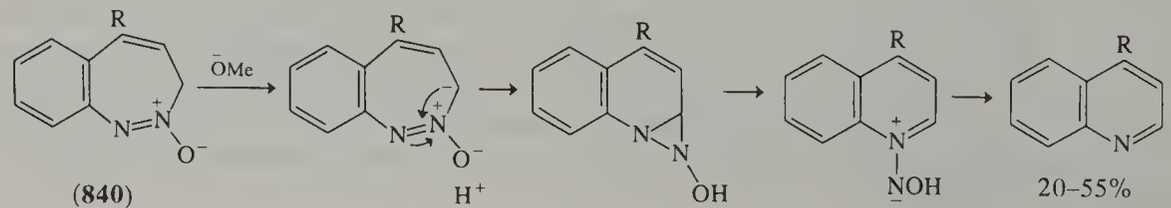


The dihydro-1,2-diazepin-4-ones (**835**) undergo a very interesting series of rearrangements with acids, summarized in equation (98), and with bases, summarized in equation (99). The mechanisms are discussed at length in a review ⟨B-73MI20800, B-73MI20801⟩; earlier references will be found in the papers ⟨64JOC2124, 59JA6029⟩. The 1-methyldiazepinone (**836**) is converted by photolysis into the same pyridine (**838**) as that obtained by treatment with base; an intermediate (**837**) has been postulated ⟨68JA4738⟩. Sodium–potassium alloy converts the 3*H*-1,2-diazepine (**839**) into 2,4,6-triphenylpyridine, possibly *via* the antiaromatic anion ⟨72TL4891⟩.

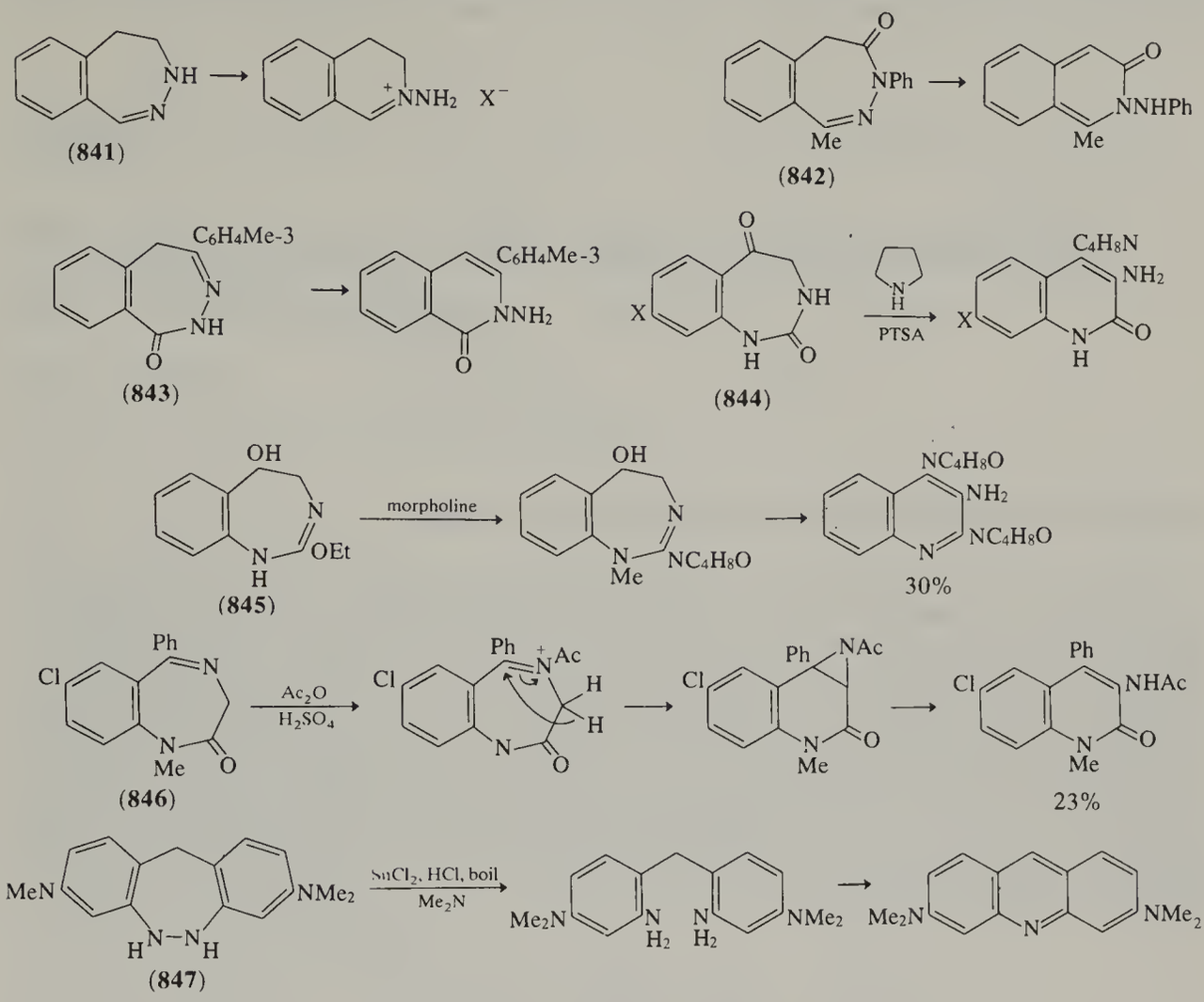




A number of benzodiazepines undergo ring contraction to quinolines or isoquinolines. 1,2-Benzodiazepine oxides (**840**) react with sodium methoxide with extrusion of N-2 to give quinolines ⟨76CC419⟩. The dihydro-2,3-benzodiazepine (**841**) when treated with acids gives *N*-aminodihydroisoquinolinium salts ⟨62CB2012⟩. Other derivatives (**842**) and (**843**) of the same system also give *N*-aminoisoquinoline derivatives ⟨61JOC1898, 05CB3845, 05CB3853⟩. Both the 1,3-benzodiazepine derivatives (**844**) and (**845**) react with secondary amines to give 3-aminoquinolines ⟨76JCS(P1)1331⟩. 1,4-Benzodiazepinone (**846**) reacts with acetic anhydride to give a 3-acetamidoquinol-2-one ⟨65JOC524⟩. The dihydrodibenzo[*c*,*f*]-

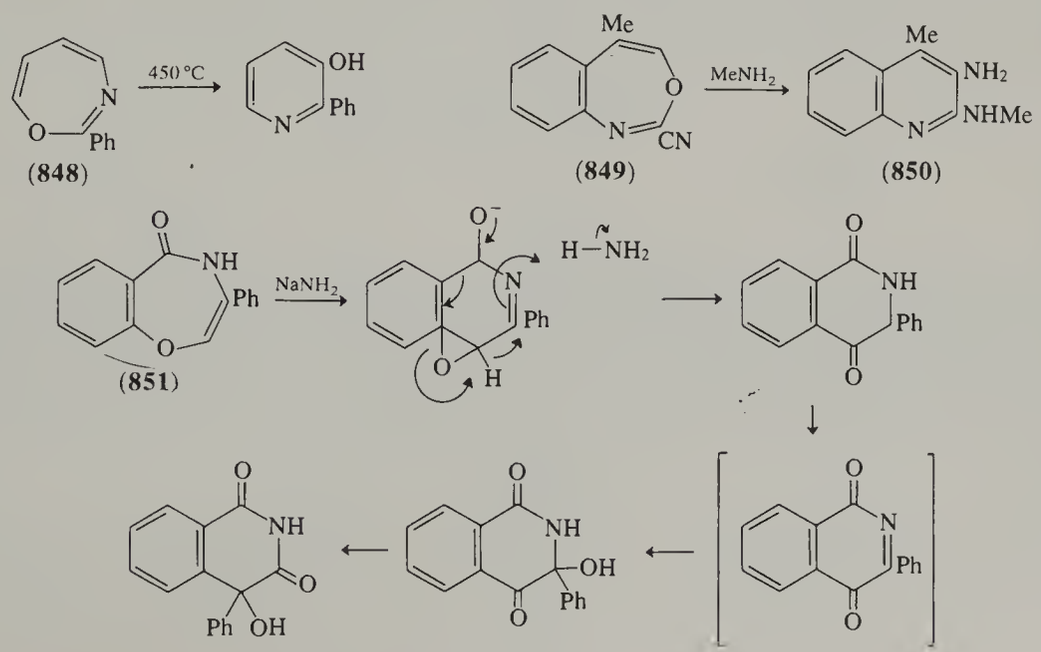


[1,2]diazepine (**847**) is converted into an acridine on reduction, presumably *via* the diaminodiphenylmethane ⟨10BSF527⟩.



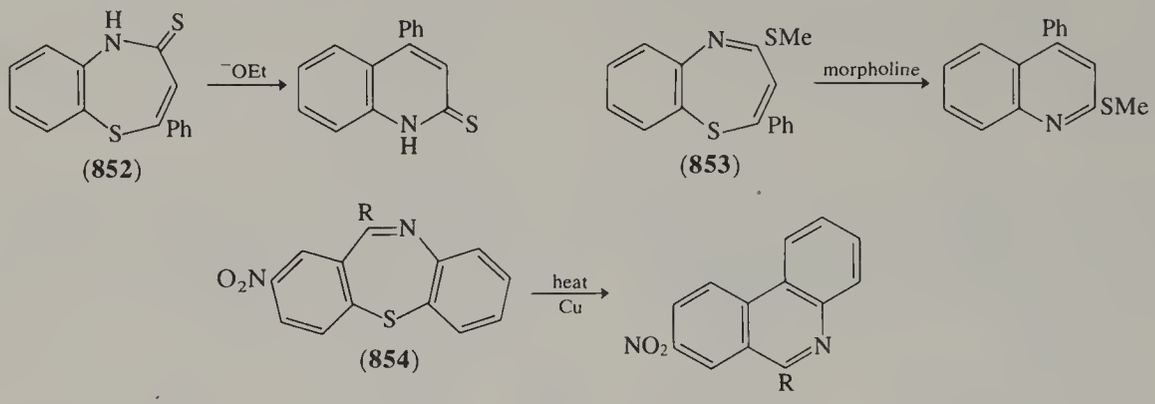
2.08.3.5.2 Oxazepines, benzoxazepines, benzothiazepines and dibenzothiazepines

The 1,3-oxazepine (**848**) is thermally labile; the main products are formylpyrroles but some 3-hydroxy-2-phenylpyridine is obtained ⟨75TL1067⟩. The benzoxazepines of type (**849**) are intermediates in the photochemical breakdown of quinoline *N*-oxides and can sometimes be isolated. They normally break down to give 3-hydroxyquinolines ⟨66TL2145, 67CPB663⟩, but compound (**849**) can be converted by methylamine into the diaminoquinoline (**850**) ⟨67TL5237⟩. The benzoxazepinone (**851**) with sodamide forms a mixture of three isoquinoline



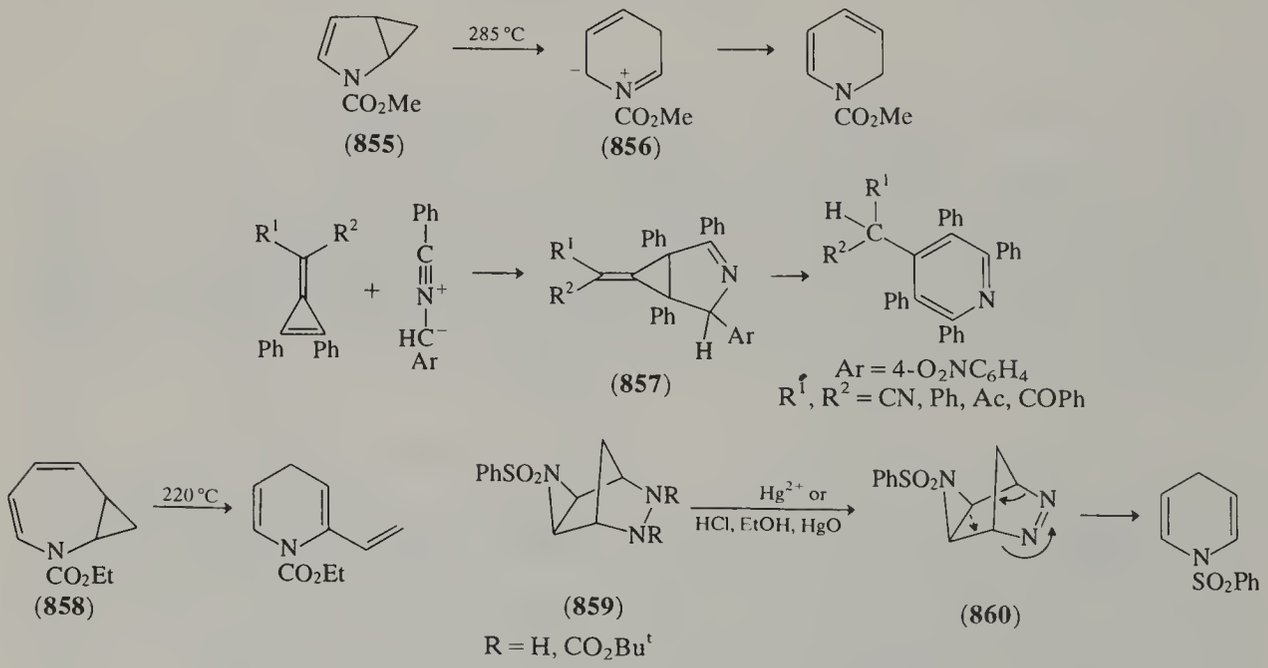
(100)

derivatives in the sequence shown in equation (100) ⟨68HCA413⟩. The benzothiazepinethione (**852**) and its methyl ether (**853**) are both converted by base into isoquinolines ⟨70HCA1697⟩, while heating the dibenzothiazepines (**854**) produces phenanthridines ⟨57JCS3818⟩.



2.08.3.6 From Miscellaneous Bicyclic and Tricyclic Systems

The carbene adduct (**855**) from *N*-methoxycarbonylpyrrole undergoes ring expansion on pyrolysis (it is suggested that a charged intermediate (**856**) is involved) to produce a 1,2-dihydropyridine; lithium aluminum hydride reduction produces a mixture of 1,2-dihydro- and 1,2,5,6-tetrahydro-*N*-methylpyridines ⟨72JA6495⟩. Deuterium labelling of the carbene shows that there is a hydrogen shift during the rearrangement. The slightly more complex compound (**857**), an isolated intermediate in one case, gives pentasubstituted pyridines, the hydrogen shift being to the *exo*-methylene carbon atom ⟨75CC384⟩. A carbene adduct from an azepine opens thermally with ring contraction to give a vinyldihydropyridine ⟨69TL4717⟩. Another route to 1,4-dihydropyridines starts from the diazanorbornene (**860**) which is obtained from the dihydro derivative (**859**; R = H) or from the di-*t*-butyl ester (**859**; R = CO_2Bu^t) ⟨72CC1260⟩.



2.09

Pyridines and their Benzo Derivatives: (vi) Applications

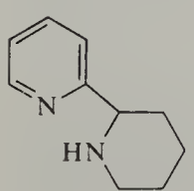
F. S. YATES
Synthetic Chemicals Ltd., Wolverhampton

2.09.1 INTRODUCTION

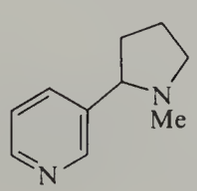
The amount of literature on applications of pyridine and benzopyridine derivatives is particularly vast. This necessarily abbreviated presentation is written not as a definitive text, but as an overview in an attempt to convey to the reader the importance and variety of pyridine derivatives in the industrial sphere.

2.09.2 NATURAL PRODUCTS

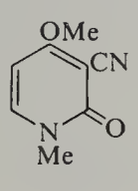
The pyridine alkaloids anabasine (**1**), nicotine (**2**), ricinine (**3**), nornicotine (**4**) and trigonelline (**5**) form an important group of natural products. Thus anabasine (**1**) is extracted on a large scale in the Soviet Union ⟨56MI20900⟩ and functions as an insecticide with acute and subacute toxicity. Nicotine (**2**) has been used as an anthelmintic but more widely as an agricultural insecticide, functioning as a contact poison when combined with oleic acid



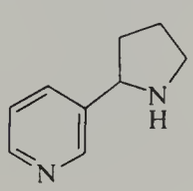
(**1**)



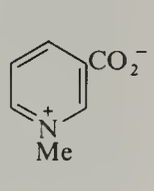
(**2**)



(**3**)



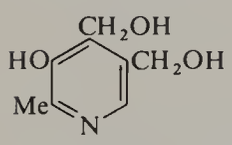
(**4**)



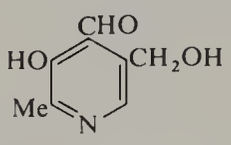
(**5**)

or as a stomach poison in combination with bentonite ⟨41CRV(41)123⟩. Nornicotine (**4**) has similar applications ⟨61CPB818⟩. The biosynthesis of ricinine (**3**), available from seeds and leaves of the castor plant, has been described ⟨61JBC(236)1186⟩.

Another important group of structurally inter-related natural products is the B_6 vitamins, pyridoxol (**6**), pyridoxal (**7**), pyridoxamine (**8**) and codecarboxylase (**9**) ⟨B-68MI20900⟩. Here the aromatic pyridine ring plays a vital role in fundamental metabolism in two ways: as (**9**) in reactions of amino acids, including racemization, decarboxylation, transamination and elimination or replacement of substituents on the β- and γ-carbon atoms ⟨B-79MI20900⟩, and as (**10**), a coenzyme, nicotinamide adenine dinucleotide (NAD^+), partaking in biological redox reactions ⟨71ACR121⟩. Synthesis of the B_6 vitamins has received significant commercial attention ⟨64USP3124587, 62USP3024244⟩. Desmosine (**11**) is a degradation product of elastin, a protein which possesses unique elasticity and tensile strength ⟨B-72MI20900⟩.



(**6**)



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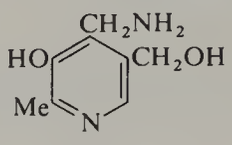

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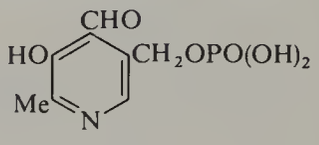
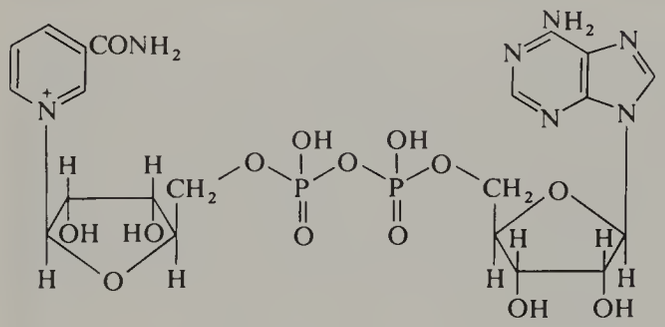
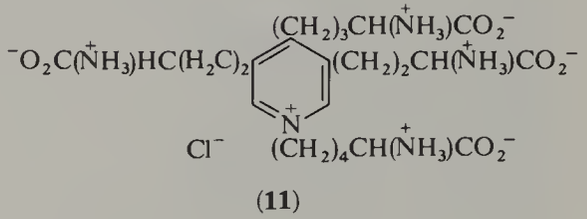


(**9**)

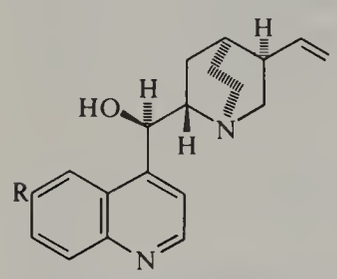


(**10**)

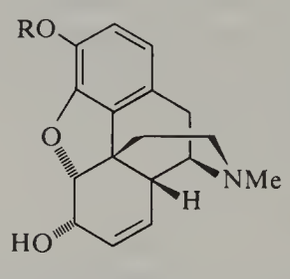


(**11**)

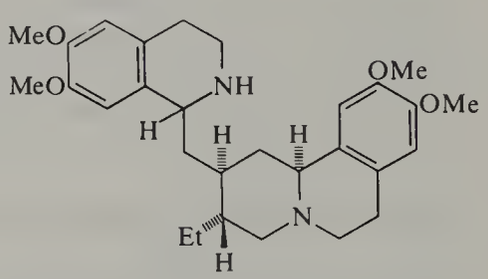
The quinoline, isoquinoline and phenanthridine ring structures are important in medicinal plant alkaloids ⟨B-70MI20900, B-70MI20902, B-70MI20903⟩ and as a consequence have found application in chemotherapy. Thus the Cinchona alkaloids ⟨B-79MI20901⟩, including cinchonine (**12**) and quinine (**13**), useful for treatment of malaria, prompted the development of a range of antimalarials (see Section 2.09.3.5). Morphine (**14**) and codeine (**15**), well-known analgesics, and emetine (**16**), an antiamoebic ⟨62BEP615033⟩, can all be regarded as tetrahydroisoquinoline derivatives. Berberine, a protoberberine dihydrodibenzoisoquinolizinium alkaloid containing the typical tetracyclic ring structure, has found application as an antibacterial, antimalarial and antipyretic ⟨B-75MI20900⟩. A small group of isoquinoline alkaloids, for example corydaldine (**17**), is known to have medicinal importance ⟨69USP3452027⟩. Finally, the fully aromatic benzylisoquinoline alkaloid papaverine (**18**) is a powerful coronary vasodilator ⟨B-75MI20901⟩.



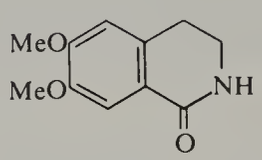
(**12**) R = H
(**13**) R = OMe



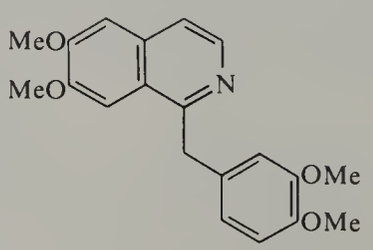
(**14**) R = H
(**15**) R = Me



(**16**)

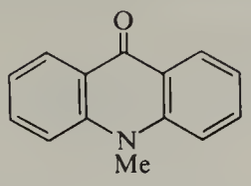


(**17**)

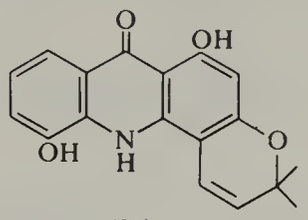


(**18**)

Alkaloids containing the acridine moiety, such as the tricyclic (**19**) and tetracyclic (**20**) acridone alkaloids, continue to be isolated from a variety of sources and are periodically reviewed ⟨B-77MI20900⟩.



(**19**)



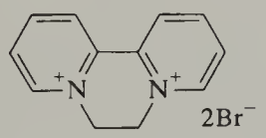
(**20**)

2.09.3 GENERAL APPLICATIONS

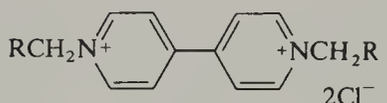
A number of excellent reviews on pyridine derivatives have been written with industrial bias ⟨B-80MI20900, 77CZ389, 70MI20901, 66MI20900⟩ and these have formed the foundation for the information presented below.

2.09.3.1 Herbicides

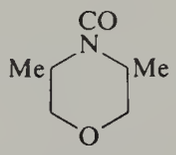
A major proportion of the pyridine manufactured is used in the production of the well-known weedkillers diquat (**21**) and paraquat (**22a**). Thus, pyridine is reacted with degassed Raney nickel to give 2,2′-bipyridyl ⟨66OS(46)5, 67BRP1202711⟩ or dehydrogenated with sodium to afford 4,4′-bipyridyl ⟨63MI20900⟩, the feedstocks for the diquaternary salts ⟨65CI(L)782⟩. Although the chemicals are marketed as formulations of their salts the herbicidal activity resides entirely in the cation. Their mode of action is considered to be *via* photolytic formation of a radical species which catalyzes production of a phytotoxic product ⟨B-72MI20901⟩. Recent studies support this view ⟨B-79MI20902⟩. More complex quaternary salts (**22b**) and (**22c**) also demonstrate herbicidal activity ⟨78SAP7706622⟩.



(**21**)



(**22a**) R = H

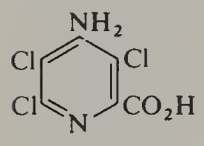


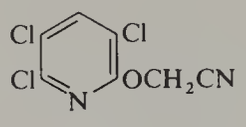
(**22b**) R =

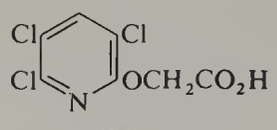
(**22c**) R = CO_2R

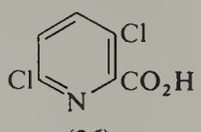
Chloropyridines feature strongly in the herbicide field and a variety of commercial products exist. For example, Picloram®, 4-amino-3,5,6-trichloropicolinic acid (**23**), manufactured from 2-methylpyridine *via* the corresponding methyltrichloro derivative ⟨63BEP628487⟩, is a potent systemic herbicide usually formulated with 2,4-D or 2,4,5-T. It exhibits a high degree of activity against most broad-leaved plants and conifers and is used in forestry to clear a variety of bush and tree species. Reaction of 2,3,5,6-tetrachloropyridine with paraformaldehyde/potassium cyanide gives the cyano compound (**24**), a precursor to (3,5,6-trichloro-2-pyridinyloxy)acetic acid (**25**) ⟨75USP3862952⟩. The latter again displays promising herbicidal action against broad-leaved and woody weeds, useful in non-crop areas. A review on Picloram and related compounds has been published ⟨B-76MI20900⟩. In contrast, the herbicide Lontrel®, 3,6-dichloropicolinic acid (**26**), is tolerated by crops such as sugar beet and small grain cereals whilst showing excellent post-emergence activity against many of the weeds tolerant to phenoxyalkanecarboxylic acids ⟨76GEP2558399⟩. More recently a new range of herbicides with reverse activity to that of the phenoxyalkanecarboxylic acids, *viz.* elimination of grass-like weeds in broad-leaved crops, is commanding much commercial attention ⟨81EUP24907, 79GEP2755536, 77EUP2925, 77EUP3877, 76GEP2546251⟩. The common structural feature of all these products is a halophenoxypyridine ring, exemplified in (**27**). Substitution patterns are the same, *i.e.* 2,3,5-pyridyl, but activity is claimed despite variation

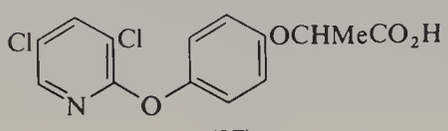
of the functional groups. A related herbicidal sulfanilide (**28**) has also been described ⟨77GEP2850821⟩. Fluoridone (**29**), a relatively new herbicide, has found application in aquatic plant management ⟨79MI20903, 79MI20904⟩ and in treatment of cotton crops ⟨B-79MI20905⟩.

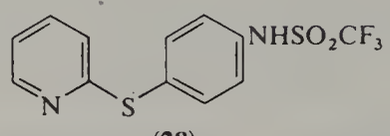

(**23**)

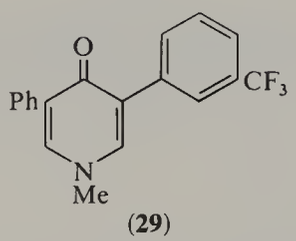

(**24**)

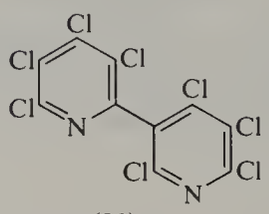

(**25**)


(**26**)


(**27**)


(**28**)

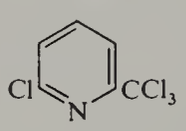

(**29**)

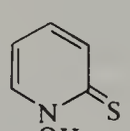

(**30**)

Development of a new method of synthesis of 2,3′-bipyridine ⟨81MI20900⟩ may permit the exploitation of the corresponding octachloro compound (**30**), derived by chlorination in the gas phase and described as a herbicide ⟨70BRP1276253⟩.

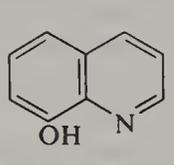
2.09.3.2 Bactericides/Fungicides

Chemicals are used widely as agricultural fungicides for control of bacteria in a variety of crops including apples, potatoes, bananas and grapes. In addition, fungicides are used to protect plastics, paints, wood and textiles and in paper production ⟨B-68MI20901, B-68MI20902⟩. The success of a potential fungicide is often determined by properties other than inherent fungitoxicity such as general toxicity, stability, resistance to leaching by water and cost of production. A number of chloropyridines or derivatives of chloropyridines exhibit fungicidal or bactericidal activity. Thus, controlled chlorination of α-picoline affords 2-chloro-6-trichloromethylpyridine (**31**) which is selectively active against *Nitrosomonas* bacteria, the organism responsible for the conversion or nitrification of ammonium ions to nitrite ions in soil ⟨61USP3135594⟩. The compound thus acts as a nitrogen stabilizer and prolongs the beneficial effects of nitrogen fertilizers. Gas-phase chlorination of pyridine affords the 2-chloro compound ⟨72GEP2252002, 63USP3153044⟩ which is in turn converted *via* the *N*-oxide into the zinc salt of 1-hydroxypyridine-2(1*H*)-thione (**32**) ⟨56BRP761171⟩, a fungicide becoming increasingly used in shampoos ⟨66USP3236733⟩.


(**31**)


(**32**)

Perhaps the most significant benzopyridine fungicides are the normal metal chelate compounds derived from 8-hydroxyquinoline (**33**), itself manufactured from quinoline by sulfonation/caustic fusion. Applications of (**33**) have been reviewed ⟨56CRV217⟩. Related compounds include quinacetol sulfate (**34**) ⟨B-77MI20901⟩ and halacrinate (**35**) ⟨B-77MI20901⟩.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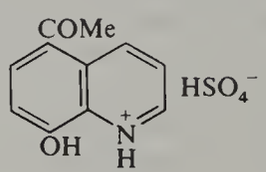
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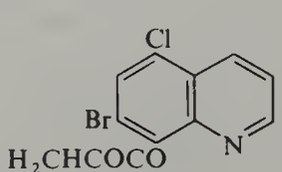
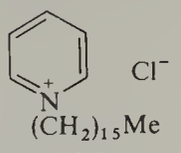

(**35**)

Pyridinium or diisoquinolinium salts, such as (**36**) and (**37**), have been used as topical antifungals ⟨60BRP839505, 33FRP738028⟩, whilst acranil (**38**), an antiprotozoal based on an aminoacridine, possesses general antiviral activity ⟨73MI20900⟩.



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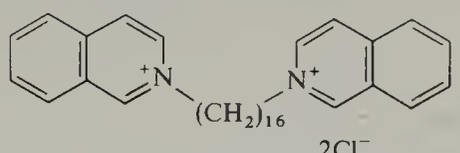

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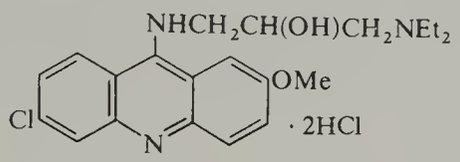

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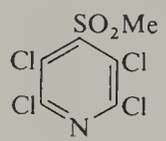
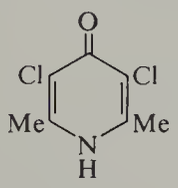


(**39**)

Paints are attacked in both the liquid and dry state by various microorganisms, particularly under damp and humid conditions. Fungicides such as Dowicil S-13® (**39**) are being used increasingly to prevent such attacks. Thus, addition of (**39**) to alkyd gloss and latex paint increased the mold resistance for two years in the tropics, with loss of the fungicide occurring through decomposition in sunlight and leaching by water ⟨71MI20900⟩.

2.09.3.3 Veterinary Products

A number of pyridine and quinoline derivatives have featured significantly in the growth of the poultry industry since the 1940s ⟨73MI20901⟩. Clopidol® (**40**) ⟨63NEP6410223⟩, amprolium (**41**) ⟨60USP3065132⟩ and the quinolones, *e.g.* cyproquinate (**42**) ⟨68SAP6705655⟩, all function as antiparasitics in the control of coccidiosis, particularly in the broiler, the most efficient system for converting vegetable into animal protein.



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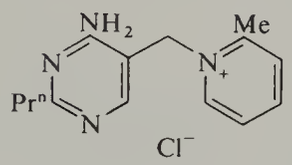

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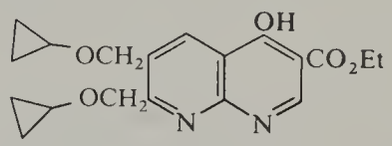
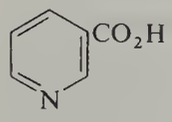
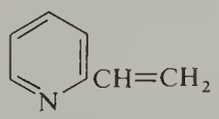


(**42**)

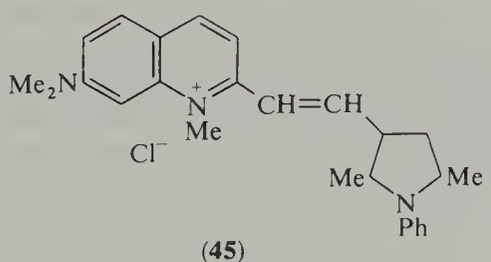
The discovery of the beneficial effects of niacin, pyridine-3-carboxylic acid (**43**), in the diets of both animals and humans (prevention of pellagra-like diseases) prompted its use as an important component of vitamin premixes in animal feeds and as a food enriching agent in cereal products. Consequently, considerable effort has been applied to its synthesis by oxidation/decarboxylation of ethylmethylpyridine with nitric acid ⟨70GEP1956117⟩ and catalytic gas-phase oxidation of 3-methylpyridine ⟨77MI20902⟩. Vapor-phase ammoxidation is another important alternative route to vitamin B_6 derivatives in general, which can be applied to both feedstocks ⟨77CZ384, 81MI20901⟩. For example, 3-methylpyridine may be mixed with ammonia and air over a metal oxide catalyst and the resulting 3-cyano derivative subsequently hydrolyzed to the corresponding acid or amide. Significant patent literature on oxidative ammonolysis exists and this has been reviewed ⟨B-80MI20900⟩.



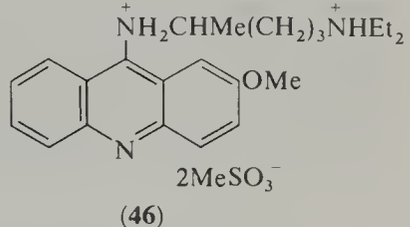
(**43**)



(**44**)



(**45**)



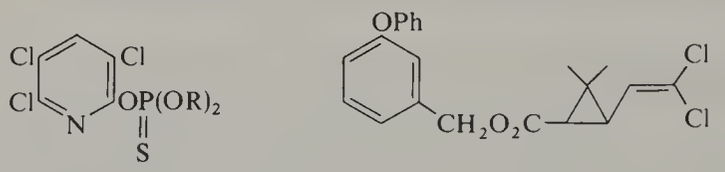
(**46**)

2-Vinylpyridine (**44**) exhibits many of the properties of a Michael acceptor. Thus, this molecule will undergo conjugate addition of methoxide ion and the product, methyridine,

is an antinematodal agent (anthelmintic) which has been used in veterinary medicine ⟨62BRP889748, 61MI20900⟩. Anthelmintics with more complex structures containing the quinoline or acridine moiety, for example (**45**) and (**46**), have been described ⟨50USP2515912, B-75MI20902⟩.

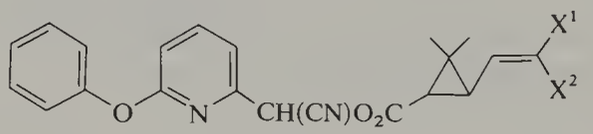
2.09.3.4 Insecticides

The pyridine ring features strongly in two important areas of insecticidal chemistry, *viz.* the organophosphates and synthetic pyrethroids. Chloropyrifos-methyl and -ethyl (**47**) are examples of patented organothiophosphate insecticides which kill on ingestion or contact ⟨64FRP1360901⟩. The chemicals function as cholinesterase inhibitors and exhibit a broad spectrum insecticidal activity and low mammalian toxicity. Synthetic pyrethroids such as permethrin (**48**) have made a significant impact on the insecticidal field ⟨76MI20901, B-73MI20902⟩, particularly in the treatment of cotton boll-weevil. As a consequence, interest in related pyridine compounds, for example (**49**), was stimulated ⟨80USP4228172, 80USP4221799, 81BRP2063878, 80JAP80115869⟩, although the necessarily more expensive pyridine ring may not prove cost-effective in certain applications. More recently, simple thiosemicarbazone derivatives of 2-acetylpyridine (**50**) have demonstrated insecticidal activity. These chemicals achieve their effect by inhibiting the molting process ⟨81MI20902⟩.

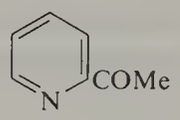


(**47**) R = Me, Et

(**48**)

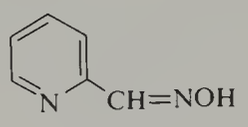


(**49**)

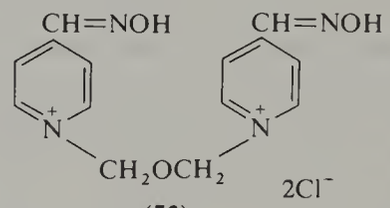


(**50**)

Cholinesterase inhibition, the mechanism whereby a number of insecticides and nerve gases function, may be reversed by acid salts of pyridine-2-carbaldehyde oxime (**51**). The chloride ⟨61JPS109, 64USP3155674⟩, iodide ⟨57USP2816113⟩ and methanesulfonate ⟨58USP2996510, 59MI20900⟩ all exhibit cholinesterase reactivation. Obidoxime chloride (**52**), based on the 4-aldoxime, has a similar function.



(**51**)



(**52**)

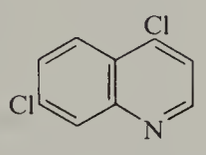
2.09.3.5 Pharmaceuticals

The commercial availability of basic pyridine derivatives has encouraged a tremendous amount of research into pharmaceutically active compounds. Two reviews in particular list a large number of medicinal compounds ⟨B-80MI20900, 77CZ389⟩ based on the pyridine ring. Likewise, the occurrence of benzopyridine natural products with chemotherapeutic activity has stimulated the production of synthetic materials from aromatic amine precursors. Some important examples are presented below.

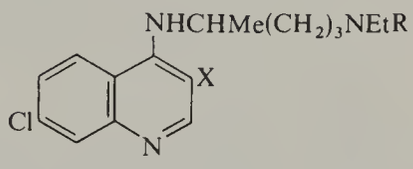
2.9.3.5.1 Natural products

Malaria in man is caused by several species of protozoan parasites known as plasmodia. The oldest effective drug for the treatment of this disease is indisputably quinine (**13**), a

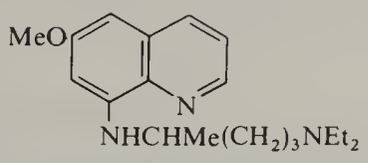
constituent of Cinchona bark. Development of synthetic substitutes for quinine was prompted by the difficulty of supply during the two World Wars. Loss of efficacy of synthetic drugs, as resistant strains of plasmodia developed, also meant continuing research into antimalarials. Two distinct classes of quinoline antimalarials exist, *viz.* the 4-amino-7-chloroquinolines and the 8-amino-6-methoxyquinolines ⟨B-77MI20903⟩. The key intermediate for the former, 4,7-dichloroquinoline (**53**), reacts with aliphatic diamines to yield the synthetics chloroquine (**54**) ⟨46JA113⟩ and hydroxychloroquine (**55**) ⟨50JA1814⟩. Introduction of a methyl group at the 3-position affords sontoquine (**56**), with retention of biological activity ⟨46JA380⟩. Pamaquine (**57**) ⟨46JA1584⟩ is an example of the 8-amino-6-methoxyquinoline antimalarials first developed in Germany in the 1930s. Recent work on chloroquinolineamines bearing an additional amino group in the side-chain led to an agent, clamoxyquine (**58**), with similar antiamoebic activity ⟨61JOC4070⟩.



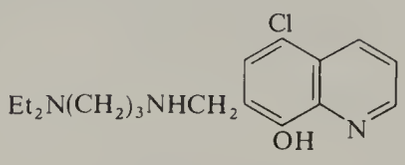
(**53**)



(**54**) R = Et, X = H
(**55**) R = CH_2CH_2OH, X = H
(**56**) R = Et, X = Me



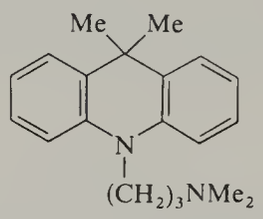
(**57**)



(**58**)

A series of acridine antimalarial compounds was developed almost simultaneously with the quinolines. For example, quinacrine (**59**) ⟨38USP2113357⟩, almost a composite of the quinoline synthetics, was used extensively in World War II under the trade name Atabrine®. Dimethacrine (**60**), an acridine with a radically different substitution pattern, still exhibits antimalarial activity ⟨63BRP933875⟩.

(**59**)

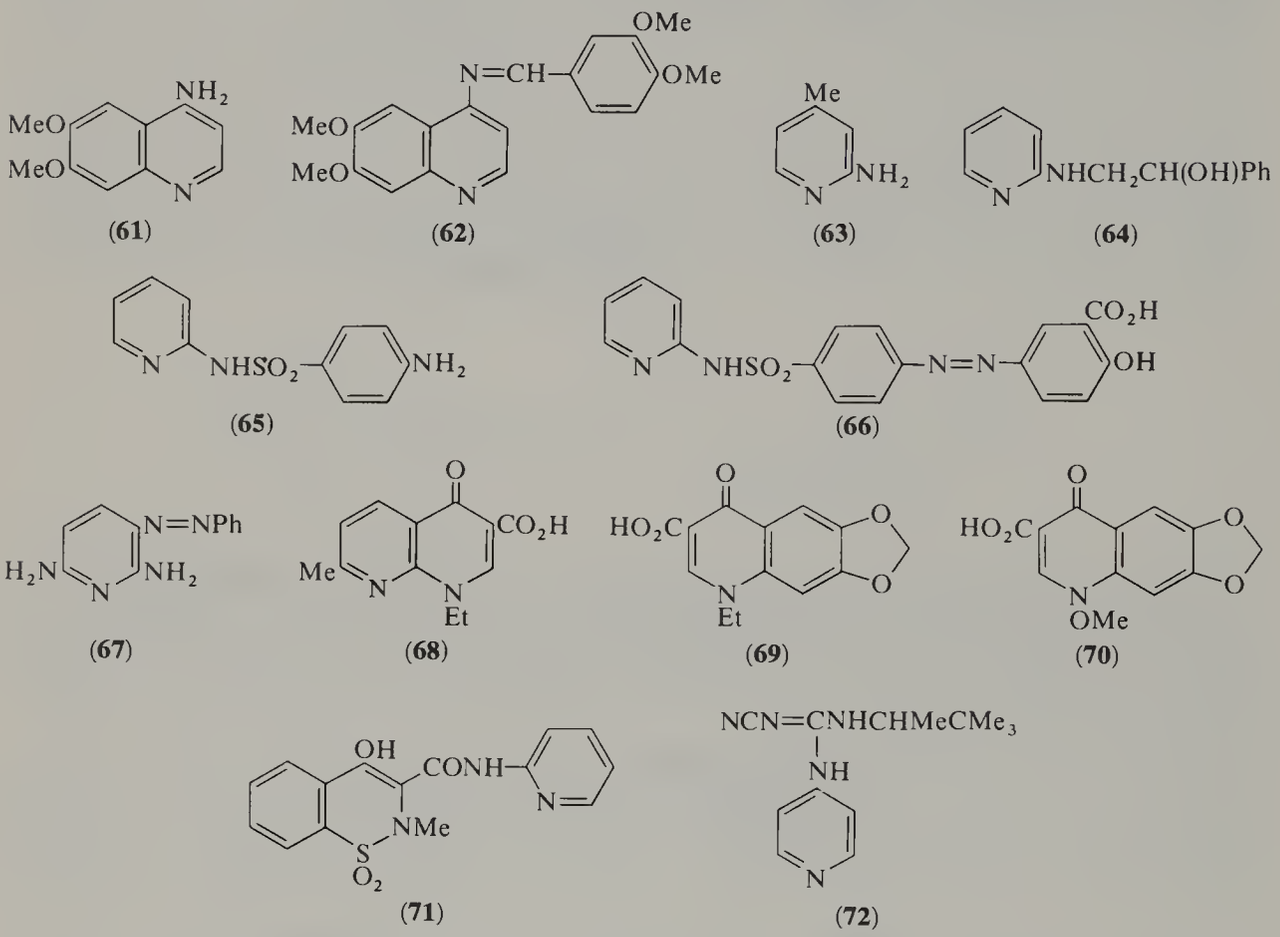


(**60**)

2.09.3.5.2 Amino derivatives

A number of relatively simple aminopyridine and benzopyridine derivatives demonstrate medicinal activity. Thus acriflavine, a mixture of 3,6-diamino-10-methylacridinium chloride and 3,6-diaminoacridine, is well established as an anti-infective. In addition, amquinsin, 4-amino-6,7-dimethoxyquinoline (**61**) ⟨65FRP1388756⟩, and its condensation product with veratraldehyde, leniquinsin (**62**) ⟨66USP3272806⟩, are hypotensive agents. Related 4-aminoquinolines have recently been described as potential analgesics, antipyretics, anti-inflammatories and antirheumatics ⟨80MI20901⟩. 2-Amino- and 2,6-diamino-pyridine derivatives are manufactured both in Europe and the USA by application of the classic Tschitschibabin reaction. Some of the simple amines are active without derivatization, for example 2-amino-4-picoline (**63**), a reported analgesic ⟨60USP2937118⟩, but generally the majority are the basic building blocks for more complex molecules. Phenyramidol (**64**), based on 2-aminopyridine, is a skeletal muscle relaxant used in the treatment of muscular rheumatism ⟨59JA4347⟩. Although sulphapyridine (**65**), an antibacterial derived again from 2-aminopyridine, is no longer used as a chemotherapeutic agent, a derivative, salazo-sulphapyridine (**66**), obtained by a diazotization/coupling reaction, finds application in the treatment of intestinal disorders ⟨77CZ389⟩. Another azo derivative, phenazopyridine (**67**),

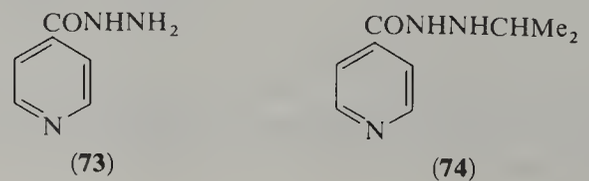
resulting from coupling of benzenediazonium chloride with 2,6-diaminopyridine, is used as a urinary tract analgesic in conjunction with antibacterial agents for treatment of urinary infections ⟨28USP1680108, 43JA2241⟩. Antibacterial activity is displayed by nalidixic acid (**68**), a 1,8-naphthyridine obtained *via* the initial reaction of 2-amino-6-methylpyridine with diethyl ethoxymethylenemalonate then cyclization ⟨62USP3149104⟩. The equivalent quinolone compound, oxolinic acid (**69**), shows similar behavior ⟨68JMC160⟩. More recently a related quinoline derivative referred to as AB206 (**70**) has similar properties to nalidixic acid but has the advantage of a more powerful action ⟨80MI20902⟩. Potent anti-inflammatory activity is displayed by piroxicam (**71**), a drug incorporating 2-aminopyridine in its structure. The absence of cardiovascular or CNS effects has encouraged its application in rheumatoid arthritis ⟨76AF1300⟩.



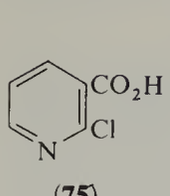
The treatment of hypertension involves much more than the simple lowering of the blood pressure by drugs which relax bronchial smooth muscle. Ideally a balanced reduction in blood pressure, without undue disturbance of the cardiovascular system generally, is required. Some pyridocyanoguanidines offer promise in this respect. For example, (**72**) has been used in preliminary clinical trials and its apparent nontoxicity justifies wider clinical evaluation ⟨72MI20902⟩.

2.09.3.5.3 Carboxylic acid derivatives

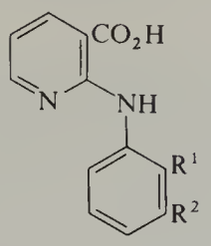
Although many antibiotics are effective to some extent in arresting the progress of tuberculosis, none is uniformly successful. One of the most effective is isonicotinic hydrazide (**73**), available from methyl isonicotinate by reaction with hydrazine ⟨B-75MI20903⟩. Extensive clinical use of this agent showed the drug to possess an additional antidepressant effect and led to the development of iproniazid (**74**), an established antidepressant ⟨53JOC994⟩.



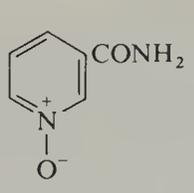
The substantial interest in the pharmacological properties of nonsteroidal anti-inflammatories prompted the development of a number of pyridine derivatives with analgesic activity. Thus, treatment of the *N*-oxide of nicotinic acid with phosphorus trichloride followed by hydrolysis of the resulting acid chloride gives (**75**), a precursor to niflumic acid (**76a**) ⟨66BSF2316⟩, flunixin (**76b**) ⟨B-80MI20903⟩ and clonixin (**76c**) ⟨67NEP6603357⟩.



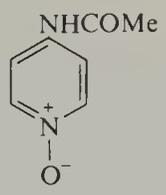
(**75**)



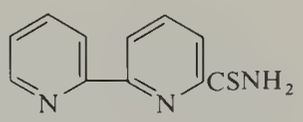
(**76a**) $R^1 = H$, $R^2 = Me$
(**76b**) $R^1 = Me$, $R^2 = CF_3$
(**76c**) $R^1 = Me$, $R^2 = Cl$



(**77**)



(**78**)

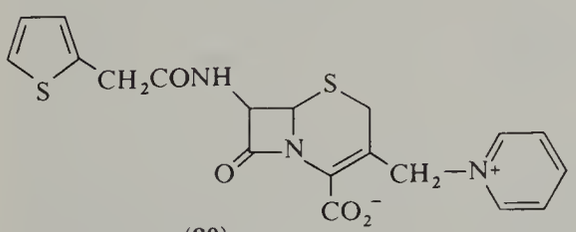


(**79**)

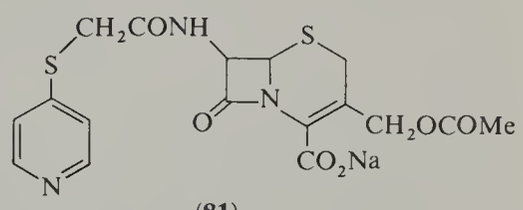
The related *N*-oxide (**77**) demonstrates pharmaceutical activity without structural modification, being used as a radiosensitizer to promote tumour regression during radiation therapy ⟨B-80MI20904⟩. Similarly, 4-acetamidopyridine 1-oxide (**78**) has been described as a neuromuscular stimulant ⟨80MI20905⟩. A carboxylic acid derivative (**79**) demonstrating anticancer activity independent of any radiation treatment has recently been reported ⟨81JMC1181⟩.

2.09.3.5.4 Quaternary salts

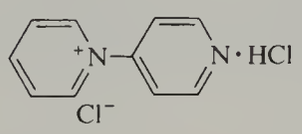
Cetylpyridinium chloride (**36**), obtained by quaternization of pyridine with cetyl chloride ⟨33FRP738028⟩, has long been used as an antiseptic for the treatment of infections and catarrhal inflammation of mucous membranes in the mouth and throat. Two semisynthetic cephalosporins contain the pyridine moiety and display antibiotic activity. Cephaloridine (**80**) ⟨65FRP1384197⟩ contains a quaternized ring, whilst cepharin sodium (**81**) ⟨71USP3578661⟩ is based on pyridine-4-thioglycollic acid. The latter is available from 4-pyridylpyridinium chloride hydrochloride (**82**), the product resulting from treatment of pyridine with thionyl chloride ⟨75GEP2347539⟩. A recent reference details a range of bis(pyridiniumthio) quaternary compounds, for example (**83**), useful in the treatment of ulcers by suppression of gastric acid secretion ⟨80BRP2038327⟩.



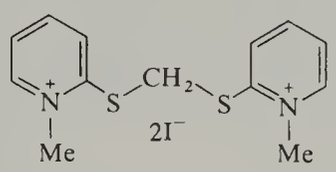
(**80**)



(**81**)



(**82**)

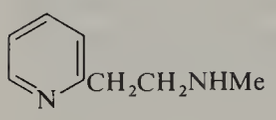


(**83**)

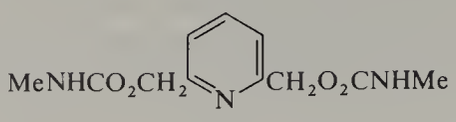
2.09.3.5.5 Alkyl derivatives

Betahistine (**84**), a vasodilator based on the readily available feedstock α-picoline, can be synthesized by a very lengthy process ⟨75MI20904⟩. A shorter route employing the commercially available 2-pyridylethanol has also been described ⟨77CZ389⟩. Reaction of (6-hydroxymethyl-2-pyridyl)methanol with methyl isocyanate, or its bis(phenylcarbonate) with methylamine ⟨66JAP6622185⟩, affords anginin (**85**), a compound used to reduce lipids and cholesterol levels in the blood. Esterification of 2-pyridylmethanol with ibuprofen

produces a product (**86**) with analgesic, antipyretic and anti-inflammatory activity ⟨80JAP8087770⟩.



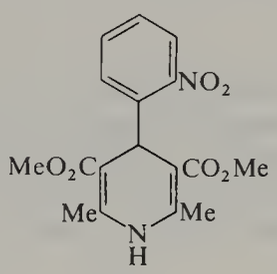
(**84**)



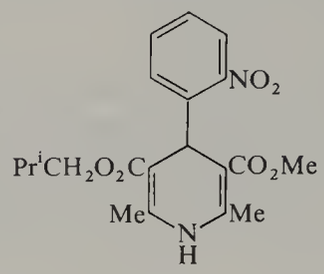
(**85**)

(**86**)

Application of part of the classical Hantzsch pyridine synthesis leads to nifedipine (**87**) ⟨81AG(E)762, 68SAP6801482⟩, a calcium antagonist useful in the treatment of angina. The pharmacology of a chemically related drug, nisoldipine (**88**), has recently been studied ⟨80AF2144⟩. Both compounds inhibit the transmembrane movement of calcium into activated smooth and cardiac muscle. Nisoldipine, however, is characterized by a high potency and uniqueness of action and may well prove to be of considerable therapeutic value.



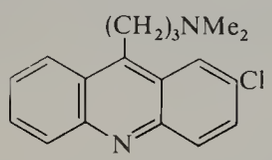
(**87**)



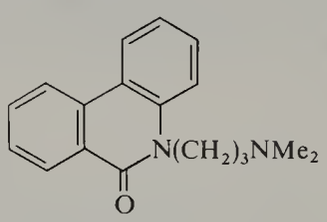
(**88**)

2.09.3.5.6 Halo derivatives

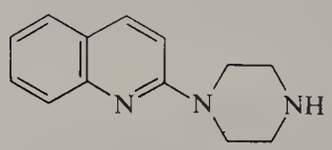
Nuclei for tricyclic antidepressants and tranquilizers, for example clomacran (**89**) ⟨64USP3131190⟩, almost invariably contain the three rings fused in a linear array. An exception to this general rule is fantridone (**90**), an antidepressant obtained by alkylation of the anion of phenanthridone with 3-chloro-*N*,*N*-dimethylpropylamine ⟨68BRP1135947⟩. Similar activity is shown by a relatively simple quinoline derivative (**91**), which is derived from 2-chloroquinoline and piperazine ⟨70GEP2006638⟩.



(**89**)

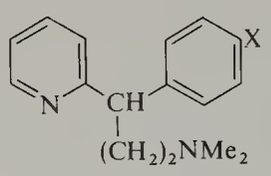


(**90**)

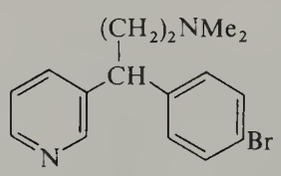


(**91**)

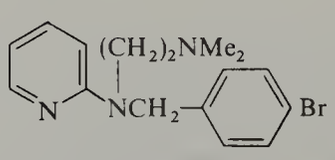
An important group of antihistamines, the pheniramines (**92**), use 2-chloropyridine as a basic feedstock. The activity of chlorpheniramine (**92**; X = Cl) as an H^1-receptor blocker has recently been reported ⟨79MI20906⟩. Zimelidine (**93**), a relatively new compound of related structure, exhibits antidepressant activity with reduced subjective side-effects found with other antidepressants ⟨79MI20907⟩. 2-Halopyridines also function as precursors to another group of antihistamines exemplified by *p*-bromotripelennamine (**94**) ⟨51USP2572569⟩.



(**92**)



(**93**)

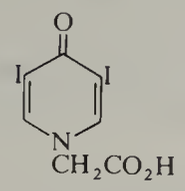


(**94**)

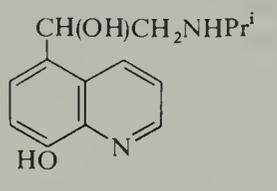
2.09.3.5.7 Hydroxy derivatives

4-Hydroxypyridine, available from pyridylpyridinium chloride hydrochloride, is the substrate for diodone (**95**) and its *n*-propyl ester, propyliodone. Both compounds are used as

X-ray contrast media ⟨73GEP2219707, 74USP3795698⟩. Drugs utilized in the treatment of asthma usually affect cardiovascular, as well as bronchial, adrenergic receptors. Considerable effort has been applied to the preparation of compounds that exhibit selectivity for the adrenergic receptors that predominate in the lung. Quinterenol (**96**) has shown promise in this direction ⟨66NEP6601980⟩.

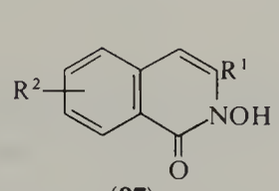


(**95**)

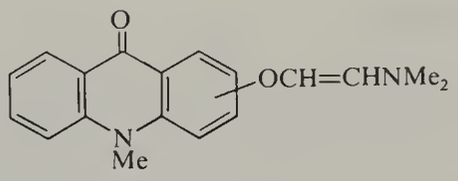


(**96**)

The synthesis of 2-hydroxycarbostyrils has recently been described ⟨81S729⟩. Patent literature also details their preparation, for example that of (**97**), and their use as anti-depressants ⟨69USP3452027⟩. A somewhat similar acridine derivative (**98**) is a reported antiviral ⟨79GEP2759468⟩.



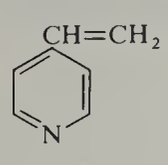
(**97**)



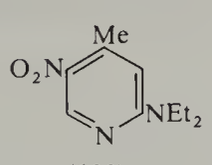
(**98**)

2.09.3.6 Miscellaneous Applications

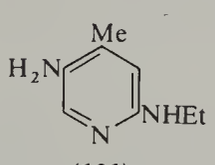
Two very significant derivatives manufactured in Europe and the USA are 2-vinylpyridine (2VP) (**44**) and 4-vinylpyridine (4VP) (**99**), both available from their respective methyl precursors. 2VP is used mainly in the form of a terpolymer latex with butadiene/styrene in conjunction with a resorcinol formaldehyde resin for the construction of synthetic textile plied tyres. The 2-vinylpyridine promotes tack. This characteristic tendency of (**44**) and (**99**) to form copolymers and indeed homopolymers has led to their use in widespread applications ranging from elastomers and ion-exchange resins to selective catalysts and pharmaceuticals ⟨72MI20903⟩. For example, 4VP/alkyl acrylate polymers have been reported to lower the pour point of crude oil for movement under low temperature conditions ⟨72NEP7202748⟩. Hydroformylation catalysts based on poly-2VP and poly-4VP copolymers continue to receive attention ⟨80BRP1579501, 80USP4198353⟩. The removal of phenols from aqueous effluents, normally effected by bacteria, has also been achieved by polyvinylpyridines ⟨81JAP8131486, 80GEP2947765⟩. Other interesting applications include lithium/iodine/polyvinylpyridine pacemaker batteries ⟨80MI20906, 80MI20907⟩, acid scavengers ⟨80EUP11370⟩ and polyvinylpyridine supported oxidizing agents ⟨81JOC1728⟩.



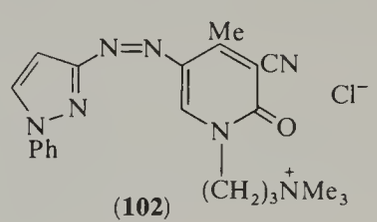
(**99**)



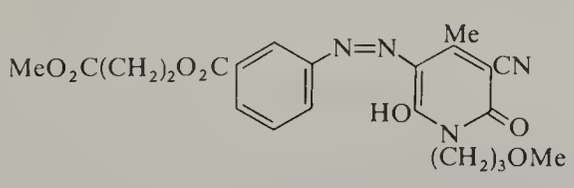
(**100**)



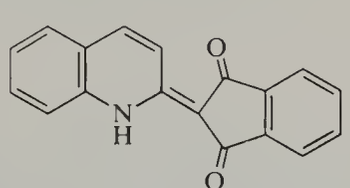
(**101**)



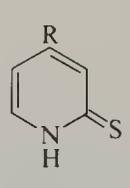
(**102**)



(**103**)



(**104**)



(**105**)

Some relatively simple pyridines have been used as hair dyes. Thus (**100**) is fast-yellow on white hair ⟨79JAP7923631⟩ and (**101**) fast-red when used in conjunction with hydrogen peroxide ⟨79JAP7928330⟩. More typical azo derivatives, for example (**102**) and (**103**), have

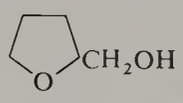
been used as dyes for acrylic ⟨79GEP2851373⟩ and polyester fibres ⟨79JAP7938332⟩ respectively. The yellow shade shows high fastness to light, sublimation, solvents and wet processing. A number of synthetic dyes contain the acridine or 9-acridanone moiety ⟨73HC(9)579⟩. The former include well-known basic dyes which contain amino or alkylamino substituents *meta* to the nitrogen atom. They are now of limited use, being water soluble and displaying disappointing light fastness. Simple 9-acridanone dyes are of interest as disperse dyes for synthetic fibres, whilst more complex quinacridones have been used as high-grade pigments ⟨73HC(9)579⟩. Quinophthalone dyes and pigments based on (**104**), though showing a small spectral coverage of yellow to orange, are outstanding for their color brilliance, light fastness and low cost of production ⟨74MI20900⟩.

A final illustration of the diverse applications of pyridines is given by 4-alkyl-2-mercaptopyridines (**105**), which are used in flotation processes for recovery of metal concentrates from metal-bearing ores ⟨80BRP2046747⟩.

2.09.4 IMPORTANT SOURCES OF PYRIDINE DERIVATIVES

2.09.4.1 Introduction

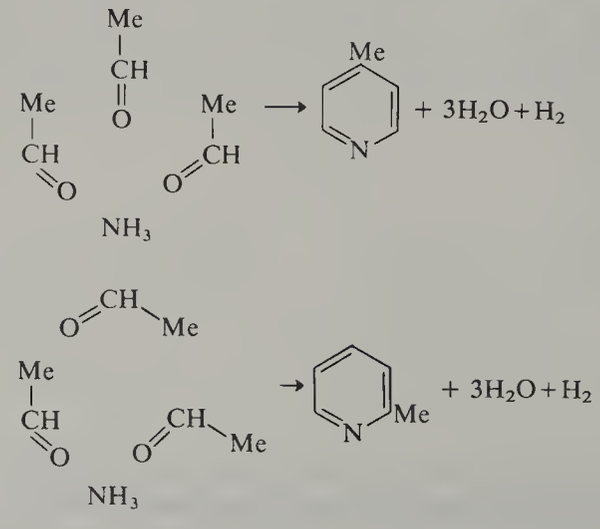
The basic building blocks pyridine and alkylpyridines and indeed, quinoline, isoquinoline and simple alkyl derivatives, have traditionally been obtained primarily from pyrolysis or carbonization of coal. Thus, fractional distillation of coal-tar with or without thermal cracking yields a range of individual tar-base components ⟨B-74MI20901⟩. Low-temperature carbonization (<900 °C) in general yields tar which contains *ca.* 1.9–2.5% total bases. Consequently large quantities of feedstock need to be processed to meet demand. The gradual dwindling of coal-tar supplies has encouraged over the years tremendous commercial interest in synthetic sources. Production from coal-tar still continues ⟨80CA(93)168078⟩ but has been somewhat superseded by a wide variety of synthetic processes. One limited approach employs other ring systems; for example tetrahydrofurfuryl alcohol (**106**) yields pyridine with ammonia by catalytic gas-phase conversion ⟨65NEP6409131⟩. More significant methods of manufacture have been detailed ⟨B-80MI20900⟩ and a summary is presented below.



(**106**)

2.09.4.2 Heterogeneous Catalyzed Gas-phase Synthesis

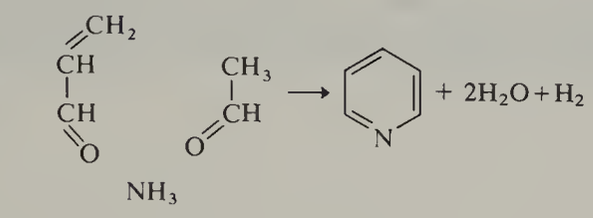
The general principle usually involves contact of an aldehyde or mixtures of aldehydes with ammonia at high temperature in the presence of an acidic catalyst. Aluminosilicate catalysts have been used ⟨80USP4220783⟩. A series of condensation reactions occurs with elimination of water and hydrogen and mixed products usually result. Acetaldehyde gives

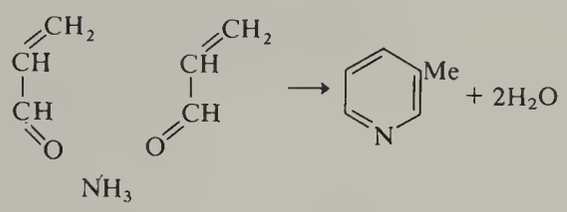


Scheme 1

mainly 2- and 4-methylpyridine with a silica–alumina catalyst ⟨71JAP7139873⟩, and promotion of the catalyst with metal oxides is claimed to improve the yield ⟨78GEP2746177⟩ (Scheme 1). Introduction of formalin into the feed changes the nature of the products, mainly to pyridine and 3-methylpyridine ⟨78USP4089863, 57USP2807618⟩. The reaction can be regarded as initial reaction of formalin with acetaldehyde to form acrolein, which in turn may self-condense or condense with acetaldehyde in the presence of ammonia (Scheme 2).

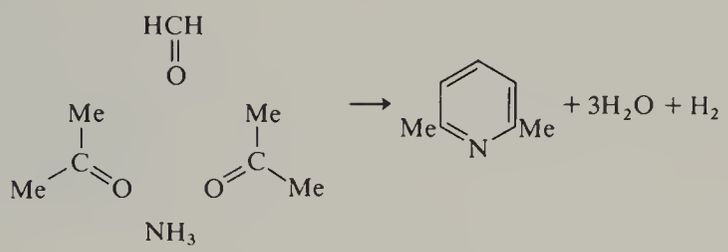
$$HCHO + MeCH{=}O \longrightarrow CH_2{=}CH{-}CH{=}O + H_2O$$





Scheme 2

Variations on this theme include the use of acrolein/ammonia ⟨72GEP2224160⟩ and acrolein/acetaldehyde/ammonia ⟨64BRP963887, 69BRP1141526⟩. Ketones can also be utilized. For example, 2,6-dimethylpyridine is obtained in 36% yield from combination of formalin/acetone/ammonia ⟨71GEP2064397⟩ (Scheme 3). This general reaction has recently been extended to include the preparation of 2,6-disubstituted ⟨78BEP858390⟩ and 2,3-disubstituted ⟨78GEP2712694⟩ pyridines from aromatic or heteroaromatic ketones/aliphatic aldehydes and ammonia.



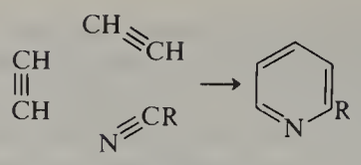
Scheme 3

2.09.4.3 Liquid-phase Synthesis

2-Methyl-5-ethylpyridine (MEP) is manufactured on a significant scale by a high-temperature liquid-phase pressure reaction of paraldehyde with ammonia. The presence of ammonium acetate catalyzes the reaction and MEP is separated from the pyridinic by-products by fractional distillation ⟨56USP2766248, 56USP2745833, 68MI20903⟩. MEP is also produced in conjunction with 2-methylpyridine in another process involving reaction of ethylene with a palladium–ammonia complex $[Pd(NH_3)_4]^{2+}$ ⟨74MI20902⟩.

2.09.4.4 Synthesis From Nitriles

Commercial development of a range of cycloalkene–cobalt homogeneous catalysts has prompted their application in the synthesis of pyridine and 2-substituted pyridines. Thus, bis(cyclopentadienyl)cobalt catalyzes the reaction of acetylene with hydrogen cyanide, acetonitrile or acrylonitrile to yield pyridine, 2-methylpyridine and 2-vinylpyridine respectively (Scheme 4; R = H, Me or $CH{=}CH_2$) ⟨76S26, 78AG(E)505, 75BEP846350⟩. The high cost of the catalyst has so far limited full commercial realization of this route. Acrylonitrile



Scheme 4

has also been used as a feedstock in processes based on an initial Michael reaction with ketones, then vapor phase cyclization of the resulting cyanoalkyl ketone in the presence of hydrogen using a nickel or palladium catalyst. Cyclohexanone yields quinoline ⟨74BRP1368506, 73BRP1304155⟩, whilst acetone affords 2-methylpyridine and 2-methylpiperidine ⟨73BRP1304155, 73BRP1303949⟩.

2.10

The Quinolizinium Ion and Aza Analogs

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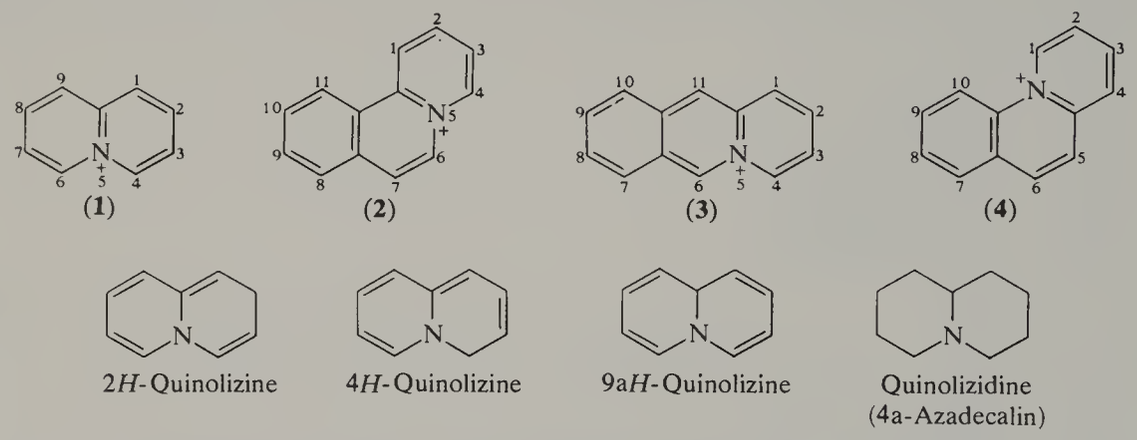
2.10.1 STRUCTURE AND PHYSICAL PROPERTIES

2.10.1.1 General

As pointed out in Chapter 2.01, the N^+ ion (azonia nitrogen) is isoelectronic with the carbon atom. When an azonia nitrogen replaces the carbon at position 4a in naphthalene, the product is the quinolizinium ion (**1**), the newest of the benzenoid aromatic heterocyclic systems having only a single nitrogen atom. While the preparation of a dibenzoquinolizinium salt was described in 1920 by Schneider *et al.* ⟨20CB(B)1459⟩, the synthesis of the parent cation (**1**) was announced for the first time by Boekelheide and Gall in 1954 ⟨54JA1832⟩. The earlier literature designated quinolizinium compounds as dehydroquinolizinium or dehydropyridocolinium derivatives, suggestions rejected by *Chemical Abstracts*. While the approved name, *quinolizinium*, does have the advantage of simplicity, it is contrary to the time-honored nomenclatural conventions ⟨64T33⟩ which would have quinolizinium imply any of the cations expected from the protonation of a quinolizine (Scheme 1). It is perhaps this inconsistency that has delayed the acceptance of quinolizinium as the correct designation for the aromatic species.



Scheme 1

As suggested by the title the principal emphasis in this chapter will be on the quinolizinium ion and its benzo analogs, with quinolizine and quinolizidine derivatives being mentioned only if they are obtained from, or transformed to, the aromatic species. For a more comprehensive treatment of these non-cationic species, the earlier reviews by Thyagarajan ⟨65AHC(5)291⟩ and by Mosby ⟨61HC(15-2)1001⟩ should be consulted.

The three possible benzo derivatives of the quinolizinium ion are each well known ⟨69ACR181⟩, the benzo[*a*]- (**2**), benzo[*b*]- (acridizinium) (**3**) and benzo[*c*]-quinolizinium (**4**) ions.

2.10.1.2 UV and Visible Spectroscopy

Although not yet confirmed by single-crystal X-ray analysis, the quinolizinium ion has been assumed to have a planar structure resembling that of naphthalene. Consistent with such an assumption is the UV spectrum of the quinolizinium ion. This may be seen in comparison with naphthalene ⟨54JA1832⟩, where it is seen that introduction of the azonia nitrogen causes a general, but non-uniform, bathochromic shift accompanied by a pronounced

intensification of absorption at longer wavelengths ⟨B-62MI21000⟩. The spectra of the benzo, dibenzo, naphtho and phenanthro derivatives of the quinolizinium ion have been found to show a similar qualitative relationship to those of their polycyclic hydrocarbon counterparts ⟨81H(16)987⟩.

Molecular orbital methods have been applied with increasing success to the calculation of the UV spectra of the quinolizinium ion ⟨71MI21000⟩ and have been extended to the three benzoquinolizinium ions as well as to some tetracyclic systems having an azonia nitrogen ⟨70G421⟩.

Differences between the absorption spectra of quinolizinium iodides and perchlorates reveal the presence of charge transfer bands believed to arise from electronic transitions from the iodide ion to either the solvent or the cation ⟨60JCS2437⟩.

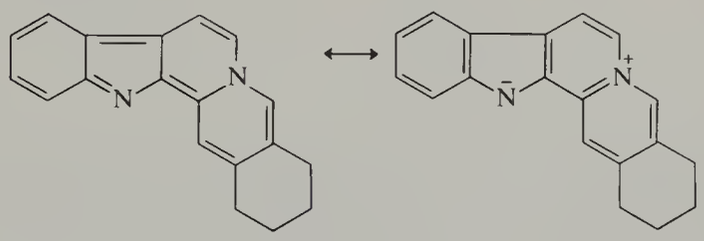
Evaluation of the UV–visible spectra has been used to demonstrate the formation of charge transfer complexes between the acridizinium (benzo[*b*]quinolizinium) ion and polycyclic aromatic hydrocarbons ⟨78ZC33⟩. Similar measurements have been employed to demonstrate the existence of an interaction between DNA and coralyne, a dibenzo[*a*,*g*]-quinolizinium salt ⟨76JMC1261⟩.

2.10.1.3 Fluorescence Spectroscopy

The acridizinium (benzo[*b*]quinolizinium) ion, being isoelectronic with anthracene, is fluorescent ⟨55JA4812⟩. The fluorescent quantum yield for acridizinium perchlorate in methanol was reported to be 0.52 ⟨80MI21000⟩. The rate of quenching of this fluorescence by alkyl halides was found to be related to the ionization potential of the halide ⟨78MI21001⟩. Quenching by anions was also measured ⟨79JPR420⟩.

2.10.1.4 IR Spectroscopy

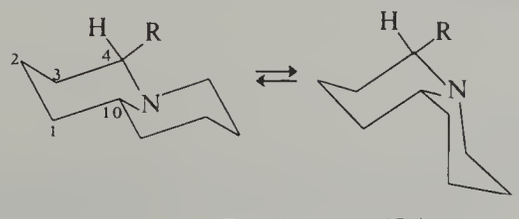
The IR spectra of aromatic quinolizinium derivatives have been used in the usual way to learn the nature of substituents. The classical example was its use by Woodward *et al.* ⟨49JA379⟩ to demonstrate the betaine structure of sempervirine (Scheme 2). Another important use in the aromatic series has been in establishing as identical the products of two different preparations of a quinolizinium derivative when, due to decomposition on heating, the usual melting point criteria are unreliable.



Sempervirine

Scheme 2

IR spectroscopy proved to be of critical importance in establishing the conformation of the quinolizidine nucleus (**5**), a completely reduced quinolizinium ring. From a study of model compounds Bohlmann concluded that *trans*-fused quinolizidine compounds in which the electrons of the nitrogen lone pair were *trans* to at least two axial hydrogens adjacent would show a significant band in the $2750 \pm 50\ cm^{-1}$ region ⟨58CB2157⟩. In an examination by Moynehan *et al.* ⟨62JCS2637⟩ of the IR spectra of eight monomethylquinolizidines, only



(**5a**) R = H (**5b**)
(**6a**) R = Me (**6b**)

the *trans*-4-methyl showed no Bohlmann band and thus must be the only one existing predominantly in the conformation having a *cis* ring fusion (**6b**).

2.10.1.5 NMR Spectroscopy

Van der Plas and coworkers ⟨81H(15)213⟩ have determined the ^{1}H NMR chemical shifts for each of the protons on quinolizinium bromide (Figure 1). For a series of quinolizinium derivatives it was found that the average values for coupling constants were: $J_{1,2} = 8–9$, $J_{2,3} = 6.5–8$, $J_{3,4} = 6.5–8$, $J_{1,3} = 2–3$, $J_{2,4} = 1–2$, $J_{1,4} \leq 1$ Hz. The same authors made use of ^{1}H NMR spectroscopy to demonstrate deuterium exchange of quinolizinium compounds in D_2O (Section 2.10.2.1.2).

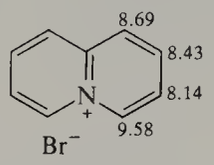
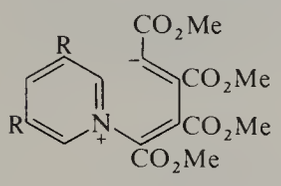
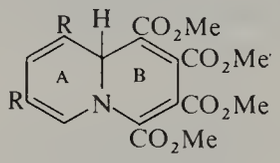


Figure 1 ^{1}H NMR chemical shifts (δ) for quinolizinium bromide

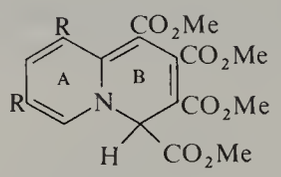
Earlier applications of ^{1}H NMR spectroscopy had led to a better understanding of the intermediates or transformation products encountered. Diels and Alder, the first to make a simple bicyclic quinolizinium derivative, discovered that the reaction of pyridine with two moles of dimethyl acetylenedicarboxylate at room temperature gave a labile adduct to which they assigned structure (**7**) ⟨34LA(510)87⟩. In a reexamination of the problem using methylpyridines, Acheson *et al.* proposed at 9a*H*-quinolizine structure (**8**) for the labile adduct and a 4*H*-quinolizine structure (**9**) for the 'stable' form obtained by heating ⟨60JCS1691⟩. The transformation (**8** → **9**) was accompanied by a downfield shift of the protons attached to the ring methyl groups (R = Me) from δ 5.4 to 5.1 p.p.m., suggesting that ring A had become aromatic. The possibility that the hydrogen atom shown at position 9a was actually at positions 6 or 8 was rejected due to lack of observation of a methylene doublet at about δ 3 p.p.m.



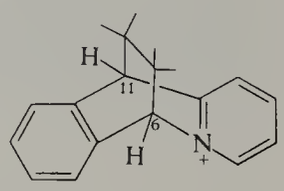
(**7**)



(**8**) R = H, Me



(**9**)



(**10**)

Following IR examination of eight monomethylquinolizidines (Section 2.10.1.4), Moynehan *et al.* ⟨62JCS2637⟩ measured the ^{1}H NMR spectrum of each and found no signal which could be used to distinguish the *trans* (**5a**) from the *cis* (**5b**) ring fusion. A study of the methiodides of the eight isomeric bases showed that the salts derived from the 1-, 2- and 3-methyl bases fell into two separate groups with regard to the *N*-methyl signal. Those falling into the δ 2.94–2.97 p.p.m. range were assigned the *trans* configuration while those in the 3.14–3.16 p.p.m. range were considered to be *cis*.

After the study of a number of cycloadducts (**10**) obtained by reaction of alkenes with the benzo[*b*]quinolizinium ion, Fields *et al.* ⟨68JOC390⟩ found that the two bridgehead protons could be easily distinguished. That at position 6, strongly deshielded by the adjacent positive charge, could be found at δ 6.63 ± 0.14 p.p.m. while the more remote proton at C-11 could be found in the range δ 5.49 ± 0.21 p.p.m. The multiplicities of these signals are indicative of the regiochemistry of addition.

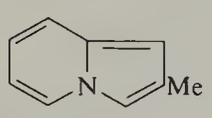
2.10.1.6 Electrical Conductivity

The conductivity of anhydrous acridizinium (benzo[*b*]quinolizinium) bromide in the form of void-free plates has been reported to be 1.2 Ω^{-1} cm^{-1} at 90 °C ⟨68JA3120⟩. It was believed that most of the current was carried by bromide ion either interstitially or through anion

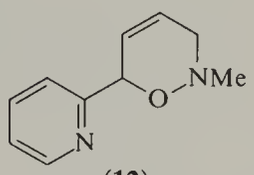
vacancies. The conductivity and dielectric constant of acridizinium TCNQ salts have been measured at various temperatures ⟨76MI21000⟩.

2.10.1.7 Mass Spectrometry

Perhaps partly due to the difficulty of introducing solid salts into the ionization chamber, mass spectrometry has, to date, played an insignificant role in the study of quinolizinium compounds. It is of interest that a peak at *m/e* 130 which appears in the mass spectrum of 2-methylindolizine (**11**) ⟨70OMS(3)1489⟩ and in that of 6-(2-pyridyl)-3,6-dihydro-2*H*-1,2-oxazine (**12**) ⟨74BSB147⟩ has been assigned to the quinolizinium ion (**1**). Evidence was presented that the ion next lost HCN to give a metastable ion of *m/e* 103 followed by loss of acetylene to afford a fragment of *m/e* 77.



(**11**)



(**12**)

2.10.2 REACTIVITY

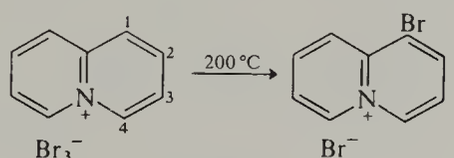
2.10.2.1 Reactivity of Ring Atoms

2.10.2.1.1 General

The symmetry of the quinolizinium ion is such that only four monosubstitution products are possible for any given substituent. On the basis of a computation using the Pariser–Parr–Pople method, including all singlet mono-excited electronic configurations, Galasso ⟨68MI21000⟩ concluded: 'The carbon atoms at 3 and 7 are expected to be most reactive towards electrophilic substitution.'

2.10.2.1.2 Towards electrophiles

Addition of bromine to quinolizinium bromide results in formation of the perbromide salt (**13**). The formation of this salt is reversible, for treatment with an easily brominated solvent like acetone regenerates the original bromide. Van der Plas and coworkers ⟨81H(15)213⟩ have shown that if the perbromide salt (**13**) is heated at 200 °C it is converted into 1-bromoquinolizinium bromide (Scheme 3). While the high temperature suggests that this may be a radical reaction, the orientation (at a carbon atom of lower positive charge, although not the 3-position predicted above) is consistent with an electrophilic mechanism.



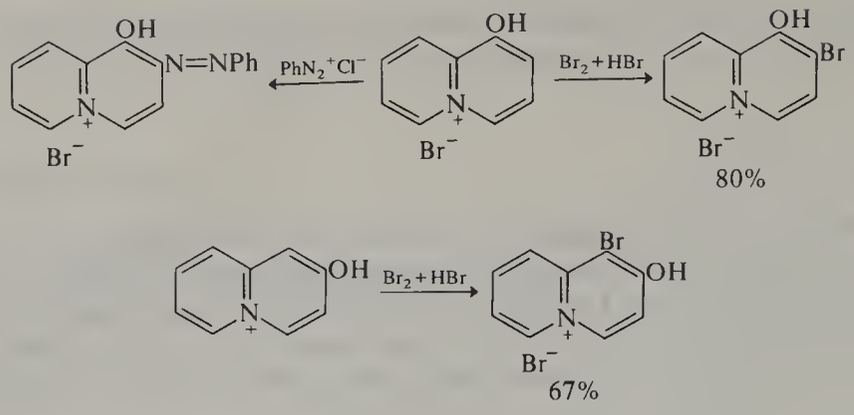
Br_3^- Br^-

(**13**) 69%

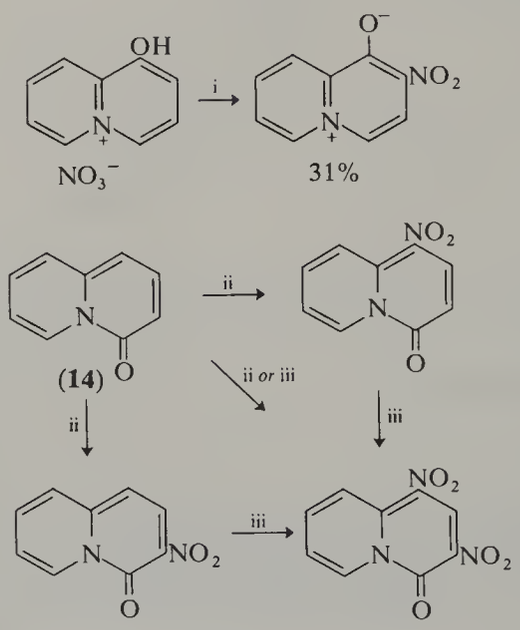
Scheme 3

While there does not appear to be any unequivocal case of the electrophilic substitution of the unactivated quinolizinium ion, such substitution does occur (Schemes 4 and 5) when strongly electron-releasing groups are present ⟨63JCS2203, 64JCS2760⟩.

Nitration of 1-hydroxyquinolizinium nitrate affords only a 31% yield of the betaine nitrated at the 2-position ⟨64JCS3030⟩. With quinolizin-4-one (**14**), which may be regarded as the betaine of 4-hydroxyquinolizinium ion, nitration in acetic acid at room temperature gives a 43% yield of 1,3-dinitroquinolizone. Only by use of cupric nitrate in acetic anhydride is there some mononitration (a mixture of 1- and 3-isomers), but here again the major product is the dinitro compound ⟨64T1051⟩.



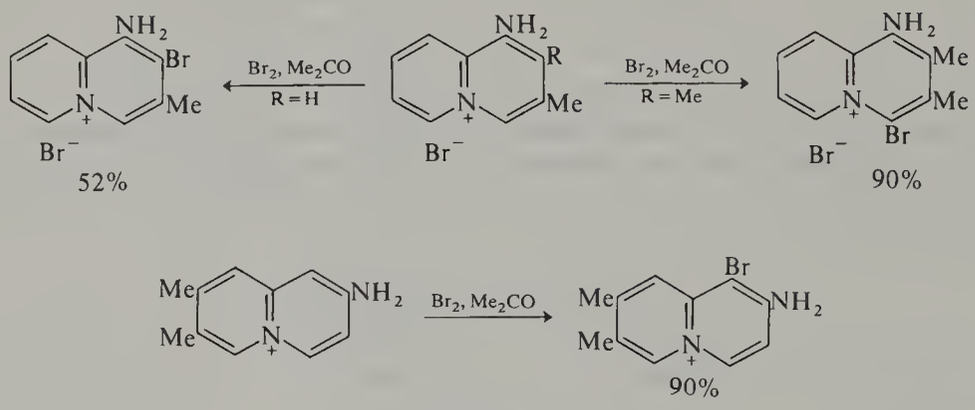
Scheme 4



i, 7% aq HNO_3, 15 s; ii, $Ca(NO_3)_2 \cdot 3H_2O + Ac_2O$, room temp.; iii, conc. HNO_3 in HOAc, room temp.

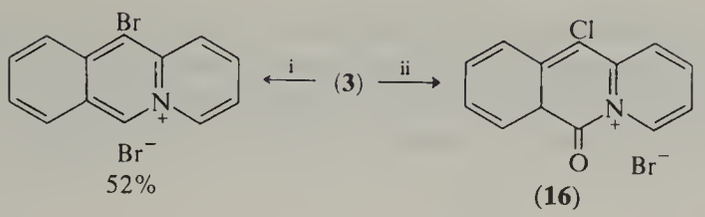
Scheme 5

As may be seen in Scheme 6, an amino group at position 1 promotes substitution in position 2, if vacant, otherwise at position 4.

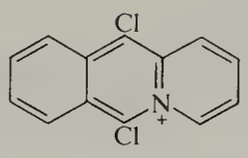


Scheme 6

Another example of the effect of a substituent on the course of reaction may be seen in the halogenation of benzo[*b*]quinolizinium ion (**3**) in the presence of aluminum halides. As will be seen in Section 2.10.2.2, electrophilic attack on a benzoquinolizinium salt usually occurs in the 'side-chain' ring but at 100 °C, in the presence of aluminum halides, the halogen enters the central nucleus (Scheme 7). Details of the mechanism, including whether it is indeed ionic, are unknown, but it has been suggested ⟨67JOC1169⟩ that in the chlorination reaction the 6,11-dichloroacridizinium ion (**15**) may be formed first and subsequently converted into the chlorobenzoquinolizinone (**16**) on nucleophilic attack by water.



(16)



(15)

i, $AlBr_3$ in dry DMF, excess Br_2 at 100 °C, Me_2CO; ii, $AlCl_3$, dry DMF, SO_2Cl_2 at 100 °C, Br_2+HBr, Me_2CO

Scheme 7

2.10.2.1.3 Towards nucleophiles

The susceptibility of the quinolizinium ion to attack by nucleophiles varies with the nucleophile and the conditions.

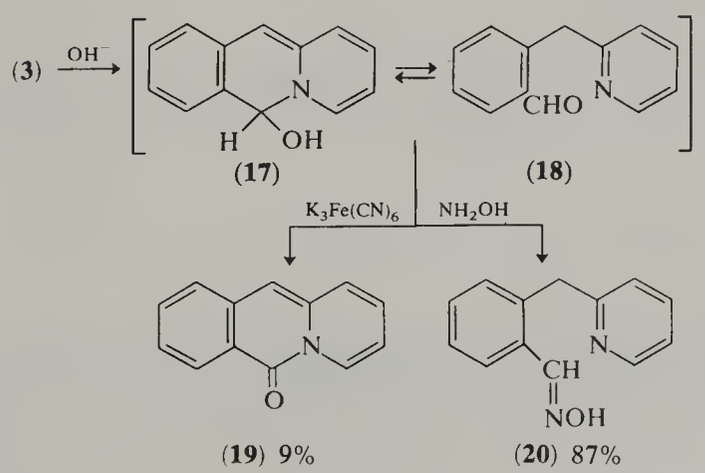
(i) With D_2O

At 220 °C the protons at positions 4 and 6 of the quinolizinium nucleus will undergo complete exchange, as evidenced by ^1H NMR ⟨81H(15)213⟩.

(ii) With hydroxide ion

Stevens *et al.* ⟨58JCS3067⟩ found that when quinolizinium iodide was treated with silver oxide, or when it was warmed with 10N NaOH, there was no evidence of the *C*-hydroxylation (pseudobase formation) that is characteristic of the methiodides of the azanaphthalenes. Their suggestion that this resistance of the quinolizinium ion is understandable, in that *C*-hydroxylation would destroy the aromaticity of both rings, is probably correct.

The *C*-hydroxylation of benzoquinolizinium ions is easier and, although the position of the attack on benzo[*a*]quinolizinium (**2**) salts is not known, it has been demonstrated ⟨67JOC733⟩ that hydroxylation of the acridizinium (benzo[*b*]quinolizinium, **3**) ion must occur at position 6 (Scheme 8). It was not possible to obtain a pure sample of the pseudobase (**17**) or the 2-(2-formylbenzyl)pyridine (**18**) in equilibrium with it, but oxidation of the mixture with ferricyanide afforded a small amount of benzo[*b*]quinolizinone (**19**) ⟨62CI(L)1292⟩, while reaction with hydroxylamine afforded a good yield of 2-(2-pyridylmethyl)benzaldoxime (**20**) ⟨67JOC733⟩.



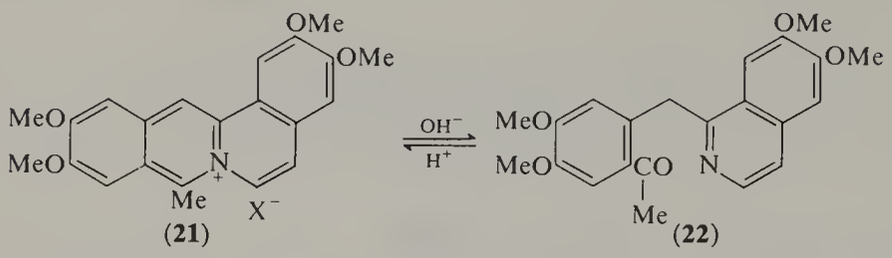
(17) **(18)**

(19) 9% **(20)** 87%

Scheme 8

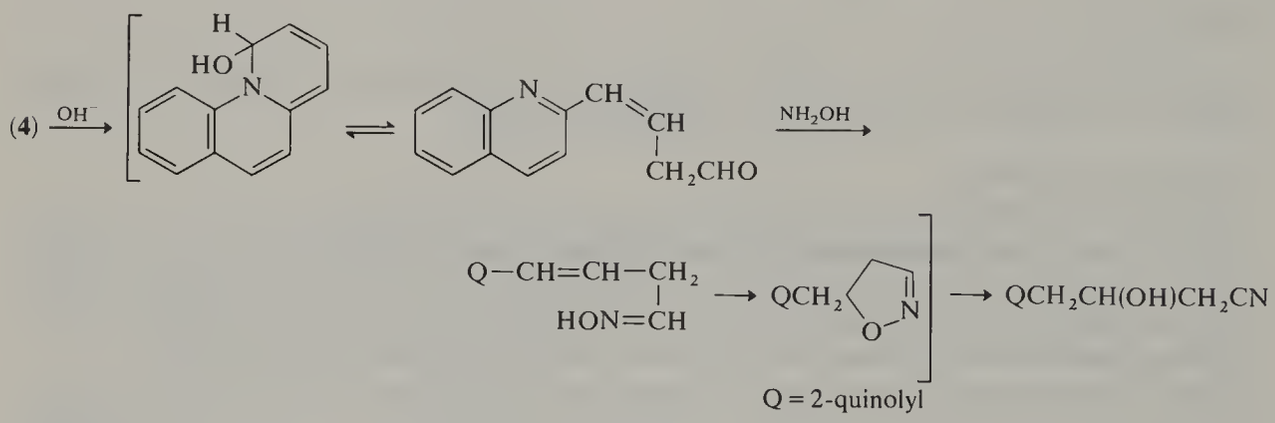
Certainly the first, and perhaps the only, example of the isolation of a pure carbonyl compound by the reaction of hydroxide ion with a quinolizinium derivative was provided

in the pioneering work by Schneider *et al.* ⟨20CB(B)1459⟩ on coralyne (**21**), a dibenzo[*a*,*g*]quinolizinium derivative (Scheme 9). The fluorescent coralyne ion (**21**) in strongly alkaline solution precipitates the non-fluorescent acetopapaverine (**22**) in 87% yield. Solutions of the ketone (**22**) in methanol–water increase in alkalinity with time as coralyne (**21**) is formed once more.



Scheme 9

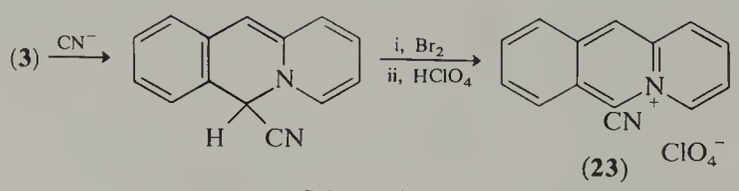
It appears likely that the benzo[*c*]quinolizinium ion is attacked by hydroxyl ion and that the resulting pseudobase is in ring–chain tautomerism with 4-(2-quinolyl)but-3-enal (Scheme 10). An attempt to trap this aldehyde by reaction with hydroxylamine ⟨71JCS(C)3650⟩ afforded a product having the properties of a hydroxynitrile. Since published reports ⟨62HC(17)96⟩ suggested that an unsaturated oxime of the anticipated structure (Scheme 10) would undergo cyclization to afford an isoxazoline, the formation of a hydroxynitrile by subsequent cleavage is easily rationalized.



Scheme 10

(iii) With cyanide ion

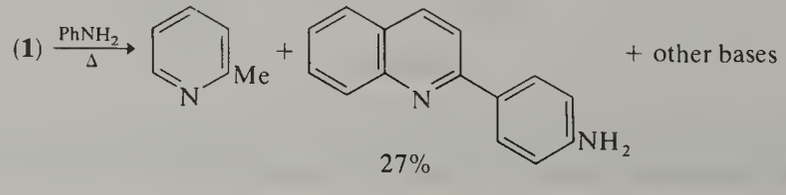
The simplest quinolizinium derivative which reacts with cyanide ion is the acridizinium ion (**3**) ⟨58JCS3067, 59JA1938⟩; it gives an unstable product (Scheme 11) which was not isolated, but was dehydrogenated by bromine to afford what was believed to be the 6-cyanoacridizinium ion (**23**).



Scheme 11

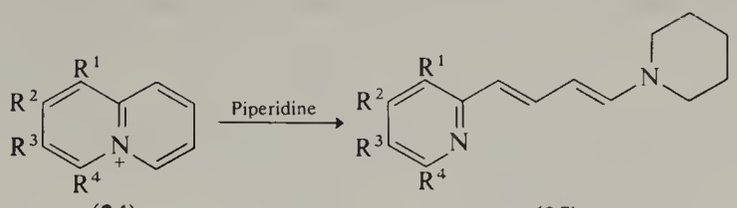
(iv) With amines

When quinolizinium bromide is heated with aniline, fragmentation products ranging in complexity from α-picoline to 2-(4-aminophenyl)quinoline are obtained (Scheme 12) ⟨69T837⟩. With secondary aliphatic amines it has proved possible to obtain good yields of



Scheme 12

products in which the bond between C-4 and nitrogen has been cleaved (Scheme 13) to afford a 1-piperidinyl-4-(2-pyridyl)butadiene (**25a**) in which the tetramethine chain is *trans*, *trans* ⟨71LA(744)65⟩. Benzo[*a*]quinolizinium ion (**24b**) and the benzo[*c*]quinolizinium ion (**24c**) undergo parallel ring-opening reactions with piperidine. Similar reactions have been carried out with morpholine.

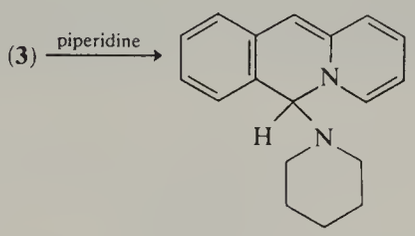


(**24**) (**25**)

a; $R^1 = R^2 = R^3 = R^4 = H$ (68%)
b; $R^1—R^2 = CH=CH—CH=CH$, $R^3 = R^4 = H$ (76%)
c; $R^1 = R^2 = H$, $R^3—R^4 = CH=CH—CH=CH$ (100%)

Scheme 13

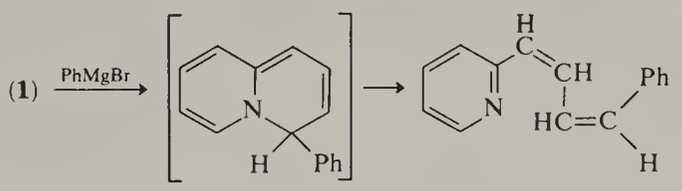
With the benzo[*b*]quinolizinium (acridizinium) ion, ring opening has not been observed; instead an unstable substance believed to be a piperidinylbenzoquinolizine was obtained (Scheme 14).



Scheme 14

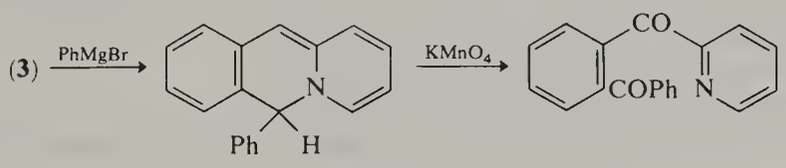
(v) With Grignard reagents

Miyadera *et al.* ⟨64CPB1344⟩ have shown that Grignard reagents likewise cleave the bond between C-4 and nitrogen of the quinolizinium nucleus. With phenylmagnesium bromide the principal product is the *cis,trans* adduct (Scheme 15). A similar *cis,trans* ring opening has been reported ⟨78CPB2334⟩ for benzo[*a*]- (**2**) and for benzo[*c*]-quinolizinium (**4**) bromide.



Scheme 15

It has been demonstrated ⟨59JA1938⟩ that the attack of phenylmagnesium bromide on acridizinium bromide (**3**) is at position 6, for oxidation afforded 2-(2-benzoylbenzoyl)pyridine (Scheme 16).

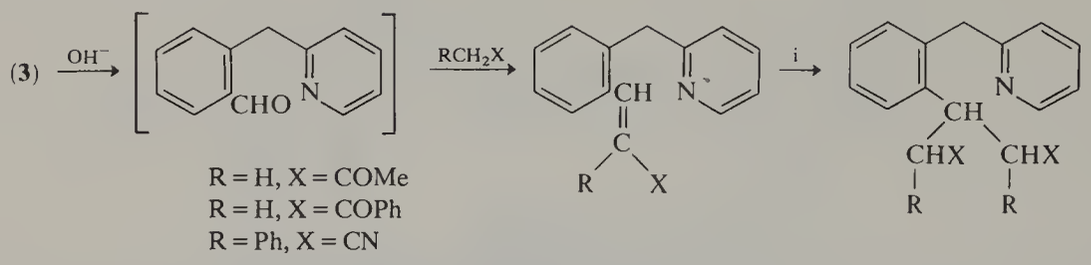


Scheme 16

(vi) With carbanions

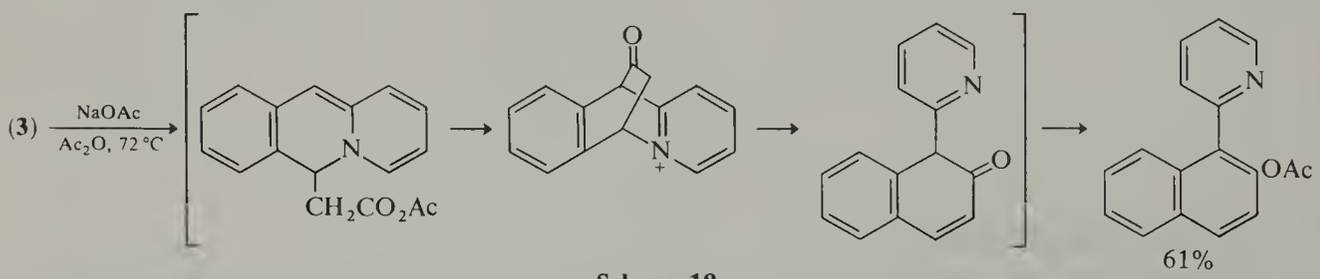
There are no reported examples of the reaction of the quinolizinium ion or its angular benzo derivatives with active methyl and methylene compounds. The linear benzo[*b*]quinolizinium (**3**) bromide and some of its derivatives have been found to react with acetone, acetophenone and phenylacetonitrile in the presence of hydroxide ion ⟨59JA1938⟩. On the basis of ^{1}H NMR data obtained later ⟨67JOC733⟩, it is clear that the reaction product of

phenylacetonitrile with acridizinium bromide is not, as was at first supposed, a benzoquinolizine derivative but instead an *o*-(2-pyridylmethyl)benzylidene derivative of the active methylene compound (Scheme 17). It appears likely that all of these aqueous hydroxide ion-catalyzed reactions of the acridizinium ion with active methyl or methylene compounds go *via* 2-(2-pyridylmethyl)benzaldehyde to form benzylidene derivatives, and, as was observed in the reaction with acetophenone, a Michael addition may ensue.

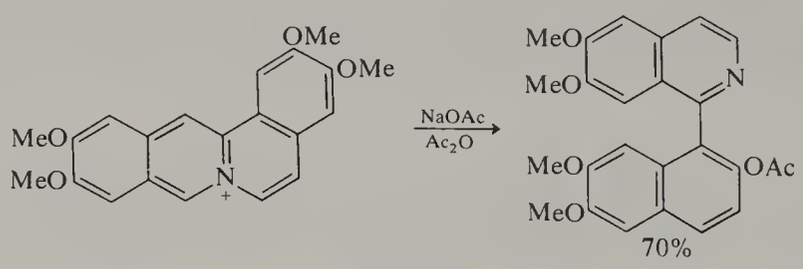


Scheme 17

It is probable that under non-aqueous conditions a benzoquinolizine derivative is formed by attack of a carbanion on the acridizinium nucleus. When the activating group of the carbanion is combined with a good leaving group, the result is an interesting cyclization and ring opening developed by Shamma *et al.* (Scheme 18) ⟨77T2907⟩ which, in this case, leads to the acetate of 1-(2-pyridyl)-2-naphthol. Under similar conditions a dibenzo[*a*,*g*]quinolizinium derivative afforded the acetate of a 1-(1-isoquinolinyl)-2-naphthol (Scheme 19).



Scheme 18

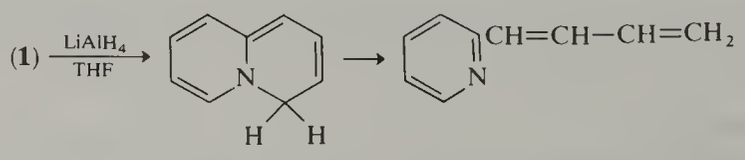


Scheme 19

(*vii*) *Reduction*

(*a*) *Electrochemical.* At the dropping mercury electrode, 7-methylbenzo[*a*]quinolizinium bromide showed a well-formed reduction wave, the half-wave potential being −1.202 V *vs.* the calomel electrode ⟨63RTC828⟩. Under the same circumstances the acridizinium ion (**3**) was reduced in two one-electron stages at potentials of −0.807 and −1.022 V, these potentials being independent of pH over a wide range.

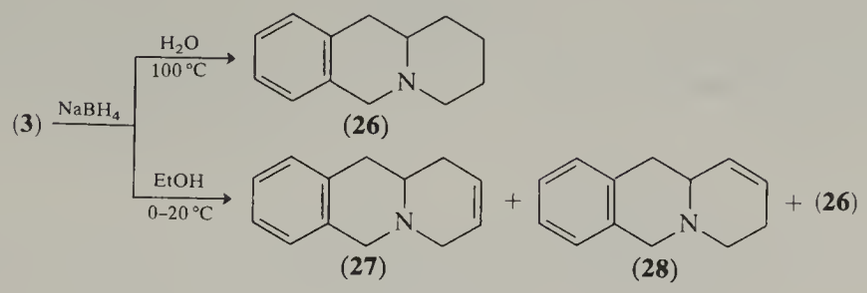
(*b*) *With hydrides.* The reaction of the quinolizinium ion (**1**) with lithium aluminum hydride yields 1-(2-pyridyl)-1,3-butadiene, evidently *via* the 4*H*-quinolizine (Scheme 20).



Scheme 20

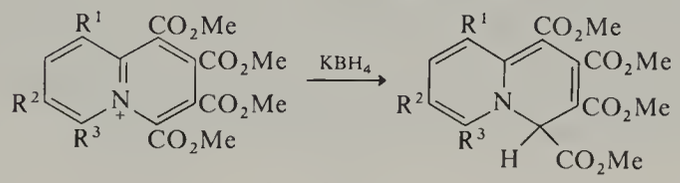
The stereochemistry was presumed to be *cis* ⟨69T397⟩. Reduction of quinolizinium ion in ethanol with sodium borohydride gave a mixture of tetrahydro and hexahydro products. The reduction of the acridizinium ion (**3**) in water at 100 °C with sodium borohydride

appears to yield only benzo[*b*]quinolizidine (**26**; Scheme 21) ⟨60JOC294⟩. If the reduction was carried out at 0–20 °C in ethanol the major product was a tetrahydrobenzoquinolizine (**27**), with much smaller quantities of an isomer (**28**) and of benzo[*b*]quinolizidine (**26**) ⟨69T5189⟩.



Scheme 21

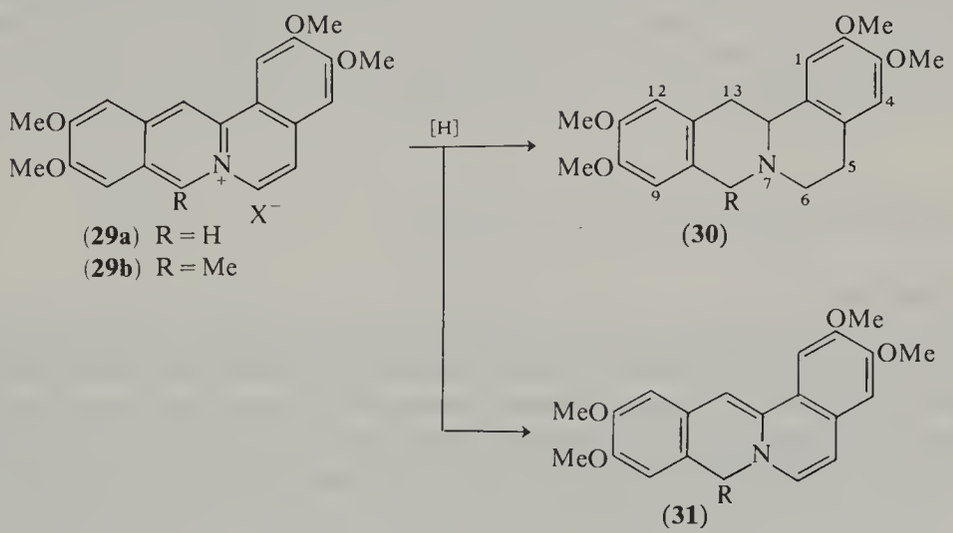
Although there is no recorded example of the reduction of the parent quinolizinium ion to a quinolizine, it has been reported that certain 1,2,3,4-tetramethoxycarbonylquinolizinium salts can be reduced to the corresponding 4*H*-quinolizines by the action of potassium borohydride (Scheme 22) or by dithionite ⟨68JCS(C)351, 64JCS3225⟩.



a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^2 = H$, $R^3 = PhCH{=}CH$
c; $R^1 = R^2 = Me$, $R^3 = H$

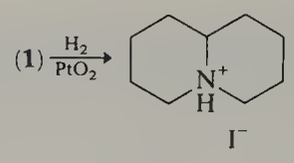
Scheme 22

(*c*) *With zinc and acid.* Schneider *et al.* ⟨21CB(B)2021⟩ demonstrated that zinc in a mixture of acetic acid and 10% H_2SO_4 reduced coralyne (**29b**) to α-coralydine (**30b**), an 8*H*-5,6,13,13a-tetrahydrodibenzo[*a*,*g*]quinolizine derivative (Scheme 23). If the reaction was interrupted earlier, the principal product was the dibenzoquinolizine (**31b**). Recent improvements in the zinc–acid reduction procedure have made possible selective reduction of (**29b**) to (**30b**) or (**31b**) in excellent yield ⟨76H(5)153⟩. An alternative approach to (**31b**) is suggested by the observation of Shamma *et al.* ⟨76TL1415⟩ that norcoralyne (**29a**) can be reduced to the dibenzoquinolizine (**31a**) by the action of $NaBH_4$ in pyridine.

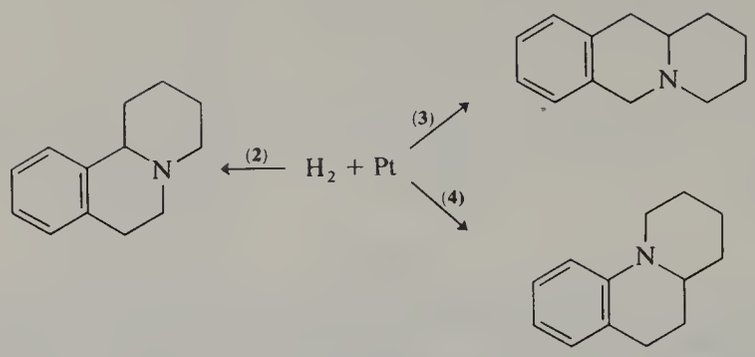


Scheme 23

(*d*) *Catalytic reduction.* As part of the demonstration of the structure of quinolizinium (**1**) iodide, Boekelheide *et al.* ⟨54JA1832⟩ showed that, in the presence of Adams catalyst, it absorbed five moles of hydrogen to afford quinolizidine hydriodide (Scheme 24). The hydrogenation of the benzo derivatives (Scheme 25) is believed to follow a parallel course when Adams catalyst is used, four molecules of hydrogen being absorbed to yield hexahydrobenzoquinolizines ⟨55JA453, 55JA4812, 71JCS(C)3650⟩.

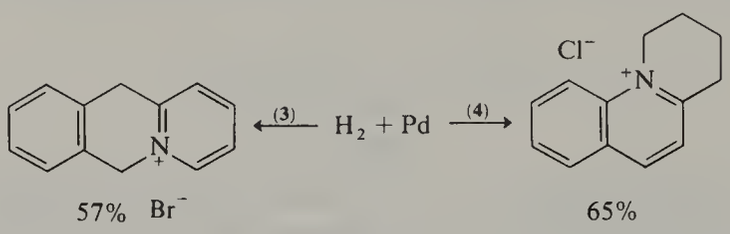


Scheme 24



Scheme 25

The hydrogenation of acridizinium bromide (Scheme 26) with a palladium catalyst can be carried out so that only one mole of hydrogen is absorbed to afford a 6,11-dihydroacridizinium salt ⟨68JOC1296⟩. With the same catalyst the hydrogenation of benzo[*c*]quinolizinium chloride slows after the addition of two moles of hydrogen and gives 1,2,3,4-tetrahydrobenzo[*c*]quinolizinium chloride ⟨71JCS(C)3650⟩.



Scheme 26

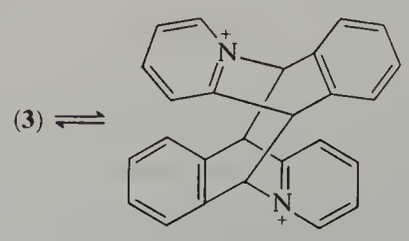
2.10.2.1.4 Towards radicals

While there appear to have been no deliberate efforts to bring about radical reactions with quinolizinium and its congeners, there remains the possibility that such might occur. In particular, the phenomenon of halogenation of the acridizinium ion (**3**) in the central nucleus at 100 °C (Section 2.10.2.1.2) may possibly have a radical explanation.

2.10.2.1.5 Reactions with cyclic transition states

(*i*) *Photodimerization*

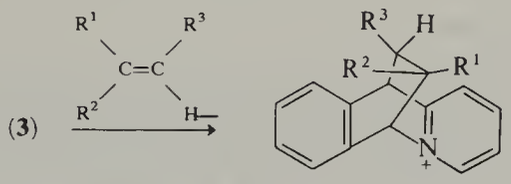
Although the quinolizinium ion (**1**), like naphthalene, does not undergo photodimerization, its linear benzo derivative, the acridizinium ion, like anthracene, does so readily (Scheme 27) ⟨57JOC1740⟩. The photodimer dissociates when heated in ethanol. It has been reported that both the dimerization and dissociation in methanol are light-catalyzed and that the quantum yields for the two reactions are 0.23 and 0.49 respectively ⟨78JPR739⟩.



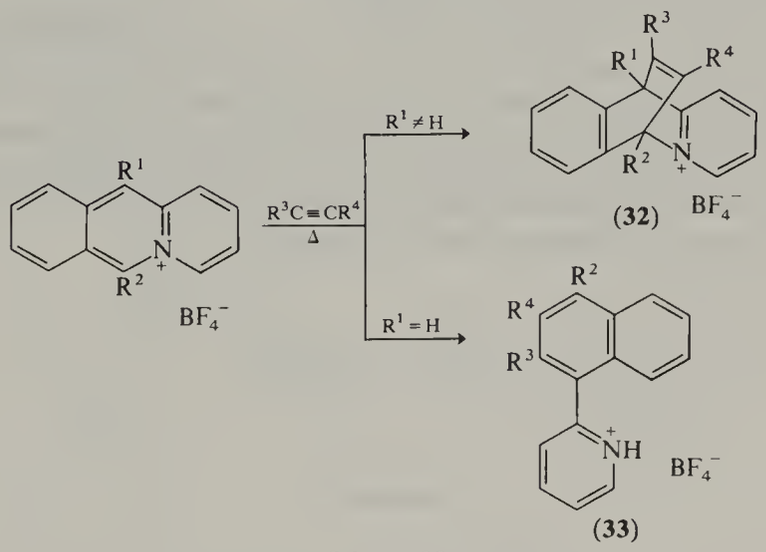
Scheme 27

(ii) Cycloaddition

Following the discovery that the acridizinium ion adds to maleic anhydride, maleate and fumarate esters, as well as acrylonitrile ⟨58JA933⟩ across the 6 and 11 positions, Fields *et al.* ⟨68JOC390⟩ demonstrated that with the same substrate ethylene and a great many substituted ethylenes undergo what has been referred to as polar cycloaddition (Scheme 28) ⟨74AHC(16)289⟩. Addition of alkynes (Scheme 29) gives an etheno-bridged adduct (**32**) provided a substituent is present at position 11 of the acridizinium compound. In the absence of such a substituent, ring-opening occurs to yield a 1-(2-pyridyl)naphthalene (**33**).

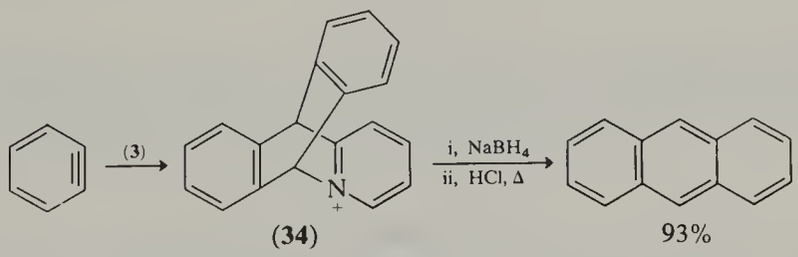


Scheme 28



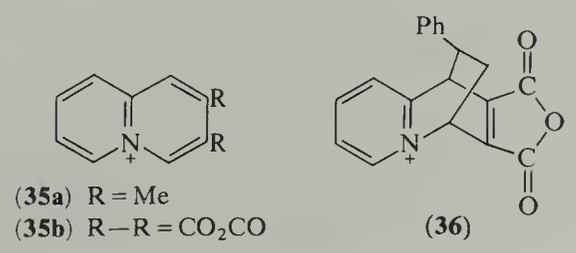
Scheme 29

The discovery that benzyne (Scheme 30) adds to acridizinium ion to produce an azoniatriptycene (**34**) which, on reduction with sodium borohydride followed by hydrolysis, affords anthracene, offers a new route to the synthesis of related hydrocarbons ⟨71JOC3002⟩. This, the Fields anthracene synthesis, has already found application in the preparation of 1,4,5,8,9-pentamethylanthracene ⟨75TL4639⟩.



Scheme 30

It is now clear that acridizinium compounds and their benzo analogs are more susceptible to cycloaddition than are their quinolizinium counterparts. Fields *et al.* ⟨68JOC390⟩ showed that, even with the strong nucleophile 1,1-diethoxyethylene, 2,3-dimethylquinolizinium ion (**35a**) does not react. As yet the only quinolizinium derivative known to undergo cycloaddition is the anhydride (**35b**) of quinolizinium-2,3-dicarboxylic acid which, because of the increased electrophilicity provided by the electron-withdrawing substituents, undergoes cycloaddition even with the more moderately nucleophilic styrene to yield (**36**).



2.10.2.2 Reactivity of Substituents

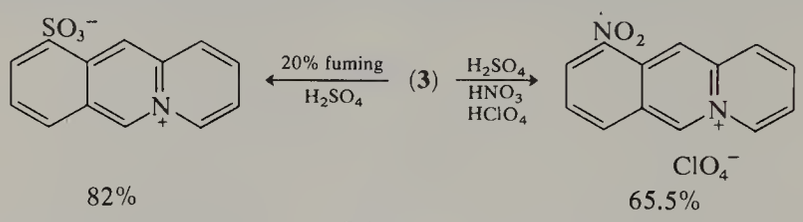
2.10.2.2.1 General

As would be expected from the principles set forth in Section 2.04.1, substituents which are α (positions 4 and 6) or γ (positions 2 and 8) to the positive charge on the quinolizinium nucleus are most strongly influenced by it.

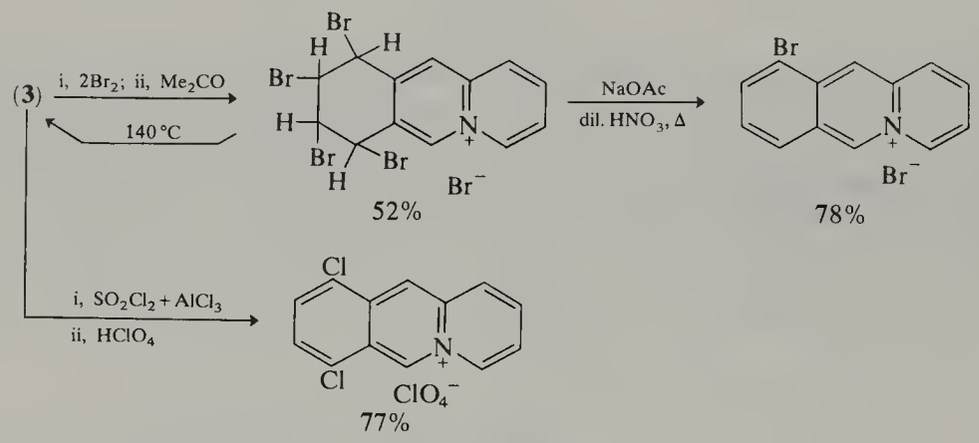
2.10.2.2.2 Fused benzene rings

Since the quinolizinium nucleus is so inert to electrophilic attack (Section 2.10.2.1.2), it is predictable that the simple benzoquinolizinium derivatives will undergo electrophilic attack in the 'side-chain' ring. Although this prediction has yet to be tested on the benzo[*a*]quinolizinium ion, the behavior of the isomeric benzo[*b*]- and benzo[*c*]-quinolizinium ions has been examined with some care.

Sulfonation ⟨66JOC565⟩ or nitration ⟨74JOC1157⟩ of the acridizinium (benzo[*b*]quinolizinium) ion (**3**) occurs at position 10 (Scheme 31). When acridizinium bromide is dissolved in liquid bromine and allowed to stand for 15 h the perbromide salt of 7,8,9,10-tetrabromo-7,8,9,10-tetrahydroacridizinium ion is formed and this is easily converted to the simple bromide by the action of acetone. If the tetrabromo salt is refluxed in xylene, it is reconverted to acridizinium bromide (**3**) in good yield. Treatment of the tetrabromide with sodium acetate gives 10-bromoacridinium bromide (Scheme 32).



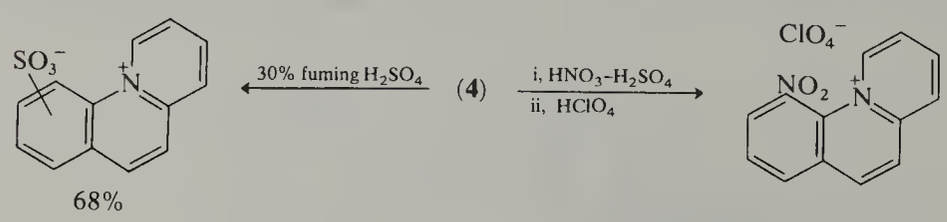
Scheme 31



Scheme 32

Acridizinium chloride is easily chlorinated by the action of sulfuryl chloride containing aluminum chloride to give 7,10-dichloroacridizinium ion. It has not been demonstrated that an electrophilic substitution is involved and if so in what order the two substituents are introduced.

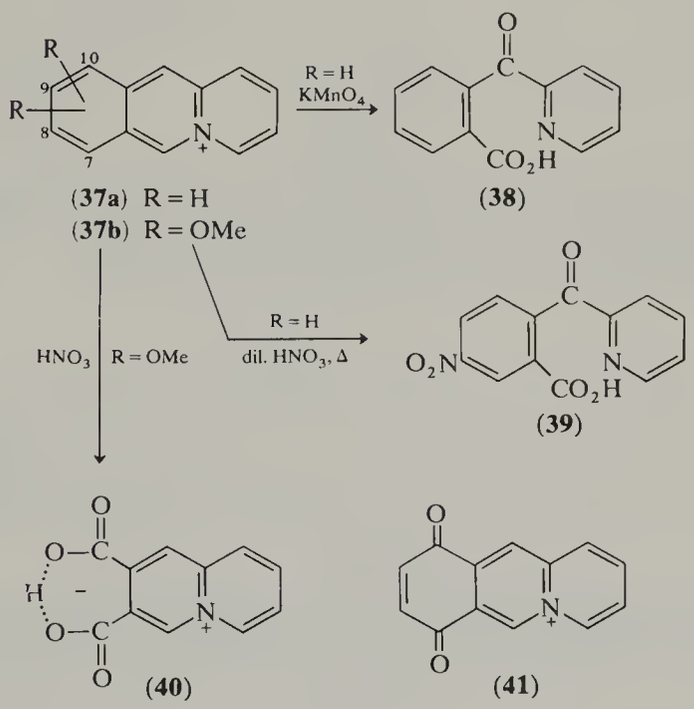
Nitration of benzo[*c*]quinolizinium ion (Scheme 33) has been shown ⟨71JCS(C)3650⟩ to occur at position 10 and it appears likely that the betaine obtained by sulfonation is substituted at the same position.



Scheme 33

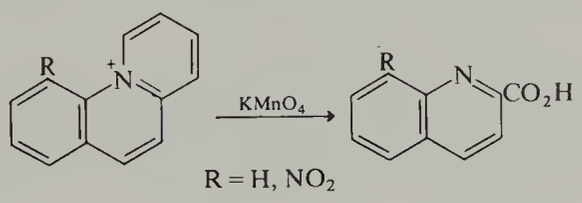
It is significant that in the two benzoquinolizinium systems examined to date, nitration, a typical electrophilic substitution reaction, occurs in the 'side-chain' ring at the α-position which could not bear a positive charge in structures contributing to the resonance hybrid. From this it seems likely that when the benzo[*a*]quinolizinium system (**2**) undergoes electrophilic attack, position 8 will be preferred.

In view of the electron-withdrawing nature of the quinolizinium nucleus, it might appear likely that the principal point of oxidative attack on the benzoquinolizinium nucleus should be on the 'side-chain' aromatic ring. Actually such an attack has only been encountered under special circumstances. The action of permanganate on the acridizinium ion (**37a**) is to attack the quinolizinium nucleus and give 2-(2-carboxybenzoyl)pyridine (**38**) ⟨74JOC1157⟩. When the oxidant is 12M nitric acid, nitration occurs as well as oxidation, yielding (**39**) ⟨64JOC452⟩. It was shown that (**38**) was not an intermediate in the formation of (**39**). If the 'side-chain' ring is activated by having two methoxy groups present at positions 7,8- or 7,10-, oxidation affords the betaine (**40**) of 2,3-dicarboxyquinolizinium hydroxide. Fields *et al.* have shown that careful oxidation of the 7,10-dihydroxyacridizinium ion yields the expected quinone (**41**) ⟨70JHC91⟩.



Scheme 34

Permanganate oxidation of the benzo[*c*]quinolizinium ion (Scheme 35) likewise involves attack of the quinolizinium nucleus to produce quinoline-2-carboxylic acid. Similar behavior is shown by the 10-nitrobenzo[*c*]quinolizinium ion ⟨71JCS(C)3650⟩.

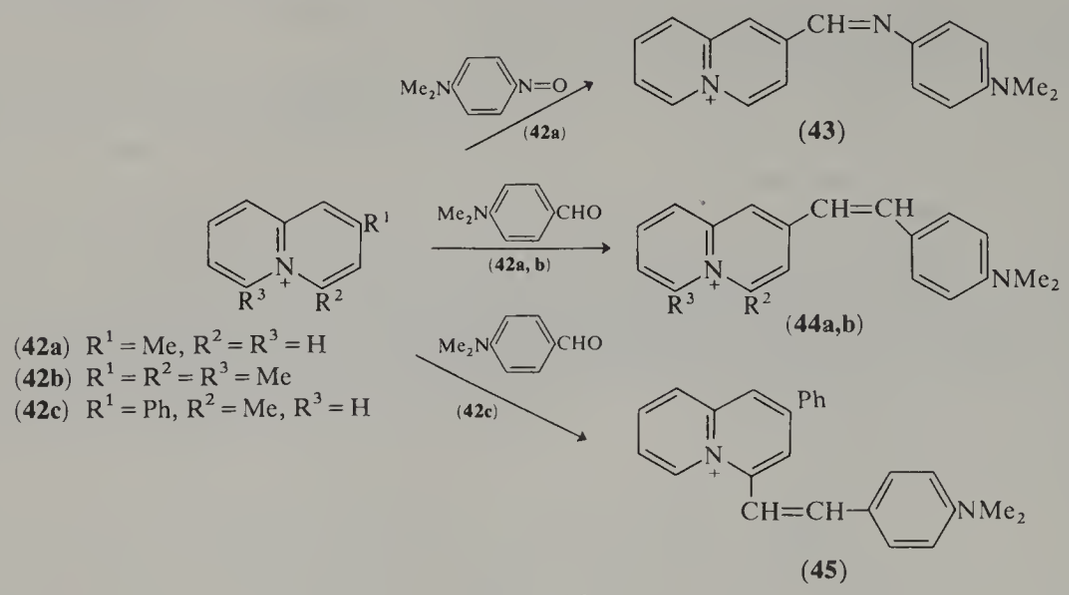


Scheme 35

2.10.2.2.3 Alkyl groups

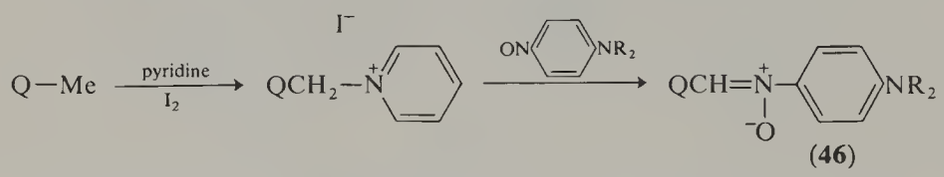
As was indicated in Section 2.04.2.1, alkyl groups which are α or γ to the quaternary nitrogen of the quinolizinium ion should be acidic and the anion resulting from deprotonation should be capable of entering into base-catalyzed condensation reactions. 2-Methylquinolizinium ion (**42a**) condenses with *p*-dimethylaminonitrosobenzene (Scheme 36) to produce the anil (**43**) or with *p*-dimethylaminobenzaldehyde (piperidine catalyst) to yield the *p*-dimethylaminostyryl derivative (**44a**) ⟨58JCS3067⟩. It is interesting that 2,4,6-trimethylquinolizinium ion (**42b**), which has two methyl groups α and one γ to the

heteroatom, also undergoes condensation with dimethylaminobenzaldehyde at position 2 to give (**44b**) ⟨63JOC393⟩. Condensation at the α-position is indeed possible, as may be seen in the condensation of 4-methyl-2-phenylquinolizinium bromide to afford (**45**) in 58% yield.



Scheme 36

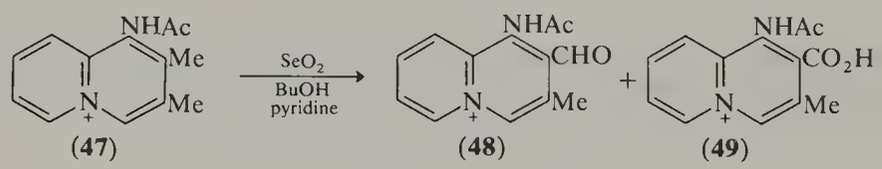
Both 2-methyl- and 4-methyl-quinolizinium salts undergo the Ortoleva–King reaction (Scheme 37) to produce the expected pyridinium salts and these with *p*-dialkylamino-nitrosobenzenes were found to give nitrones (**46**) ⟨65JPR(27)306⟩.



Q = 2-quinolizinyl-5-ium, 4-quinolizinyl-5-ium, R = CH_2CH_2OH, CH_2CH_2Cl

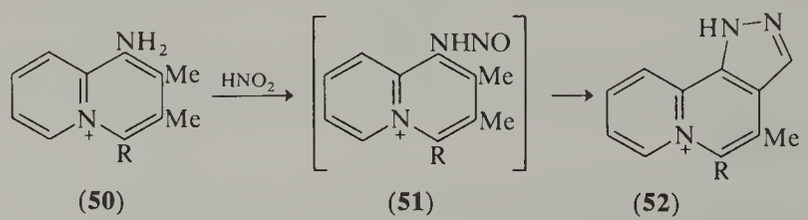
Scheme 37

The effect of the electron deficiency at the γ-position may be seen in the selective oxidation of the methyl group at position 2 in 1-acetylamino-2,3-dimethylquinolizinium ion (**47**; Scheme 38). A mixture of the aldehyde (**48**; 33%) and acid (**49**; 35%) was obtained ⟨68JCS(C)1082⟩.



Scheme 38

The action of nitrous acid on 1-amino-2,3-dimethylquinolizinium bromide (**50**) resulted in the formation of pyrazoloquinolizinium derivative (**52**), perhaps as the result of the attack of an intermediate nitrosoamine upon the activated methyl group (Scheme 39) ⟨68JCS(C)1088⟩.

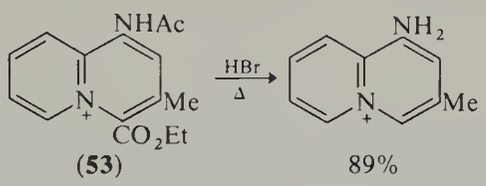


Scheme 39

2.10.2.2.4 Carboxylic acids and esters

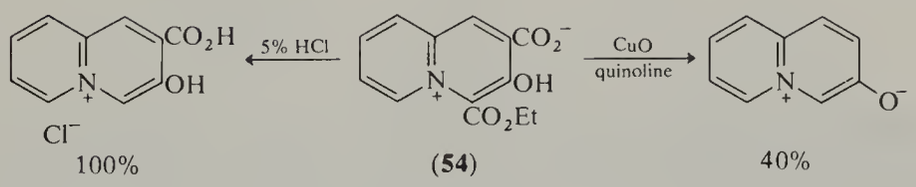
It appears that a carboxyl group (or ester) at the 4-position of the quinolizinium ion is easily removed by heating with aqueous acid. One example (Scheme 40) is the removal of

the ethoxycarbonyl group from (**53**) by refluxing in 48% HBr ⟨68JCS(C)1082⟩. An example which must involve the selective and quantitative removal of the carboxyl at position 4 in the presence of one at position 2 may be seen in Scheme 41 ⟨67AC(R)269⟩. Removal of both the ester and carboxylate groups from (**54**) may be accomplished by heating with CuO in quinoline but only in moderate yield. As an explanation for the reluctance of (**55a**) to undergo decarboxylation and the failure of (**55b**) to do so, it was pointed out ⟨68JCS(C)1082⟩ that the relative rates for the decarboxylation of α- and γ-pyridinium carboxylates are 1600 : 1 ⟨65AG(E)691⟩.



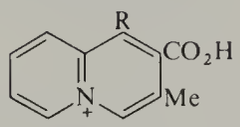
(**53**) 89%

Scheme 40



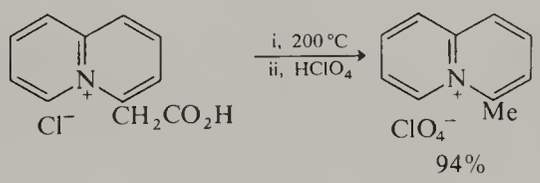
100% (**54**) 40%

Scheme 41



(**55a**) R = H
(**55b**) R = NHAc

A carboxymethyl group at position 4 of the quinolizinium ring undergoes decarboxylation in excellent yield (Scheme 42) ⟨76JCS(P1)341⟩.

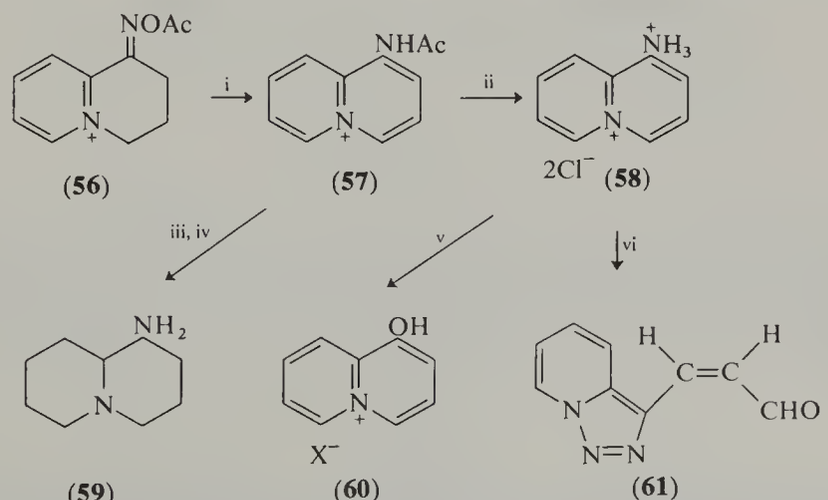


94%

Scheme 42

2.10.2.2.5 N-Linked substituents

1-Aminoquinolizinium derivatives were first prepared ⟨60JCS4101⟩ by the Wolff aromatization (Scheme 43) of the *O*-acetyl oxime (**56**) obtained from 1-oxo-1,2,3,4-tetrahydroquinolizin-5-ium bromide ⟨56CI(L)1456⟩. The aromatization product (**57**) on catalytic



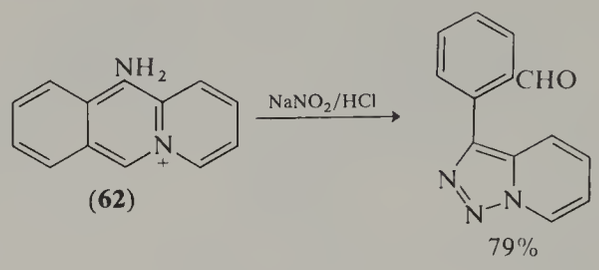
(**56**) (**57**) (**58**)

(**59**) (**60**) (**61**)

i, HCl in HOAc–Ac_2O; ii, HCl, heat; iii, H_2, PtO_2; iv, HCl, heat; v, pentyl nitrite, EtOH, then picric acid; vi, $NaNO_2$ + HCl

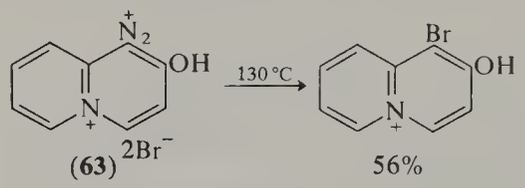
Scheme 43

reduction and hydrolysis yielded 1-aminoquinolizidine (**59**). 1-Aminoquinolizinium hydrochloride (**58**) in ethanol with pentyl nitrite gave 1-hydroxyquinolizinium ion, isolated as the picrate. If diazotization was carried out in dilute hydrochloric acid by addition of sodium nitrite, a ring opening and cyclization occurred to yield [1,2,3]triazolo[1,5-*a*]pyridylacrolein (**61**) ⟨69TL1549⟩. A parallel observation was made when 1-amino-3-methylquinolizinium was diazotized in aqueous solution, and it was proposed that the ring opening involved the attack by a water molecule at the 4-position of the diazonium salt. Similar behavior was shown when 11-aminoacridizinium salts (**62**) were diazotized in aqueous solution (Scheme 44) ⟨73JOC4167⟩.



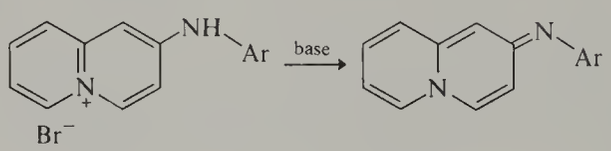
Scheme 44

Not all 1-aminoquinolizinium salts undergo ring opening when diazotized in aqueous solution; the diazonium bromide (**63**) from 1-amino-2-hydroxyquinolizinium ion can be isolated and decomposed at 130 °C to afford 1-bromo-2-hydroxyquinolizinium bromide (Scheme 45) ⟨64JCS2763⟩. As was pointed out earlier (Section 2.10.2.2.3), attempts to diazotize 1-amino-2,3-dimethylquinolizinium led not to ring opening but instead to a pyrazole ring closure (Scheme 39).

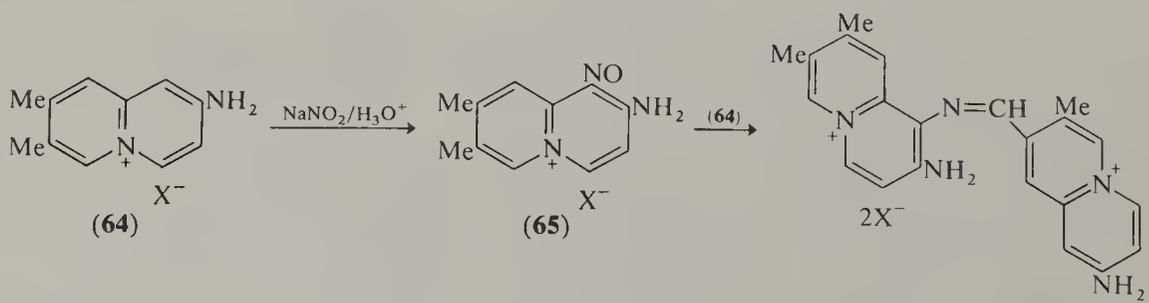


Scheme 45

Although a large number of *N*-substituted 2-aminoquinolizinium salts have been described ⟨70JMC554, 74JPS1939⟩, the parent 2-aminoquinolizinium ion appears to be unknown. Fortunately, a few ring-substituted 2-aminoquinolizinium salts are available to enable us to predict with some certainty the reactions of the parent compound. First, the amino group situated γ to the cationic center is not very basic; indeed, *N*-arylamines (Scheme 46) have been shown to lose a proton easily to form 2-arylimino-2*H*-quinolizines ⟨78JPS1183⟩. A further consequence of the lack of basicity of the amino group at position 2 may be seen in attempts to bring about diazotization in acid solution by addition of sodium nitrite (Scheme 47). It was suggested ⟨68JCS(C)1088⟩ that nitrosation at position 1 of (**64**) occurred, followed by condensation of the nitroso group of (**65**) with the methyl group of another molecule of (**64**).



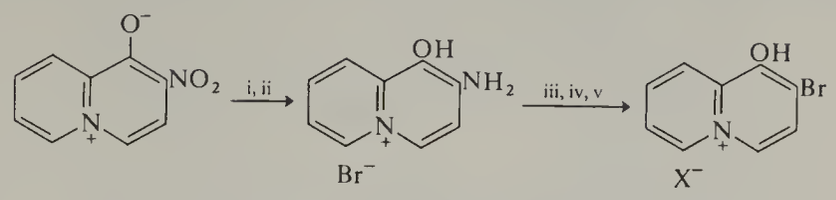
Scheme 46



Scheme 47

Normal diazotization of a 2-amino group was achieved (Scheme 48) when there was an electron-releasing hydroxyl group in position 1. In this way, 1-hydroxy-2-

aminoquinolizinium ion (**67**), available by reduction of the nitrobetaine (**66**), was converted into 2-bromo-1-hydroxyquinolizinium picrate ⟨64JCS3030⟩.

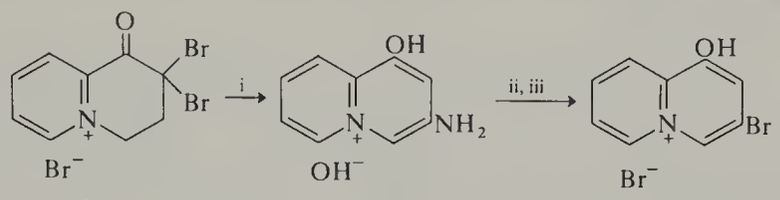


(**66**) (**67**) (**68**) 56%

i, H_2/Pd; ii, Br^-; iii, HBr/$NaNO_2$; iv, heat, dry salt in DMF; v, picric acid

Scheme 48

The only example of a 3-aminoquinolizinium ion is 3-amino-1-hydroxyquinolizinium hydroxide (Scheme 49), available from the dibromo ketone (**69**) *via* what may be a pyridyne reaction ⟨63JCS2203⟩. The amino group of (**70**) may be diazotized and replaced with bromine.

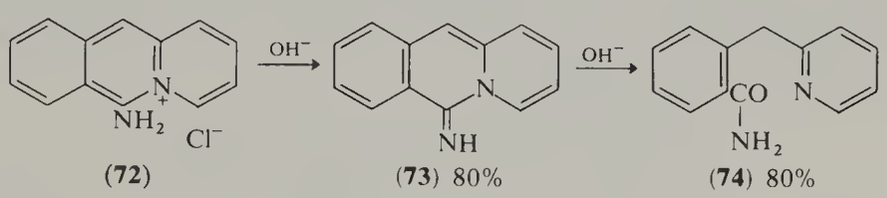


(**69**) (**70**) 48% (**71**) 25%

i, aq. NH_3; ii, dissolve in EtOH, add HBr, pentyl nitrite; iii, concentrate, add HBr, heat

Scheme 49

Although no 4-aminoquinolizinium derivatives are known, a benzo derivative, 6-amino-acridizinium ion (**72**; Scheme 50), has been prepared ⟨67JOC733⟩. In the presence of hydroxide ion the amino group loses a proton to form a benzo[*b*]quinolizin-6-imine (**73**). Alkaline hydrolysis opens the ring to give the amide (**74**).



(**72**) (**73**) 80% (**74**) 80%

Scheme 50

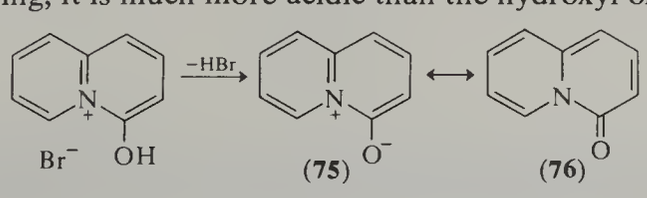
2.10.2.2.6 O-Linked substituents

Hida *et al.* ⟨78NKK1249⟩ have determined the acidity of all four hydroxyquinolizinium bromides by UV spectroscopy (Table 1). It is significant that the hydroxyl at position 2 (γ to the cationic center) is more acidic than that at position 1 or 3 (β to the cationic center),

Table 1 pK_a of Hydroxyquinolizinium Bromides

Position of OH	pK_a	*Position of OH*	pK_a
1	5.03 ± 0.69	3	5.06 ± 0.47
2	4.14 ± 0.66	4	<2

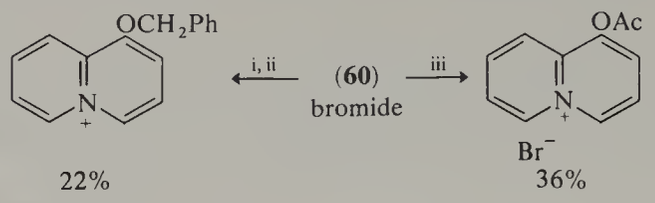
and also that the hydroxyl at position 4 is so acidic that the molecule loses HBr with extreme readiness to form a resonance hybrid (Scheme 51) involving the betaine (**75**) and 4-quinolizone (**76**). Finally, it is notable that regardless of where the hydroxyl may be located on the quinolizinium ring, it is much more acidic than the hydroxyl of a naphthol.



(**75**) (**76**)

Scheme 51

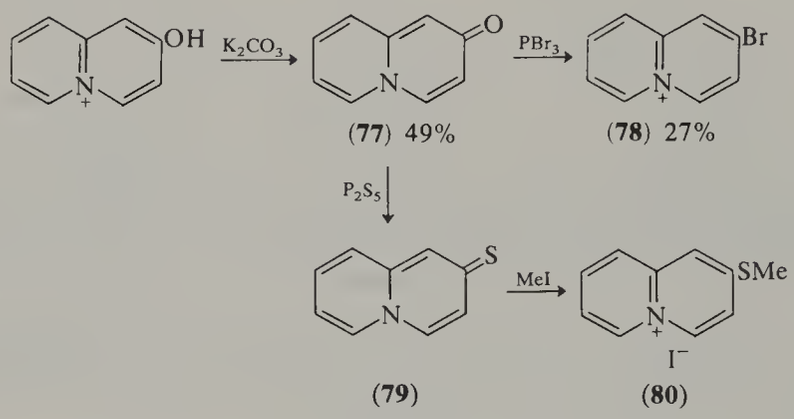
1-Hydroxyquinolizinium ion (**60**) can be acetylated ⟨63JCS2203⟩ or benzylated by more or less conventional means (Scheme 52).



i, Na_2CO_3; ii, $PhCH_2Br$; iii, Ac_2O/H_2SO_4

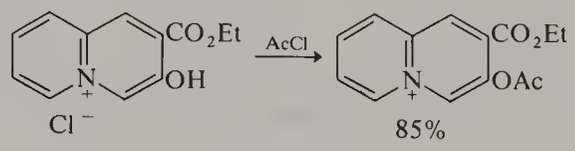
Scheme 52

2-Hydroxyquinolizinium ion can be converted to quinolizin-2-one (**77**) by the action of K_2CO_3 ⟨64JCS2760⟩. PBr_3 converts (**77**) to 2-bromoquinolizinium ion (**78**), while P_2S_5 affords quinolizine-2-thione (**79**) which was not purified but converted into 2-methylthioquinolizinium iodide (**80**).



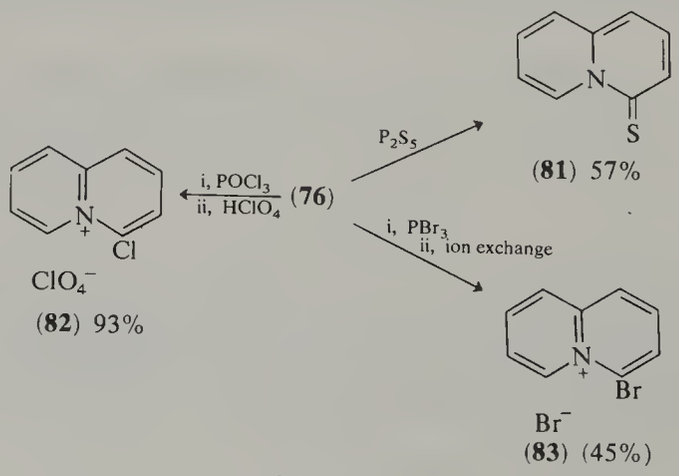
Scheme 53

2-Ethoxycarbonyl-3-hydroxyquinolinium ion appears to be acetylated normally with acetyl chloride (Scheme 54) ⟨67AC(R)269⟩.



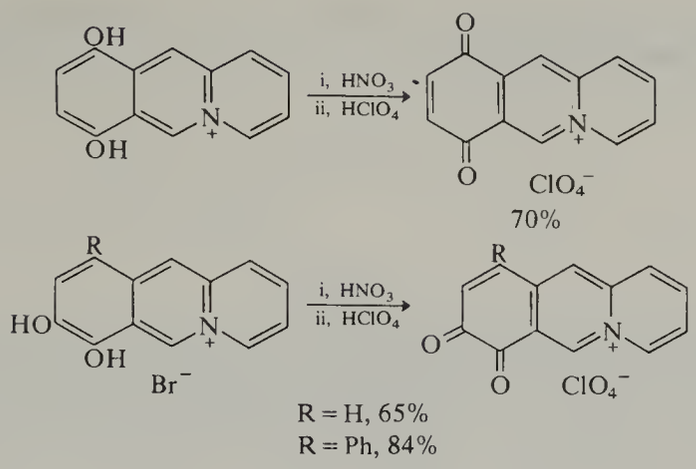
Scheme 54

Quinolizin-4-one has proved to be a more valuable intermediate (Scheme 55) than its 2-isomer. Conversion to quinolizin-4-thione (**81**) ⟨51JA3681⟩, 4-chloroquinolizinium perchlorate (**82**) ⟨63JOC1022⟩ and 4-bromoquinolizinium bromide (**83**) ⟨81H(15)213⟩ can be accomplished.



Scheme 55

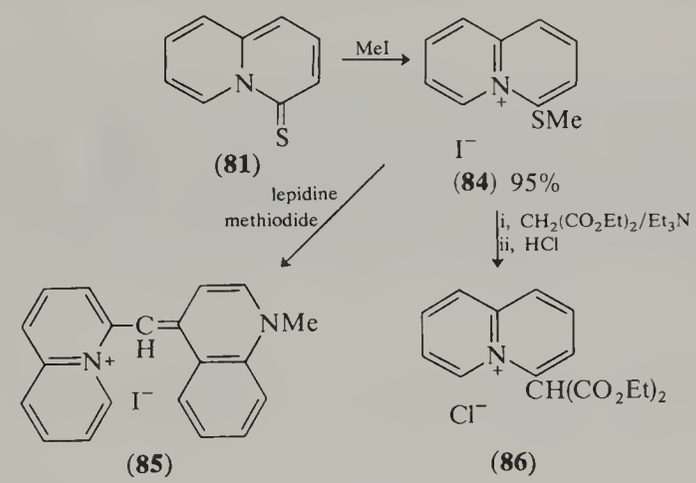
Although there has been no example of a quinone within the quinolizinium ring system, oxidation of suitable benzo[*b*]quinolizinium bromides with two hydroxyl groups on the fused ring has afforded quinones (Scheme 56) in good yields ⟨70JHC91⟩.



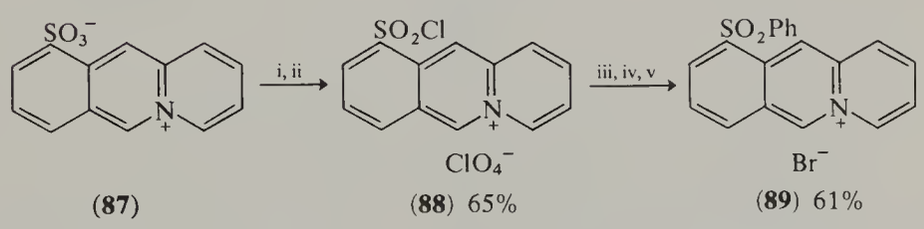
Scheme 56

2.10.2.2.7 S-Linked substituents

Quinolizine-4-thione reacts with methyl iodide (Scheme 57) to produce 4-methylthioquinolizinium (**84**) in excellent yield ⟨54JOC499⟩. The methylthio group at position 4 is evidently a good leaving group, for nucleophilic attack by lepidine methiodide afforded a cyanine dye (**85**) while with malonic ester the product, after acidification, was 4-diethoxycarbonylmethylquinolizinium chloride (**86**). Quinolizine-2-thione reacts with methyl iodide to yield 2-methylthioquinolizinium iodide (Scheme 53). The sulfonic acid group on a quinolizinium ring should make a very stable betaine. Although no such sulfoquinolizinium betaine is known, the betaine of 10-sulfoacridizinium hydroxide is available by direct sulfonation of acridizinium bromide (Scheme 31). The betaine (**87**; Scheme 58) was converted into the corresponding sulfonyl chloride (**88**) which was used in a Friedel–Crafts reaction with benzene to afford 10-(phenylsulfonyl)acridizinium ion (**89**), recovered as the bromide.



Scheme 57



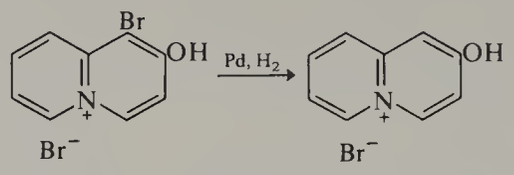
i, $ClSO_2OH$; ii, $HClO_4$; iii, C_6H_6–$AlCl_3$; iv, Br_2–HBr; v, Me_2CO–MeOH

Scheme 58

2.10.2.2.8 Halogen substituents

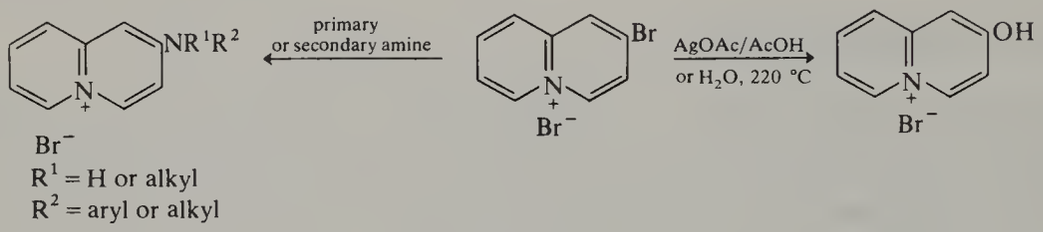
Although all four of the possible bromoquinolizinium bromides are known ⟨81H(15)213⟩, their reactivity has not been studied systematically. The hydrogenolysis of 1-bromo-2-

hydroxyquinolizinium bromide (Scheme 59) has been accomplished but does not appear to be an efficient process ⟨64JCS2763⟩.



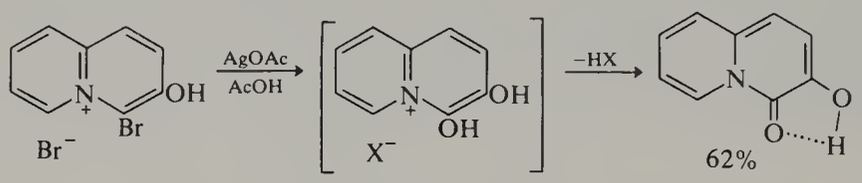
Scheme 59

Either silver acetate ⟨64JCS2760⟩ or hot water ⟨81H(15)213⟩ may be used to convert 2-bromoquinolizinium bromide to the 2-hydroxy analog in excellent yield (Scheme 60). By far the most extensive application of this or any bromoquinolizinium salt has been in the preparation of *N*-substituted 2-aminoquinolizinium salts ⟨70JMC554⟩. A similar reaction of 2-bromo-1-hydroxyquinoliziniùm bromide and arylamines has been patented ⟨77USP4020075⟩.



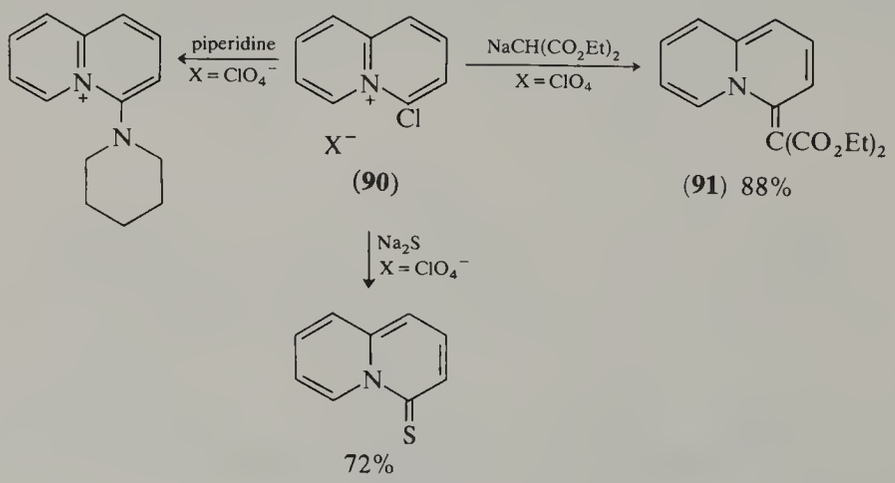
Scheme 60

The reaction of silver acetate with 4-bromo-3-hydroxyquinolizinium bromide (Scheme 61) gives 3-hydroxyquinolizin-4-one ⟨65JOC526⟩.

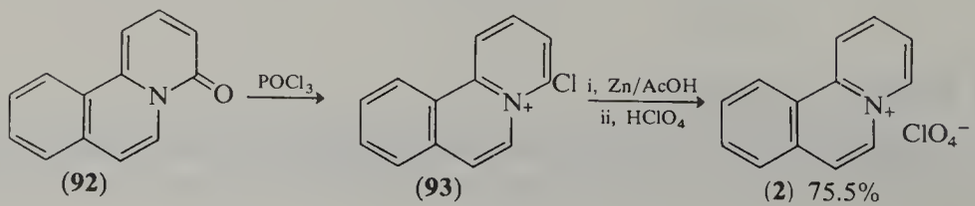


Scheme 61

4-Chloroquinolizinium salts are useful intermediates (Scheme 62). In the preparation of diethylquinolizin-4-ylidene malonate the perchlorate (**90**; X = ClO_4) is reported ⟨76JCS(P1)341⟩ to be superior to 4-methylthioquinolizinium iodide used earlier ⟨54JOC499⟩. The perchlorate of (**90**) also reacts in good yield with sodium sulfide to produce quinolizine-4-thione ⟨63JOC1022⟩. Less satisfactory results were obtained in the reaction of the cation (**90**) with piperidine.



Scheme 62



Scheme 63

The reduction of a crude 4-chlorobenzo[*a*]quinolizinium salt by action of zinc and acetic acid made possible the transformation of benzo[*a*]quinolizin-4-one to benzo[*a*]quinolizinium perchlorate (**2**) in an overall yield of 75.5% (Scheme 63) ⟨77JOC1122⟩.

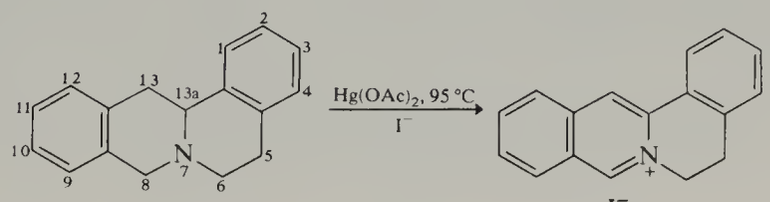
2.10.2.2.9 Partially saturated compounds

(i) General

The partially saturated compounds derived from the quinolizinium ion embrace the quinolizines (and reduction products) as well as the reduction products of the quinolizinium ion itself. This section will largely be concerned with efforts to change these partially saturated compounds into quinolizinium derivatives.

(ii) Dihydroquinolizines

The protoberberinium alkaloids are derivatives of the 5,6-dihydrodibenzo[*a*,*g*]quinolizinium ion (**95**). There exist also alkaloids which are derivatives of berbine (5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine, **94**). Ban *et al.* have shown that dehydrogenation of berbine with mercury(II) acetate will afford the parent protoberberinium salt (**95**) in 75% yield ⟨60CPB183⟩.

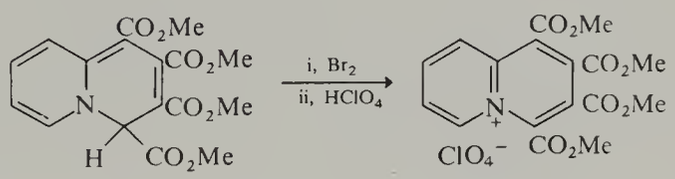


(**94**) (**95**) 75%

Scheme 64

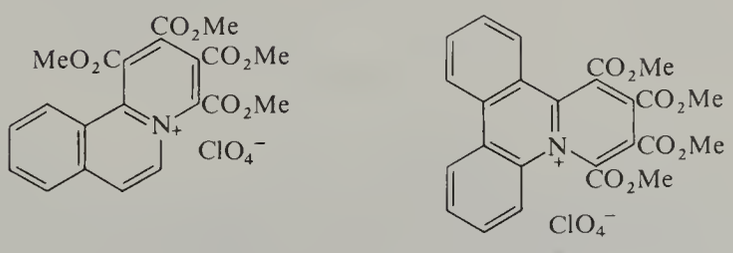
(iii) Quinolizines

In a reinvestigation of earlier work ⟨33LA(505)103⟩ by Diels and Alder, Acheson *et al.* ⟨60JCS1691⟩ established that the 'stable' isomer obtained by addition of two moles of dimethyl acetylenedicarboxylate to one of pyridine was the 4*H*-quinolizine (**96**) and that this with bromine was oxidized to a quinolizinium salt (**97**; Scheme 65). 4*H*-Quinolizines obtained from isoquinoline ⟨62JCS748⟩ and phenanthridine ⟨63JCS3888⟩ were similarly aromatized to afford benzo[*a*]quinolizinium (**98**) and dibenzo[*a*,*c*]quinolizinium ions (**99**) respectively.



(**96**) (**97**)

Scheme 65

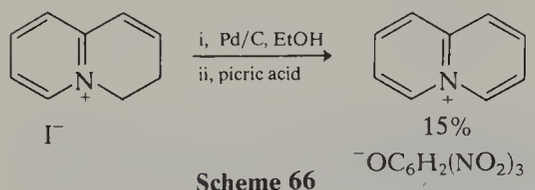


(**98**) (**99**)

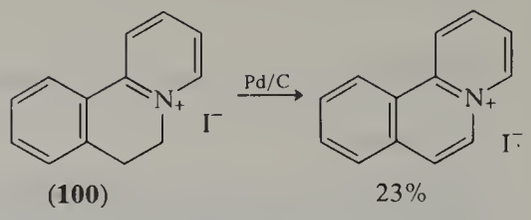
(iv) Dihydroquinolizinium ions

In the first published account of the synthesis of the quinolizinium ion, Boekelheide and Gall ⟨54JA1832⟩ described the dehydrogenation of 3,4-dihydroquinolizinium iodide (Scheme 66) using Pd/C in boiling ethanol. Subsequently it was found that the yield of the picrate

could be raised to 34% if boiling butanol were used as the solvent. The dehydrogenation (Scheme 67) of 6,7-dihydrobenzo[*a*]quinolizinium iodide (**100**) has been carried out in 23% yield ⟨63YZ1067⟩.

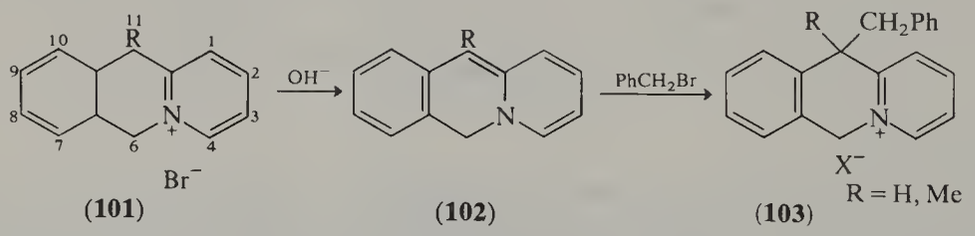


Scheme 66

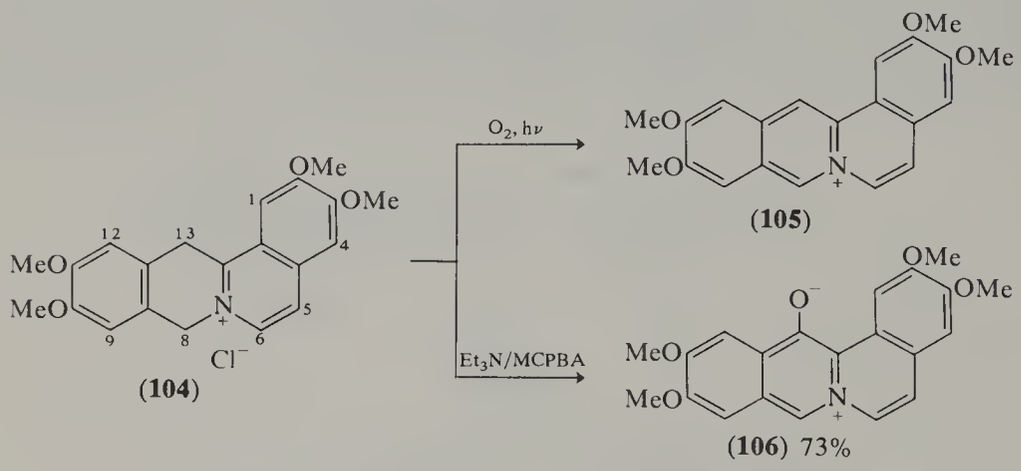


Scheme 67

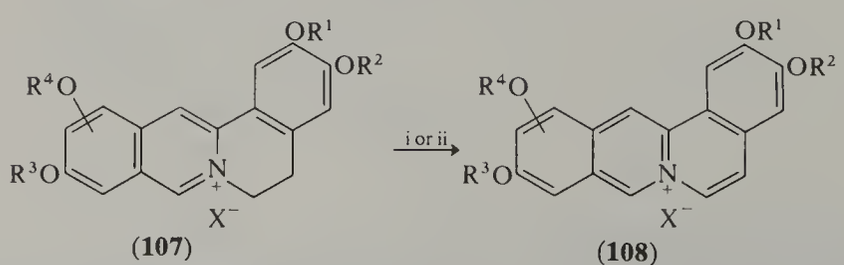
It was observed that 6,11-dihydroacridizinium ion (**101**; Scheme 68) reacts with hydroxide ion to yield acridizine (6*H*-benzo[*b*]quinolizine) (**102**; R = H). The quinolizine (**102**; R = H) is unstable, but since it is in an enamine it may be benzylated and gives an overall yield of 17% of 6-benzyl-6,11-dihydroacridizinium ion (**103**; R = H). When the experiment was repeated with the 11-methyl analog (**101**; R = Me), the quinolizine form (**102**; R = Me) was stable enough for analysis, and benzylation was accomplished in 50% yield ⟨68JOC1296⟩. The closely related 8,13-dihydro-2,3,10,11-tetramethoxydibenzo[*a*,*g*]quinolizinium chloride (**104**) was shown ⟨77H(6)959⟩ to be aromatized to norcoralynium ion (**105**) under photooxidation conditions (Scheme 69). Oxidation of (**104**) with *m*-chloroperbenzoic acid yielded the aromatic 13-oxybetaine (**106**). Protoberberinium alkaloids (**107**) are not fully aromatic but instead are 5,6-dihydrodibenzo[*a*,*g*]quinolizinium salts bearing alkoxy or hydroxy groups. It is reported that aromatization of these dihydro compounds (**107**) can be accomplished either by use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) ⟨76JAP(K)7616698⟩ or by use of a palladium catalyst ⟨76JAP(K)7616696⟩ (Scheme 70).



Scheme 68



Scheme 69

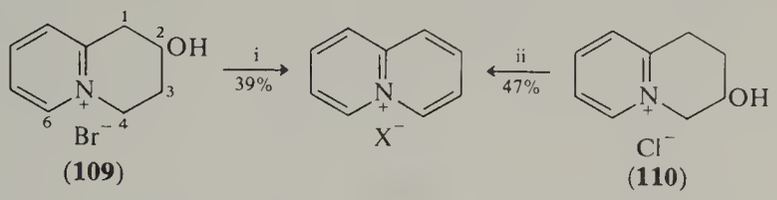


i, DDQ; ii, metal catalyst, *e.g.* Pd/C at 220 °C

Scheme 70

(*v*) *Hydroxytetrahydroquinolizinium ion*

A 1,2,3,4-tetrahydroquinolizinium salt with a hydroxy group attached to the reduced ring could, in theory, undergo dehydration and then dehydrogenation when refluxed in butanol in the presence of Pd/C. This has been shown to work well (Scheme 71) when the hydroxy group is at position 2, providing a 39% yield of quinolizinium bromide ⟨64T33⟩. However, attempts to extend the reaction to the homolog with methyl groups at both the 4 and 6 positions failed. The dehydration–dehydrogenation of (**110**), having a hydroxyl at the 3-position, resulted in a 47% yield of quinolizinium salt ⟨69CB1309⟩.



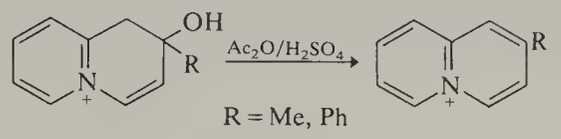
(**109**) (**110**)

i, Pd/C in boiling Bu^nOH; ii, Pd/C in refluxing n-$C_8H_{17}OH$

Scheme 71

(*vi*) *Hydroxydihydroquinolizinium ions*

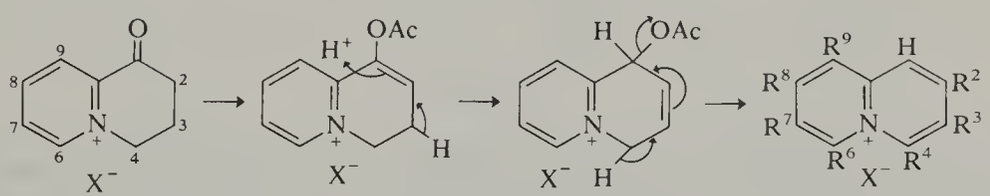
Dihydroquinolizinium ions bearing a hydroxyl group on an sp^3-bonded carbon can be dehydrated to the fully aromatic structure. Two examples appear in Scheme 72 ⟨57DOK(116)93⟩.



Scheme 72

(*vii*) *1-Oxo-1,2,3,4-tetrahydroquinolizinium ion*

An important advance in quinolizinium chemistry came with the discovery by Glover and Jones ⟨56CI(L)1456⟩ that the action of acetic anhydride on 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (**111**; Scheme 73) would dehydrate it to afford the quinolizinium ion. The Glover and Jones aromatization, which has no precedent either in carbocyclic or heterocyclic chemistry, is thought to occur *via* the enol acetate ⟨58JCS3021⟩. The acetate is believed to rearrange to a 1,4-dihydro derivative which undergoes a concerted elimination of acetic acid (Scheme 73). Some indication of the use which has been made of the new reaction is provided by Table 2. It should be noted that the aromatization has been successfully carried out with substituents at any of the seven positions available on the ketone (**111**). Also notable are the three benzo derivatives of the ketone, which in the order of the table lead to the benzo[*c*]- (**4**) benzo[*b*]- (**3**) and benzo[*a*]-quinolizinium (**2**) ions. Significantly, for the first and last of these three benzoquinolizinium ions the reference cited provides the first description of the parent (unsubstituted) ion.



(**111**)

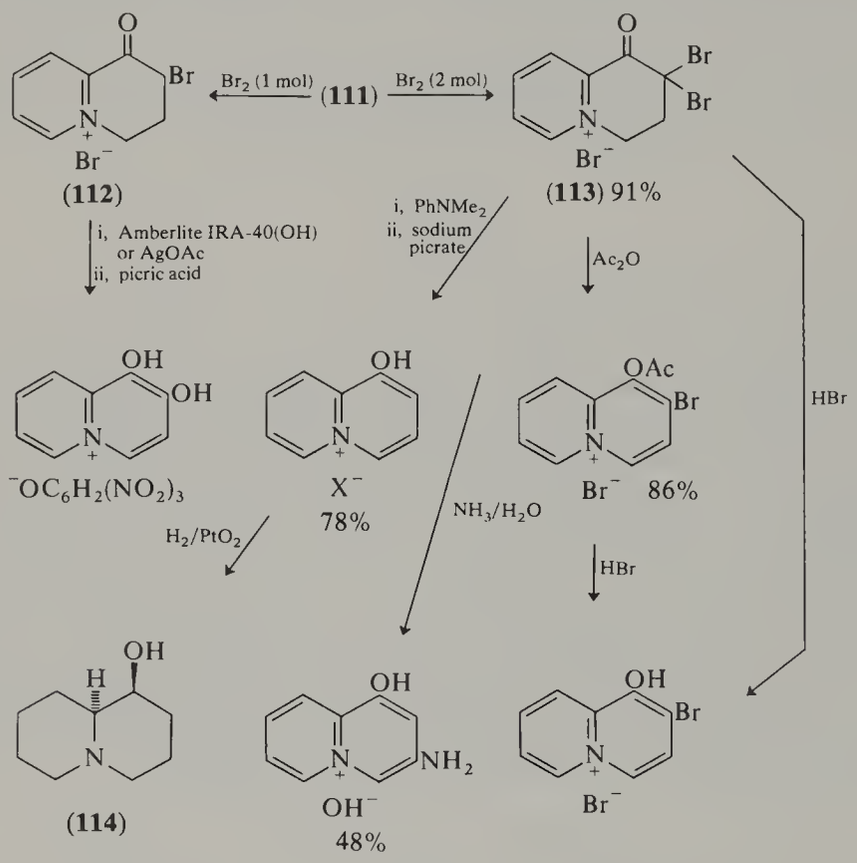
Scheme 73

Alternatively, 1-oxo-1,2,3,4-tetrahydroquinolizinium ion (**111**; Scheme 73) and its congeners may be converted to derivatives of 1-hydroxyquinolizinium ion ⟨63JCS2203⟩. The bicyclic ketone (**111**) can be brominated to yield the 2-bromo (**112**) or the 2,2-dibromo derivative (**113**). Action of boiling acetic anhydride converts the monobromo ketone (**112**) to 2-bromoquinolizinium bromide (Table 2). If the same bromo ketone (**112**) is heated with ion-exchange resin (Amberlite IRA-400) loaded with hydroxyl ions or, alternatively, heated with silver acetate in water, the 1,2-dihydroxyquinolizinium ion is formed and may be recovered as the picrate (Scheme 74).

Table 2 Glover and Jones Aromatization (Scheme 73)

R^2	R^3	R^4	R^6	R^7	R^8	R^9	*Yield* (%)	*Ref.*
—	—	—	—	—	—	—	63, 100	56CI(L)1456, 64CPB1338
Me	—	—	—	—	—	—	65	58JCS3021
Ph	—	—	—	—	—	—	—[a]	67JCS(C)1112
$PhCH_2$	—	—	—	—	—	—	—[a]	67JCS(C)1112
Ph	—	—	—	—	—	—	88	58JCS3021
Cl	—	—	—	—	—	—	60	81H(15)213
Br	—	—	—	—	—	—	74	81H(15)213
—	Me	—	—	—	—	—	100	58JCS3021
—	—	Me	—	—	—	—	65	58JCS3021
—	—	—	Me	—	—	—	77, 100	62JCS2637, 81H(15)213
—	—	—	—	Me	—	—	79, 100	62JCS2637, 81H(15)213
—	—	—	—	Br	—	—	67	81H(15)213
—	—	—	—	—	Me	—	79	62JCS2637
—	—	—	—	—	—	Me	80, 69	62JCS2637, 64CPB1338
Br	—	—	—	Br	—	—	72	81H(15)213
—	—	—	benzo		—	—	75	58JCS3021
—	—	—	—	benzo		—	62	58JCS3021
—	—	—	—	—	benzo		80	58JCS3021

[a] Not reported



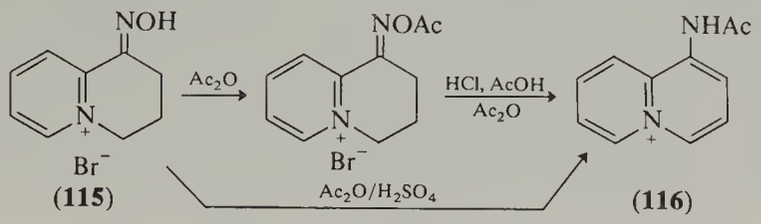
Scheme 74

The dibromo ketone (**113**) when treated with acetic anhydride affords a good yield of 1-acetoxy-2-bromoquinolizinium bromide, which can be hydrolyzed to 1-hydroxy-2-bromoquinolizinium bromide in 57% yield. A better route to the latter compound is by direct hydrolysis of the dibromo ketone (**113**) with hydrobromic acid (70% yield).

Efficient conversion of the dibromo ketone (**113**) to 1-hydroxyquinolizinium ion was accomplished by heating it with dimethylaniline. The 1-hydroxyquinolizinium ion (as the bromide) could be reduced to 1-hydroxyquinolizidine (**114**). When the dibromo ketone (**113**) was heated with aqueous ammonia, a product, believed to be 3-amino-1-hydroxyquinolizinium, was formed in 48% yield, perhaps by a pyridyne mechanism ⟨64JCS2763⟩.

The aromatization of the oxime (**115**) of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (**111**) is carried out best by a modification of the Semmler–Wolff aromatization reaction

(Scheme 75) ⟨60JCS4101⟩. Following the classical procedure, the oxime was acetylated (43% yield) and aromatized in acetic anhydride solution by the action of HCl gas (18% yield). This procedure could be simplified and improved by refluxing the oxime in acetic anhydride containing a few drops of sulfuric acid. Presumably both acetylation and aromatization were accomplished in the same operation, providing 1-acetylaminoquinolizinium bromide (**116**) in an overall yield of 43%.



Scheme 75

2.10.3 SYNTHESES

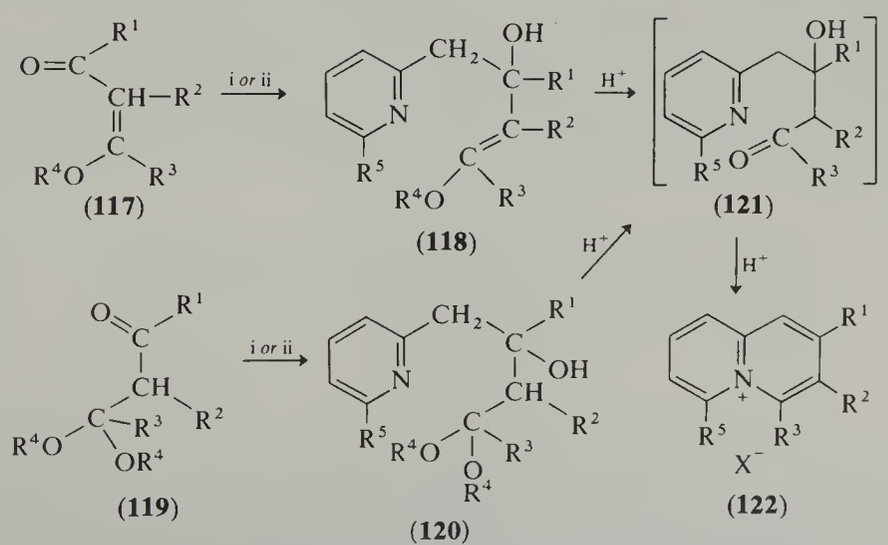
2.10.3.1 General

Following the precedent set in earlier chapters, this discussion of synthesis will be organized according to the mode of bond formation involved in the establishment of the, in this case, second heterocyclic ring. For syntheses in which the newly formed ring is wholly or partially saturated, the chemistry involved in aromatization has been described in Sections 2.10.2.2.9(ii)–(vii).

2.10.3.2 Bond Formed Adjacent to the Heteroatom

2.10.3.2.1 Aldehydes and ketones

In their study of coralyne, the first compound demonstrated to have a fully aromatic quinolizinium nucleus, Schneider and Schroeter showed that the ring-opened product acetopapaverine (Scheme 9) could be recyclized in acid solution ⟨20CB(B)1459⟩. It is likely that this example of a cyclization, involving the acid-catalyzed attack of a carbonyl group on the nitrogen atom of the isoquinoline moiety, provided Woodward with the essential clue for the development of his quinolizinium synthesis ⟨49JA379⟩, used in the synthesis of sempervirine methochloride. The Woodward method required a 1,3-dicarbonyl compound having one carbonyl group protected as a vinyl ether. In a later modification ⟨57DOK(116)93⟩, one carbonyl group was protected as an acetal or ketal. Reaction of the free carbonyl group (Scheme 76) with 2-picolyllithium (or 6-methyl-2-picolyllithium) gave an alcohol (**118** or



i, 2-picolyllithium; ii 6-methyl-2-picolyllithium

Scheme 76

120) which underwent acid hydrolysis of the vinyl ether or acetal linkage to afford a hydroxy aldehyde or ketone (**121**) that could cyclize in the presence of acid to a quinolizinium derivative (**122**). The choice of enol ether *vs.* acetal or ketal appears to have been made on the basis of availability rather than any other synthetic strategy, and one group has made use of mixtures of the two types ⟨58JCS3067⟩.

It is not customary to attempt the isolation of ketone or aldehyde intermediates (**121**); the formula serves merely as a reminder that once hydrolysis of the protecting enol ether or acetal occurs, the same type of structure is formed from any given dicarbonyl compound. Cyclization has been carried out in refluxing ethanolic picric acid or acetic anhydride with a few drops of sulfuric acid, but Hansen and Amstutz ⟨63JOC393⟩ offered excellent theoretical reasons for avoiding an excess of acid, and reported that best results (Table 3) can be obtained by refluxing the dry hydrobromide in acetic anhydride containing no sulfuric acid.

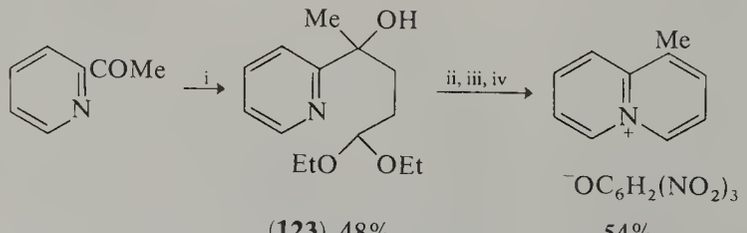
Table 3 Woodward Quinolizinium Synthesis (Scheme 76)

R^1	R^2	R^3	R^4	R^5	*Overall yield (%) of* (**122**) *via* (**118**)	(**120**)	*Ref.*
H	H	H	Pr^i	H	—[a]	—	51TH21000
Me	H	H	Me	H	—	27	57DOK(116)93
Pr	H	H	Me	H	—	30	57DOK(116)93
Ph	H	H	Me	H	—	21	57DOK(116)93
$-(CH_2)_4-$		H	Me	H	51[b]	—	49JA379
Me	H	H	—[c]	H	—	—[d]	58JCS3067
Pr^i	H	H	—[c]	H	—[d,e]	—	58JCS3067
Bu^t	H	H	—[c]	H	—[d,e]	—	58JCS3067
Ph	H	H	—[c]	H	—[d,e]	—	58JCS3067
Me	Me	H	—[c]	H	—	—	58JCS3067
Me	H	Me	—[c]	H	—[d]	—	58JCS3067
Et	Me	H	—[c]	H	—	—[d,e]	58JCS3067
Ph	H	Me	Et	H	27	—	63JOC393
Me	H	H	Me	Me	—	34	63JOC393
Me	H	Me	—[f]	Me	—	31	63JOC393
Ph	H	Me	Et	Me	60.5	—	63JOC393
Me	H	Ph	Et	Me	5	—	64T33

[a] Yield 'very poor'.
[b] Reported by Boekelheide.
[c] Me and Et (mixture).
[d] 'Good yield'.
[e] Mixture of acetal and enol ether.
[f] Acetal with ethylene glycol.

From the table it is clear that the synthesis has not proved useful except in the preparation of substituted quinolizinium compounds having at least one of its substituents at position 2. Beaman ⟨51TH21000⟩, in Woodward's laboratory, did succeed in obtaining some unsubstituted quinolizinium salts but the yields were reported to be very poor.

For the synthesis of the 1-methylquinolizinium ion (Scheme 77), Glover and Jones ⟨59JCS1686⟩ allowed 3,3-diethoxypropylmagnesium chloride to react with 2-acetopyridine to produce an intermediate (**123**) similar to that in the Woodward synthesis (*cf.* **120**) except for the location of the hydroxy group.



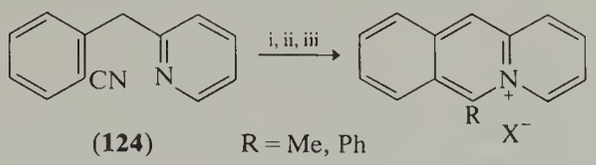
(**123**) 48% 54%

i, $(EtO)_2CHCH_2CH_2MgCl$, THF; ii, HBr, heat; iii, Ac_2O, heat; iv, sodium picrate

Scheme 77

The Woodward quinolizinium synthesis does not appear to have been applied to the synthesis of derivatives of benzoquinolizinium ions, but there are examples of the formation

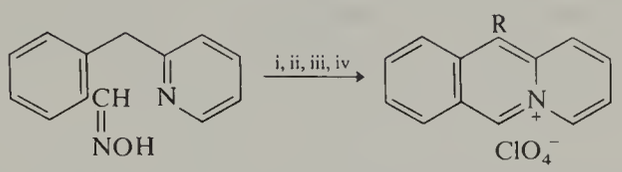
of the acridizinium nucleus thought to occur through acid-catalyzed attack of a ketone or aldehyde carbonyl on a pyridine nitrogen. Treatment of 2-(2-picolyl)benzonitrile (**124**) with the appropriate Grignard reagent, followed by hydrolysis to the crude ketone, and cyclization, furnished 6-substituted acridizinium salts in poor yield (Scheme 78) ⟨67JOC733⟩. Of more synthetic interest is the alkylation of the dianion obtained by treatment of 2-(2-picolyl)benzaldoxime (**125**; Scheme 79) with two equivalents of sodium amide. The alkylated oximes, which could not be purified, were hydrolyzed and cyclized by hydrochloric acid to afford 11-alkylacridizinium salts in yields of 41–61% ⟨71JHC157⟩.



(**124**) R = Me, Ph

i, MeMgI or PhMgBr; ii, 6N HCl, 100 °C; iii, conc. H_2SO_4

Scheme 78

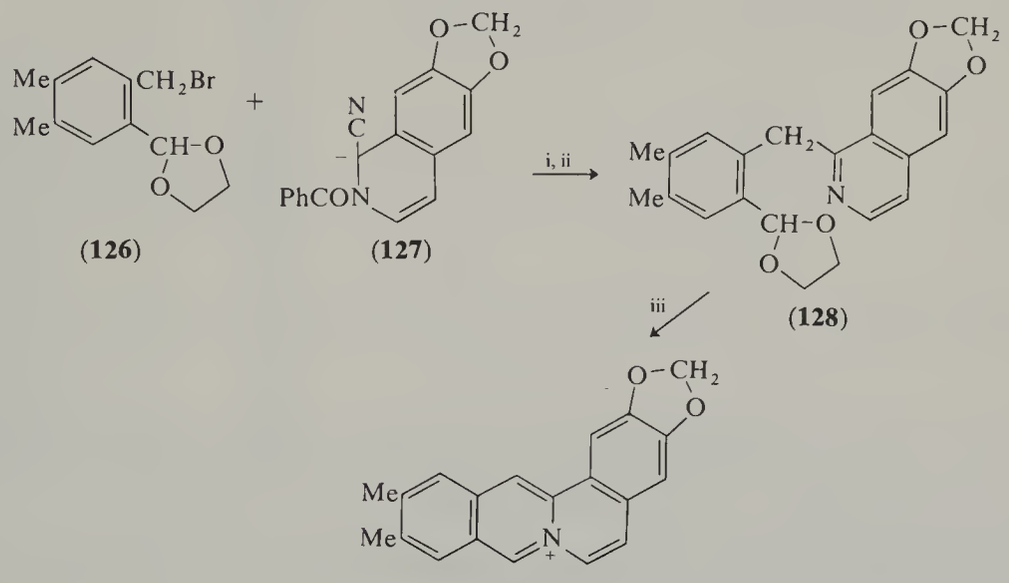


(**125**) R = Me, Bu, $PhCH_2$

i, $NaNH_2$ (2 mol); ii, RX; iii, 10% HCl, 100 °C; iv, $HClO_4$

Scheme 79

A new synthesis of dibenzo[*a*,*g*]quinolizinium derivatives also makes use of an aldehyde cyclization (Scheme 80) ⟨75JAP(K)7596599⟩. In one example, a benzyl bromide bearing an acetal-masked aldehyde group in the *ortho* position (**126**) was allowed to react with the anion (**127**) generated by the action of phenyllithium on a Reissert compound. The condensation product was heated with alkali to cleave the benzoyl and cyano groups to yield the isoquinoline (**128**), then the acetal was cleaved and the resulting aldehyde cyclized to (**129**), presumably under acid conditions.



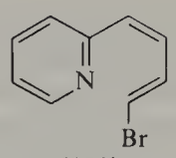
(**126**) (**127**) (**128**) (**129**)

i, condensation; ii, alcoholic KOH; iii, (presumably) H_3O^+

Scheme 80

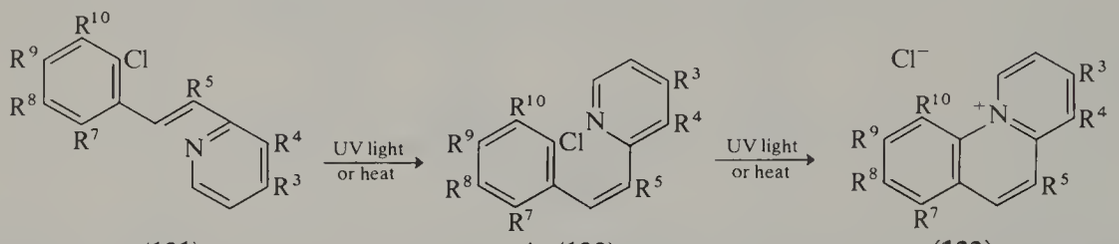
2.10.3.2.2 Halides

The remaining reactions for the establishment of a bond adjacent to the pyridine nitrogen of a potential quinolizinium ring are presumed to involve the attack of the unshared pair of electrons of the nitrogen upon a carbon bearing a halogen atom. The most direct synthesis of this type might involve the cyclization of 1-(2-pyridyl)-4-halobutadiene (**130**)



(130)

which, if it existed in the proper configuration, could (in theory) cyclize directly to quinolizinium bromide. While this cyclization to form the quinolizinium ion is unknown, the cyclization of a benzo derivative of (**130**) is not only known, but provides the most convenient route to the benzo[*c*]quinolizinium ion (**4**) and some related compounds (Scheme 81). The chlorostilbazoles (**131**) obtained by the condensation of 2-picolines with *o*-chlorobenzaldehydes were usually assumed to be in the *trans* configuration, and after irradiation with UV light for 48 h there was usually a shift to shorter wavelengths in the UV absorption spectrum. The *cis*-chlorostilbazole (**132**) obtained in this way usually cyclized in good yield on heating (Table 4). Where a nitro group was *para* to the chlorine ($R^8 = NO_2$) cyclization occurred at room temperature during irradiation. A few stilbazoles did not require irradiation and were shown to be cyclized by heating alone, although the reaction temperatures were usually higher and the products more difficult to purify (Table 4).



trans (**131**) *cis* (**132**) (**133**)

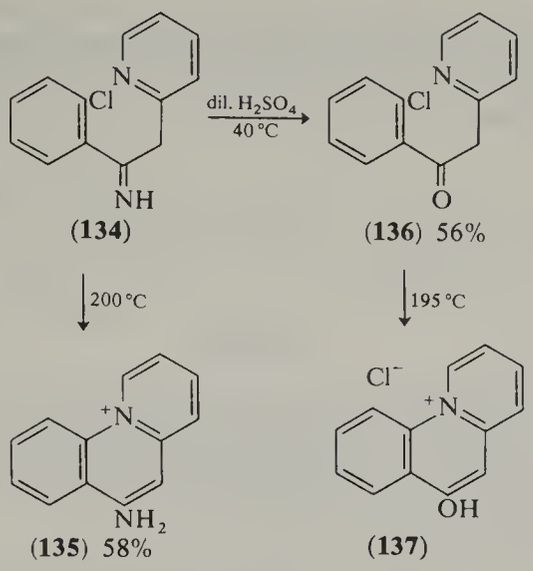
Scheme 81

Table 4 Cyclization of Chlorostilbazoles (Scheme 81)

R^3	R^4	R^5	R^7	R^8	R^9	R^{10}	*Irradiation*[a]	*Cyclization temp.* (°C)	*Yield* (%)	*Ref.*
—	—	—	—	—	—	—	+	170	50	66JOC2616
—	—	—	—	—	—	—	−	240	54[b]	66JOC2616
—	—	—	—	NO_2	—	—	+	25	80	66JOC2616
—	—	—	—	—	Cl	—	+	170	70	66JOC2616
—	Me	—	—	—	—	—	+	165	69	66JOC2616
—	—	Me	—	—	—	—	+	210	55	66JOC2616
—	—	Ph	—	—	—	—	+	200	50[b]	66JOC2616
—	Me	—	—	NO_2	—	—	+	25	80	66JOC2616
—	Me	—	—	—	Cl	—	+	155	77	66JOC2616
—	—	CO_2Et[c]	—	—	—	—	−	140	20	66JOC2616
benzo[d]		—	—	—	—	—	−[e]	200	70	66JOC3683
—	—	—	benzo[f]		—	—	+	180	75	66JOC3683
—	—	—	—	benzo[g]		—	+	180	27	66JOC3683
—	—	—	—	—	benzo[h]		+	180	50	66JOC3683

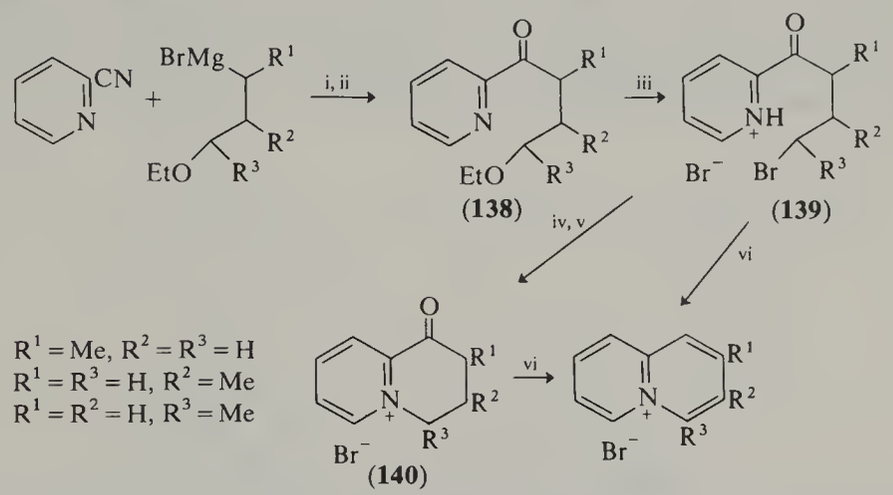
[a] +Indicates usual UV irradiation, 48 h; −indicates no irradiation.
[b] Isolated as the perchlorate.
[c] Ethyl 2-pyridylacetate and *o*-chlorobenzaldehyde were heated under reflux for 15 h in acetic anhydride.
[d] Dibenzo[*a*,*f*]quinolizinium chloride.
[e] Since this chlorostilbazole was not changed by heating, it is assumed to be already in the *cis* configuration.
[f] Naphtho[1,2-*c*]quinolizinium chloride.
[g] Naphtho[2,3-*c*]quinolizinium chloride.
[h] Naphtho[2,1-*c*]quinolizinium chloride.

A closely related cyclization (Scheme 82) has been described recently ⟨79JHC753⟩. The imine (**134**) obtained by the reaction of 2-picolyllithium with 2-chlorobenzonitrile can be cyclized by heating to 200 °C to give 6-aminobenzo[*c*]quinolizinium chloride (**135**). Alternatively, the imine can first be hydrolyzed to the ketone (**136**) which when heated gives 6-hydroxybenzo[*c*]quinolizinium chloride (**137**). A benzo derivative, the 8-aminodibenzo[*c*,*f*]quinolizinium ion, was prepared starting with quinaldinyllithium.



Scheme 82

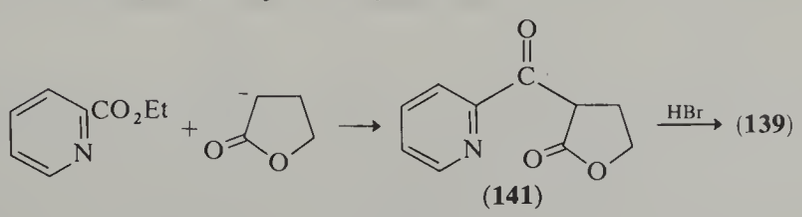
The original method for the synthesis of 1-oxo-1,2,3,4-tetrahydroquinolizinium salts is shown in Scheme 83. A 3-ethoxypropylmagnesium bromide is allowed to react with 2-cyanopyridine (or an analog) and the resulting imine hydrolyzed to the ketone (**138**). Hydrobromic acid is then used to cleave the ether and form the bromide, isolated as the hydrobromide (**139**). The original procedure ⟨58JCS3021⟩ involved neutralizing the salt and heating the resulting bromide to produce the cyclic ketone (**140**) which is shown in Table 2. More recently it has been observed ⟨67JCS(C)1112⟩ that if the bromo compound (**139**) is heated directly with acetic anhydride, it undergoes both cyclization and aromatization in good yield.



i, addition; ii, H_3O^+; iii, HBr; iv, neutralize; v, heat in $CHCl_3$; vi, reflux in Ac_2O

Scheme 83

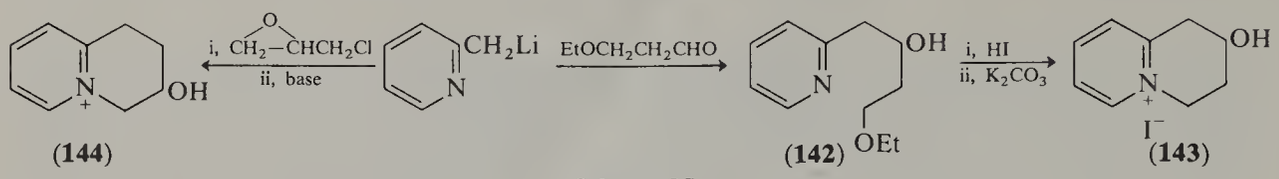
Myadera and Iwai ⟨64CPB1338⟩ have devised a convenient route to the bromide (**139**; $R^1 = R^2 = R^3 = H$) starting with commercially available materials (Scheme 84). The anion formed from γ-butyrolactone by the action of sodium hydride was allowed to react with ethyl picolinate to yield the keto lactone (**141**) which, when heated with hydrobromic acid, undergoes decarboxylation as well as bromination, yielding the bromo ketone (**139**). Several substituted ethyl picolinates have been used successfully, and it has also been found that the anion of the keto lactone (**141**) may be alkylated.



Scheme 84

The first hydroxytetrahydroquinolizinium salt was prepared starting with picolyllithium and β-ethoxypropionaldehyde (Scheme 85) ⟨54JA1832⟩. The alcohol (**142**) formed was

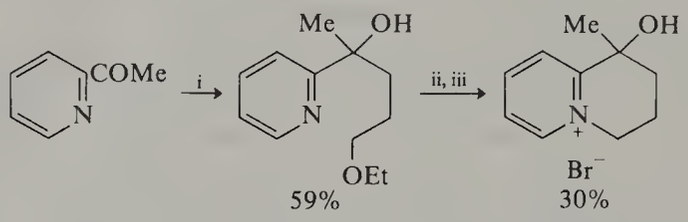
refluxed with hydriodic acid to replace the ethoxy group with iodine and the resulting halide cyclized. It was later found that the 3-hydroxy-1,2,3,4-tetrahydroquinolizinium ion (**144**) may be prepared more easily by the reaction of picolyllithium with epichlorohydrin followed by addition of base ⟨69CB1309⟩.



(**144**) (**142**) (**143**)

Scheme 85

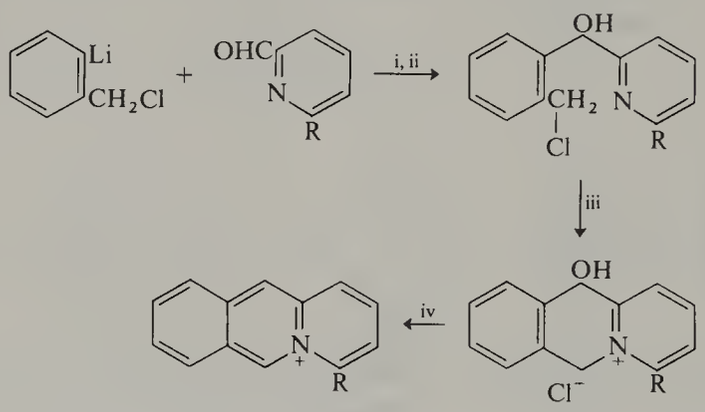
A 1-hydroxy-1-methyltetrahydroquinolizinium salt has likewise been prepared (Scheme 86) ⟨59JCS1686⟩. In general, hydroxytetrahydroquinolizinium salts, because of the problem of dehydration, are less attractive as intermediates than the 1-oxo analogs which almost uniformly can be aromatized in good yield (Table 2).



i, $EtOCH_2CH_2CH_2MgBr$; ii, HBr, boil; iii, make basic, heat

Scheme 86

An alcohol which is easily aromatized to a quinolizinium ion (albeit a benzo derivative) is (**145**; Scheme 87), an intermediate in an acridizinium synthesis ⟨80JOC4248⟩. In the preparation of 4-methylacridizinium bromide (**146**; R = Me) this route gave a better overall yield (34%) than had been obtained by other methods.



(**146**) R = H, Me (**145**)

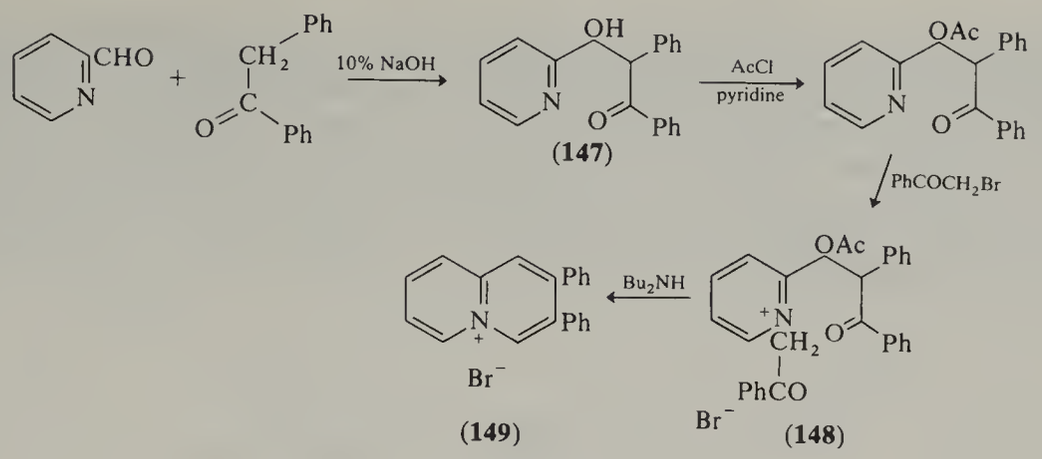
i, −100 °C; ii, EtOH at −100 °C; iii, heat; iv, HBr

Scheme 87

2.10.3.3 Formation of One Bond β to the Heteroatom

2.10.3.3.1 By condensation of a carbonyl group with an activated methyl or methylene

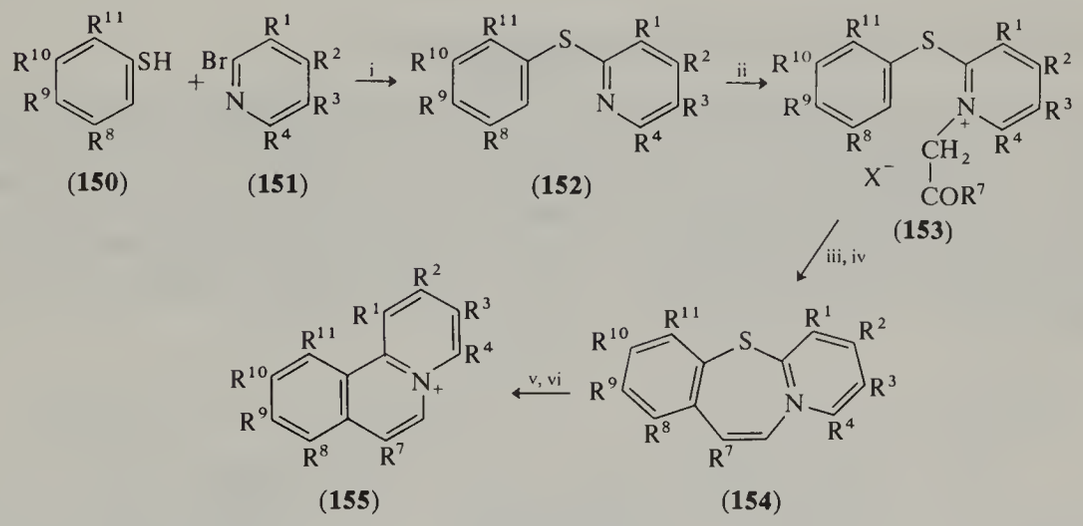
A patent ⟨67MIP21000⟩ has described a general method for the preparation of 2,3-disubstituted quinolizinium ions (**149**; Scheme 88), a method closely related to the Westphal synthesis (*viz.* [4+2] cyclizations). In the example given, 2-picolinaldehyde is allowed to react with deoxybenzoin and the resulting aldol acetylated and quaternized with phenacyl bromide to yield a salt which can be cyclized and cleaved by action of dibutylamine to afford 2,3-diphenylquinolizinium bromide (**149**) in 68–74% yield. It is claimed that quaternary salts analogous to (**148**), but formed by reaction of XCH_2R (R = alkoxycarbonyl or cyano, X = halogen) may be used likewise.



Scheme 88

2.10.3.3.2 By dethionylation of pyrido[2,1-b]benzo[f]thiazepinium salts

As part of a study of the properties of the easily prepared salts (**154**; Scheme 89) ⟨61JOC4944⟩, it was discovered that their exposure to hydrogen peroxide in acetic acid followed by warming led to ring contraction and loss of sulfur, with formation of benzo[*a*]quinolizinium salts. Present evidence ⟨62JOC4475, 66JOC978⟩ indicates that the extrusion of sulfur occurs after the salt has been oxidized to the sulfoxide level. Despite the modest yields (Table 5), this ring contraction has preparative potential as well as theoretical interest. The variety of arenethiols (**150**) and 2-bromopyridines (**151**) available makes a variety of substituted 2-phenylthiopyridines (**152**) accessible as intermediates.



i, Et_3N, heat; ii, $MeCOCH_2I$ or $ClCH_2CH{=}NOH$; iii, exchange with Cl^-; iv, PPA, 160 °C (or boiling HBr); v, H_2O_2, $MeCO_2H$ (or CF_3CO_2H), heat

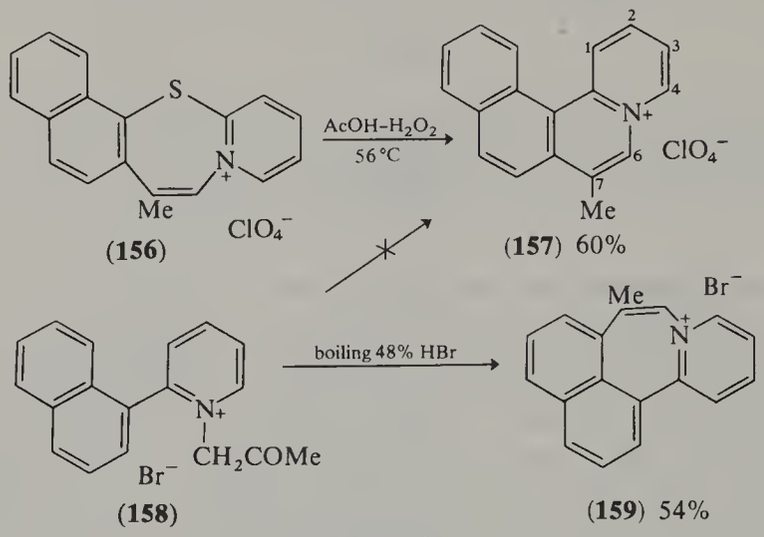
Scheme 89

Table 5 Benzo[*a*]quinolizinium Derivatives by Dethionylation of Pyrido[2,1-*b*]benzo[*f*][1,3]thiazepinium Salts (Scheme 89)

No.	R^1	R^2	R^3	R^7	R^8	R^9	R^{10}	R^{11}	*Yield of* (**155**) (%)	*Ref.*
1	—	—	—	—	—	—	—	—	63	66JOC978
2	—	—	—	Me	—	—	—	—	38	62JOC4475
3[a]	Me	—	—	Me	—	—	—	—	45	66JOC978
4[a]	—	Me	—	Me	—	—	—	—	22	62JOC4478
5[a]	—	—	Me	Me	—	—	—	—	24	62JOC4478
6[a]	—	Me	—	Me	—	—	—	Me	23	62JOC4478
7[a]	—	Me	—	Me	—	—	Me	—	37	62JOC4478
8[a]	—	—	—	—	benzo		—	—	17	62JOC4478
9[a]	—	—	—	Me	benzo		—	—	37	62JOC4482
10[a]	—	—	—	Me	—	—	benzo		60	62JOC4482

[a] Never prepared by cyclization of quaternary salts of 2-phenylpyridine and its congeners.

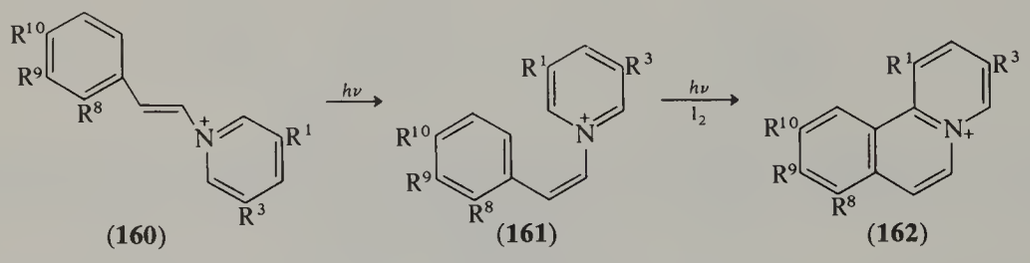
It has been found ⟨62JOC4482⟩ that the ring contraction, when performed on 7-methylnaphtho[2,1-*f*]pyrido[2,1-*b*][1,3]thiazepinium perchlorate (**156**) gave 7-methylnaphtho[1,2-*a*]quinolizinium perchlorate in 60% yield (Scheme 90). The isomeric product (**159**) produced earlier ⟨56JA2459⟩ is now believed to be that formed by attack of the aceto group upon the more reactive α-position of the naphthalene nucleus of (**158**), despite the fact that a seven-membered rather than a six-membered ring is formed (see Section 2.10.3.4). In the formation of (**156**) the choice was between the closure to form an eight-membered ring or a seven-membered ring, with the latter favored evidently due to entropy differences.



Scheme 90

2.10.3.3.3 By UV irradiation of 1-styrylpyridinium salts

The benzo[*a*]quinolizinium ion and some of its derivatives (**162**) can be prepared by UV irradiation of styrylpyridinium salts (**160**; Scheme 91) ⟨66JOC2616⟩ in the presence of iodine (Table 6). It is believed that the styryl salt (**160**) is first isomerized to the *cis* configuration (**161**), then bond formation takes place, followed by loss of hydrogen. In view of the publication of an improved method for making styrylpyridinium salts (**160**) ⟨69JMC1079⟩ the photochemical method appears to offer an advantageous route to the parent compound (**2**).



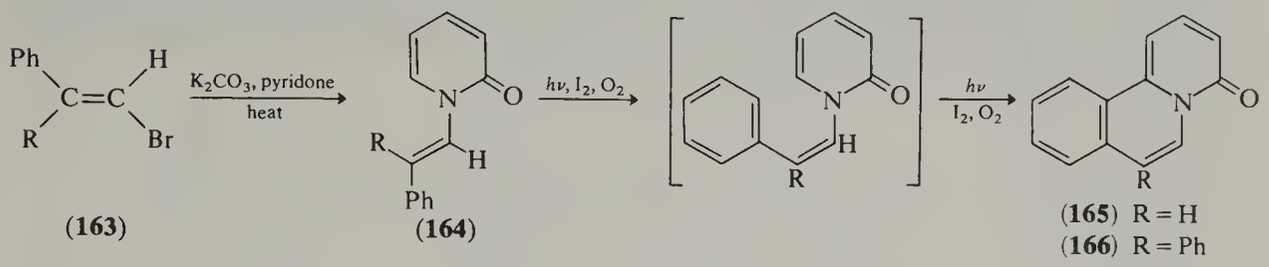
Scheme 91

Table 6 Benzo[*a*]quinolizinium Salts by Irradiation of Styrylpyridinium Salts (Scheme 91)[a]

No.	R^1	R^3	R^8	R^9	R^{10}	*Yield* (%)
1	—	—	—	—	—	60
2	Me	Me	—	—	—	47
3	Ph	Ph	—	—	—	50
4	—	—	Me	—	—	56
5	—	—	—	—	Me	66
6	—	—	OCOPh	—	—	43
7	—	—	—	—	Cl	60
8	—	—	OCOPh	OCOPh	—	25
9	—	—	OCOPh	—	OCOPh	50

[a] ⟨66JOC2616⟩.

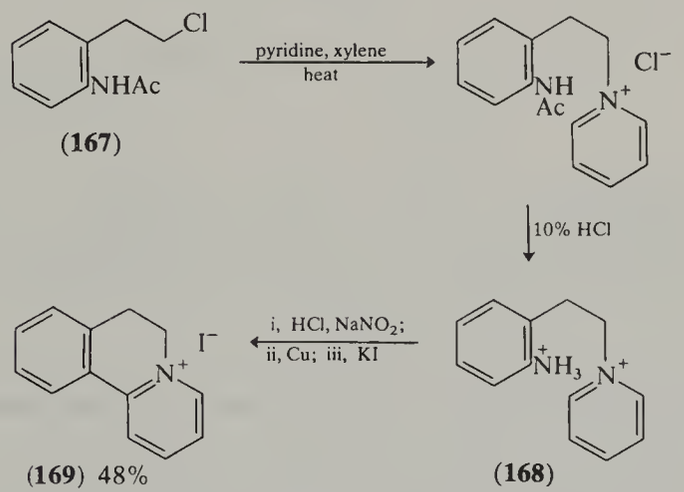
Another related photocyclodehydrogenation synthesis uses an *N*-styrylpyridinone (**164**; Scheme 92), which is generated by *N*-alkylation of pyridinone with a styryl bromide. Irradiation in acid solution in the presence of oxygen causes isomerization and cyclodehydrogenation to afford 4*H*-benzo[*a*]quinolizin-4-one (**165**) and its 7-phenyl derivative (**166**) in yields of 37% and 60% respectively ⟨77JOC1122⟩.



Scheme 92

2.10.3.3.4 Dihydrobenzo[a]quinolizinium ion by a modification of the Pschorr synthesis

Although the synthesis of 6,7-dihydrobenzo[*a*]quinolizinium salts was claimed ⟨52YZ1273⟩ many years ago, it was later shown ⟨59CPB609⟩ that the early report was in error. The first synthesis of the 6,7-dihydro derivative was finally accomplished by Akaboshi and Kato ⟨63YZ1067⟩ by a modification of the Pschorr synthesis (Scheme 93). The necessary amine (**168**) was obtained by alkylation of pyridine with 2-(2-chloroethyl)acetanilide (**167**) followed by hydrolysis. Diazotization and treatment with copper yielded the 6,7-dihydro ion (**169**).

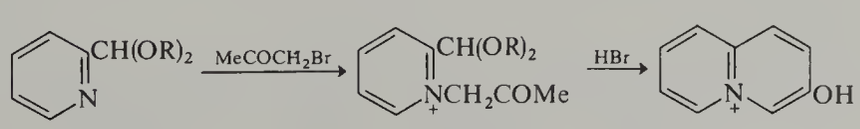


Scheme 93

2.10.3.4 Formation of One Bond γ to the Heteroatom

2.10.3.4.1 By condensation of a carbonyl group with an activated methyl or methylene group

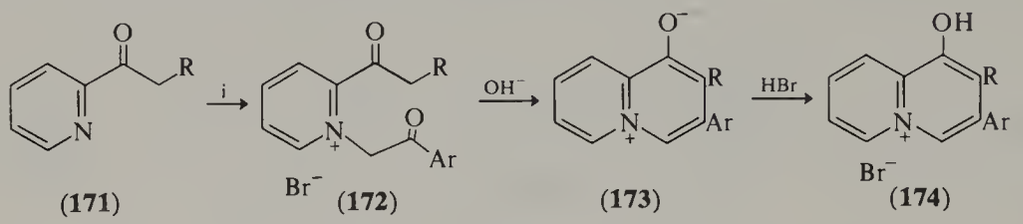
The most convenient route to the 3-hydroxyquinolizinium ion (Scheme 94) involves the quaternization of a 2-picolinaldehyde acetal with bromoacetone followed by acid-catalyzed hydrolysis and intramolecular condensation of the salt (**170**) ⟨62AG(E)593⟩. Good yields have been reported ⟨65JOC526⟩ for both steps when R—R = CH_2CH_2.



(**170**) a; R = Et
b; R—R = CH_2CH_2

Scheme 94

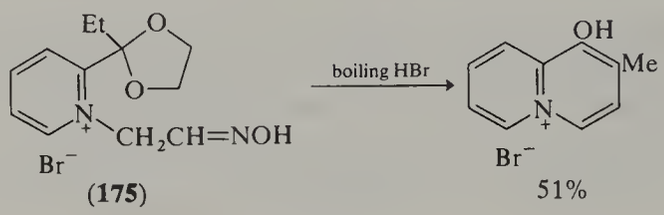
Kröhnke *et al.* ⟨64CB3566⟩ found that α-(2-pyridyl) ketones having a methyl or methylene group adjacent to the carbonyl (**171**), when quaternized with phenacyl bromides, gave salts (**172**) which, in the presence of alkali, cyclized to afford the betaine of 1-hydroxyquinolizinium hydroxide (**173**) which could be converted into the bromide (**174**; Scheme 95). In general, good yields were obtained (Table 7). The observation by Adamson *et al.* ⟨71JCS(C)861⟩ that a ketal quaternary salt (**175**; Scheme 96) underwent hydrolysis and cyclization in hydrobromic acid suggests that a general synthesis of 1-hydroxyquinolizinium salts without groups at position 3 might be available also.



(**171**) (**172**) (**173**) (**174**)

i, $PhCOCH_2Br$ or derivative

Scheme 95



(**175**) 51%

Scheme 96

Table 7 Synthesis of 1-Hydroxyquinolizinium Bromides (**174**; Scheme 95)

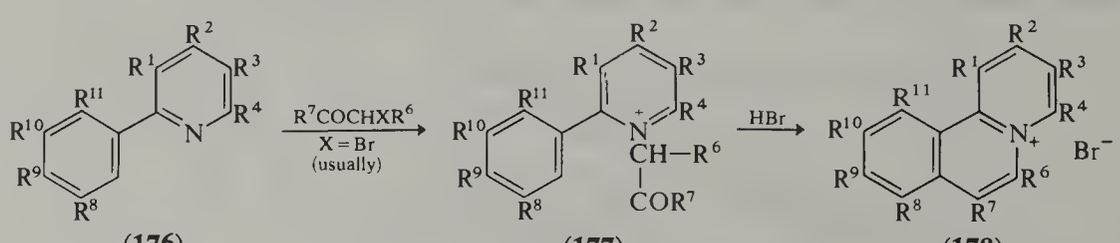
R	*Ar*	*Yield of* (**174**) (%)	*R*	*Ar*	*Yield of* (**174**) (%)
H	Ph	80	Me	Ph	47
H	*p*-$MeOC_6H_4$	76	Et	Ph	84
H	*p*-$NO_2C_6H_4$	85	Et	*p*-BrC_6H_4	88

2.10.3.4.2 By electrophilic attack of a carbonyl group upon a benzenoid ring

The aromatic cyclodehydration ⟨46CRV(38)477⟩ of suitable quaternary salts bearing carbonyl groups has provided convenient access to both benzo[*a*]- and benzo[*b*]-quinolizinium (acridizinium) salts and their benzo analogs, each of the two systems requiring a different approach. The two approaches can be classified according to their synthetic purpose as type A or type B.

(*i*) *Type A*

The cyclodehydration method used for the synthesis of benzo[*a*]quinolizinium ion and its congeners (Scheme 97) requires that phenylpyridines (**176**) (including benzo analogs) be converted into quaternary salts (**177**) by the action of α-halo ketones or α-halo aldehyde derivatives. The acid-catalyzed cyclization of these salts (**177**) has provided access to a number of compounds containing the benzo[*a*]quinolizinium system (**178**) (Table 8).



(**176**) (**177**) (**178**)

Scheme 97

Table 8 Synthesis of Benzo[*a*]quinolizinium Salts (**178**) by Cyclization of Quaternary Salts (**177**) Derived from 2-Phenylpyridine (**176**) and its Congeners (Scheme 97)

No.	R^1	R^2	R^3	R^4	R^6	R^7	R^9	R^{10}	R^{11}	*Quaternization yield (%)*	*Cyclization[a] yield (%)*	*Ref.*
1[b]	—	—	—	—	—	—	—	—	—	—	35[c]	63JOC3205
2	—	—	—	—	—	Me[d]	—	—	—	88	75	55JA453
3	—	—	—	—	—	Ph	—	—	—	68	42	55JA453
4	—	—	—	—	—	$(CH_2)_2CO_2Et$	—	—	—	—	34.5[c]	63JOC81
5[b]	—	—	—	—	—	—	Me	—	—	—	45[c]	63JOC3205
6[b]	—	—	—	—	—	—	—	Me[e]	—	—	61[c]	63JOC3205
7	—	—	—	—	—	—	—	—	Me	—	12[c]	63JOC3205
8	OH	—	—	—	—	Me[d]	—	—	—	62	50	59JA1941
9	—	—	—	—	—	Me[d]	Me	—	—	65	50.5	59JA1941
10	—	—	—	—	—	Me[d]	—	Me	—	—	64[c]	59JA1941
11	—	—	—	—	—	Me[d]	—	OMe	—	99	50	59JA1941
12	—	—	—	—	—	Me[d]	—	—	Me	50.5	9	59JA1941
13	—	—	—	—	—	$(CH_2)_2CO_2Et$	Me	—	—	—	54[c]	63JOC81
14	—	—	—	—	—	$(CH_2)_2CO_2Et$	—	Me	—	—	45[c]	63JOC81
15[f]	benzo		—	—	—	—	—	—	—	53	70[g]	65JOC1846
16	benzo		—	—	—	Me	—	—	—	81	83[h]	65JOC1846
17	benzo		—	—	Me	Me	—	—	—	43	84[h]	65JOC1846
18	—	—	—	—	—	—	benzo		Me	88	76[i]	65JHC399
19	Me	—	—	—	—	—	benzo		Me	90	48[i]	65JHC399
20	benzo		benzo		—	Me	—	OMe	—	54	55	59JOC592

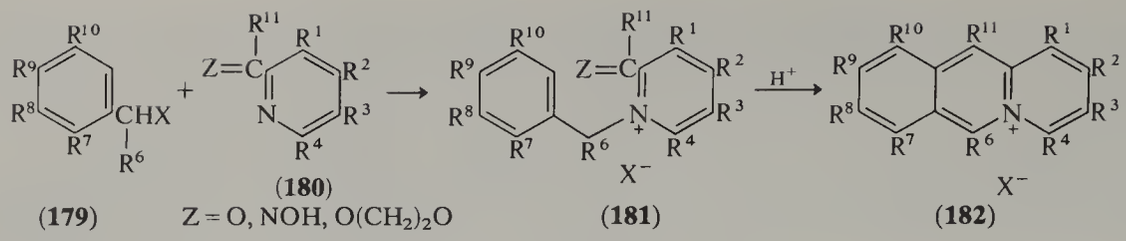
[a] Except as noted, all cyclizations employed refluxing hydrobromic acid.
[b] Quaternization was by the oxime of chloroacetaldehyde and it was the oxime of the salt (**177**) which was cyclized.
[c] Overall yield from both steps.
[d] Quaternized by use of the iodide, but the salt (**177**) was transformed into the chloride before cyclization.
[e] Assigned structure.
[f] Quaternized with the oxime of bromoacetaldehyde.
[g] Cyclized in 48% HBr at 200 °C (sealed tube).
[h] Polyphosphoric acid at 210–220 °C.
[i] Cyclization in refluxing hydrochloric acid.

It will be noted that the great majority, but not all, of the benzo[*a*]quinolizinium salts prepared have a substituent at position 7. This is due in part to delay in finding a suitable substitute for bromo- and chloro-acetaldehydes, which have proved unsatisfactory. It has been found ⟨63JOC3205⟩ that the oxime of chloroacetaldehyde works well, as does that of bromoacetaldehyde ⟨65JOC1846⟩. Poorest yields (examples 7 and 12, Table 8) were obtained when a methyl group was present at position 11 of the developing benzo[*a*]quinolizinium salt. This is believed to be due to steric interference with the achievement of the coplanarity needed for cyclization. Note, however, that in example 18 the steric arrangement is effectively the same as that for example 12 but there has been a six-fold improvement in yield. The difference is probably due to the greater reactivity of a naphthalene nucleus toward the electrophilic cyclization reaction. Cyclization was still achieved in this system (example 19) when there were methyl groups at both positions 1 and 11, albeit in lower yield. In example 20, cyclization has been made possible by activation of the position for electrophilic attack through placing of a methoxy group in the *para* position.

An alternative to the introduction of structural changes to increase reactivity is to raise the temperatures of the cyclization either through use of a sealed tube (example 15) or by use of polyphosphoric acid (examples 16 and 17).

(*ii*) *Type B*

The first synthesis of the benzo[*b*]quinolizinium ion (Scheme 98, Table 9, example 1) was by hydrobromic acid-catalyzed cyclization of the quaternary salt formed between 2-pyridinecarbaldehyde and benzyl bromide. Aromatic cyclodehydration has continued to the present as almost the only method used for the preparation of the acridizinium ion, its derivatives and benzo analogs. Because of its instability, 2-pyridinecarboxaldehyde has been replaced by more efficient derivatives. The first of these was the oxime (example 2) which not only gave a better overall yield, but also made possible the isolation of a crystalline intermediate (**181**; Z = NOH). The disadvantages are that it is not suitable for high temperature cyclizations involving polyphosphoric acid, and some products (**182**) (*e.g.* example 10, Table 10) may tend to form double salts with hydroxylamine hydrobromide.



(**179**) (**180**) Z = O, NOH, $O(CH_2)_2O$ (**181**) (**182**)

Scheme 98

Table 9 Synthesis of Acridizinium Derivatives by Cyclodehydration of Quaternary Salts (Scheme 98) (Monosubstituted)

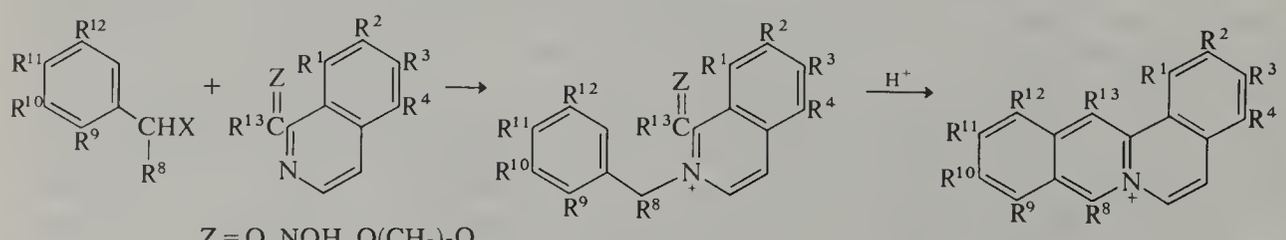
No.	R^4	R^6	R^7	R^8	R^9	R^{11}	*Reagent*	*Z*	*Yield*[a] (%)	*Ref.*
1	—	—	—	—	—	—	HBr	O	60	55JA4812
2	—	—	—	—	—	—	HBr	NOH	78	60JOC757
3	—	—	—	—	—	—	HBr	$O(CH_2)_2O$	88	63JOC83
4	Me	—	—	—	—	—	HBr	$O(CH_2)_2O$	9	63JOC83
5	—	Me	—	—	—	—	HBr	$O(CH_2)_2O$	38	64JHC121
6	—	Pr	—	—	—	—	PPA	$O(CH_2)_2O$	11	64JHC30
7	—	—	Me	—	—	—	HBr	O	46	55JA4812
8	—	—	Ph	—	—	—	HBr	NOH	59	63JOC78
9	—	—	F	—	—	—	PPA	$O(CH_2)_2O$	5	65MI21000
10	—	—	Cl	—	—	—	PPA	$O(CH_2)_2O$	38	65MI21000
11	—	—	Br	—	—	—	PPA	$O(CH_2)_2O$	53	65MI21000
12	—	—	I	—	—	—	PPA	$O(CH_2)_2O$	58	65MI21000
13	—	—	CN	—	—	—	HBr	$O(CH_2)_2O$	34[b]	65MI21000
14	—	—	NO_2	—	—	—	PPA	$O(CH_2)_2O$	32	64JHC30
15	—	—	—	MeO	—	—	HCl	NOH	39	60JOC294
16	—	—	—	Br	—	—	H_2SO_4	$O(CH_2)_2O$	59	67JOC1169
17	—	—	—	—	Me	—	HBr	NOH	92.5	60JOC757
18	—	—	—	—	Ph	—	HBr	NOH	40	63JOC78
19	—	—	—	—	F	—	PPA	$O(CH_2)_2O$	65	65MI21000
20	—	—	—	—	Cl	—	PPA	$O(CH_2)_2O$	28	65MI21000
21	—	—	—	—	Br	—	HBr	$O(CH_2)_2O$	52.5	65MI21000
22	—	—	—	—	I	—	HBr	$O(CH_2)_2O$	71	65MI21000
23	—	—	—	—	CO_2H	—	HBr	$O(CH_2)_2O$	69.5	64JHC30
24	—	—	—	—	SO_2OMe	—	HBr	$O(CH_2)_2O$	16[c]	64JHC30
25	—	—	—	—	NO_2	—	PPA	$O(CH_2)_2O$	49	64JHC30
26	—	—	—	—	—	Me	PPA	$O(CH_2)_2O$	35	63JOC83
27	—	—	—	—	—	Ph	HF	O	77	59JA2550

[a] Overall yield from (**180**).
[b] Product recovered from reaction of the 7-carboxylic acid.
[c] Product is the betaine of 9-sulfoacridizinium hydroxide.

The most advantageous 2-pyridinecarbaldehyde derivative proved to be the acetal (example 3, Table 9) although, unlike the oxime, it was not commercially available. The acetal also usually afforded crystalline intermediate salts (**181**; $Z = O(CH_2)_2O$), but in addition made possible for the first time high temperature cyclization in PPA, permitting cyclization to rings deactivated by a nitro (example 25) or sulfo group (example 24).

The salts (**181**) successfully cyclized include some bearing a ketone or ketone-derived functional group (**181**; R^{11} = alkyl or aryl) instead of an aldehyde function, providing a route to acridizinium derivatives substituted at position 11.

Dibenzo[*a*,*g*]quinolizinium ion is the prototype of a series of compounds initially prepared as intermediates for the synthesis of berbine alkaloids but which, as a class, have recently attracted medicinal interest *per se* (Scheme 99, Table 11).



Z = O, NOH, $O(CH_2)_2O$

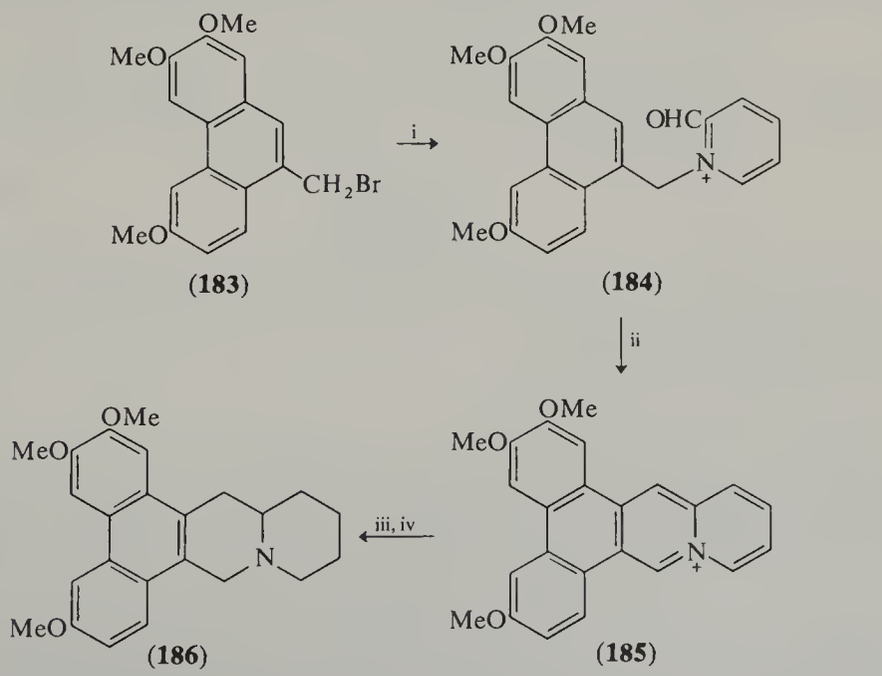
Scheme 99

Table 10 Synthesis of Acridizinium Derivatives by Cyclodehydration of Quaternary Salts (Scheme 98) (Disubstituted)

No.	R^1	R^2	R^3	R^6	R^7	R^8	R^9	R^{10}	R^{11}	*Reagent*	*Z*	*Yield*[a] (%)	*Ref.*
1	benzo		—	—	—	—	—	—	—	HCl	O	52	58JOC130
2	—	benzo		—	—	—	—	—	—	HBr	NOH	21	60JA1808
3	—	—	—	Me	—	—	—	—	Ph	HF	O	7	59JA2550
4	—	—	—	—	benzo		—	—	—	HBr	O	52	56JA2459
5	—	—	—	—	MeO	MeO	—	—	—	HBr	O	75	57JA6033
6	—	—	—	—	OCH_2O		—	—	—	HCl	O	42	57JA6033
7	—	—	—	—	OAc	OAc	—	—	—	HBr	$O(CH_2)_2O$	85[b]	65JOC252
8	—	—	—	—	Cl	MeO	—	—	—	HCl	O	—[c]	63JOC1396
9	—	—	—	—	Cl	—	Cl	—	—	H_2SO_4	$O(CH_2)_2O$	15	67JOC1169
10	—	—	—	—	MeO	—	—	MeO	—	HBr	NOH	31[d]	64JOC61
11	—	—	—	—	OAc	—	—	OAc	—	HBr	$O(CH_2)_2O$	78	64JOC61
12	—	—	—	—	F	—	—	—	Me	PPA	$O(CH_2)_2O$	42	65MI21000
13	—	—	—	—	Cl	—	—	—	Me	PPA	$O(CH_2)_2O$	54	65MI21000
14	—	—	—	—	Br	—	—	—	Me	PPA	$O(CH_2)_2O$	41	65MI21000
15	—	—	—	—	I	—	—	—	Me	PPA	$O(CH_2)_2O$	58	65MI21000
16	—	—	—	—	—	MeO	MeO	—	—	PPA	O	—[c]	66JOC1707
17	—	—	—	—	—	OCH_2O		—	—	HCl	O	31	57JA6033
18	—	—	—	—	—	Cl	Cl	—	—	PPA	$O(CH_2)_2O$	20	65MI21000
19	—	—	—	—	—	Cl	—	Cl	—	H_2SO_4	$O(CH_2)_2O$	63	67JOC1169
20	—	—	—	—	—	MeO	—	—	Ph	HF	O	41	59JA2550
21	—	—	—	—	—	MeO	—	—	Me	HBr	NOH	90[e]	60JOC757
22	—	—	—	—	—	—	benzo		—	HBr	O	72	56JA2459
23	—	—	—	—	—	—	Me	—	Me	HBr	NOH	36	60JOC757
24	—	—	—	—	—	—	Me	—	Ph	HF	O	34.5	59JA2550
25	—	—	—	—	—	—	F	—	Me	PPA	$O(CH_2)_2O$	—[c]	65MI21000
26	—	—	—	—	—	—	Cl	—	Me	PPA	$O(CH_2)_2O$	70.5	65MI21000
27	—	—	—	—	—	—	Br	—	Me	PPA	$O(CH_2)_2O$	55	65MI21000
28	—	—	—	—	—	—	I	—	Me	PPA	$O(CH_2)_2O$	70	65MI21000

[a] Overall yield from pyridine aldehyde or ketone (or benzo analog thereof).
[b] Recovered as the 7,8-dihydroxyacridizinium bromide.
[c] Yield not reported.
[d] Recovered as the mixed salt of the bromide with hydroxylamine bromide.
[e] Recovered as the 8-hydroxy-11-methylacridizinium bromide (ether cleavage).

The quaternization of 2-pyridinecarbaldehyde with 2,3,6-trimethoxy-9-phenanthrylmethyl bromide (**183**) yielded a salt (**184**) which, when cyclized, afforded a dibenz[*h*,*j*]acridizinium derivative (**185**). Reduction of the quinolizinium ring of (**185**) afforded (±)-cryptopleurine ⟨57JA3287⟩.



i, 2-pyridinecarbaldehyde, DMF; ii, PPA, 80 °C; iii, ion exchange to Cl^-; iv, H_2+PtO_2

Scheme 100

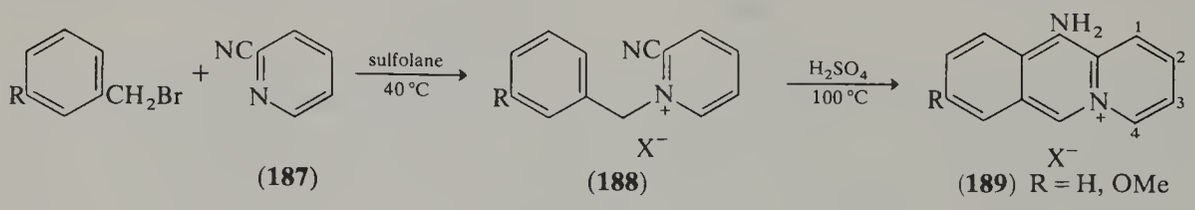
Table 11 Synthesis of Some Dibenzo[*a*,*g*]quinolizinium Derivatives (Scheme 99)

No.	R^1	R^2	R^3	R^4	R^9	R^{10}	R^{11}	*Z*	*Reagent*	*Yield* (%)	*Ref.*
1	—	—	—	—	MeO	—	—	O	HCl	78	58JOC130
2	—	—	—	—	MeO	MeO	—	O	HCl	53	58JOC130
3	—	—	—	—	OCH_2O		—	O	HCl	66	58JOC130
4	—	OCH_2O		—	MeO	MeO	—	NOH	HCl	67	60JA1145
5	—	OCH_2O		—	—	MeO	MeO	O	HCl	—[a]	60JA1145
6	—	OCH_2O		—	—	OCH_2O		O	HCl	66	60JA1145
7	—	OCH_2O		—	—	MeO	—	O	HCl	63	60JA1145
8	—	MeO	MeO	—	MeO	MeO	—	NOH	HCl	80	61JOC2231
9	—	MeO	MeO	—	OCH_2O		—	NOH	HCl	65	61JOC2231
10	—	MeO	MeO	—	—	OCH_2O		NOH	HCl	100	61JOC2231
11	—	MeO	MeO	—	—	MeO	MeO	NOH	HCl	75	61JOC2231
12	—	MeO	MeO	—	—	—	MeO	NOH	HCl	72	61JOC2231
13	—	OCH_2O		—	OCH_2O		—	NOH	HCl	85	61JOC2231
14	—	MeO	MeO	—	OH	MeO	—	NOH	HCl	100	62JOC2213
15	—	OCH_2O		—	OH	MeO	—	NOH	HCl	100	62JOC2213
16	—	MeO	MeO	—	MeO	$PhCH_2O$	—	$O(CH_2)_2O$	HBr	75[b]	65JOC752
17	—	OCH_2O		—	MeO	$PhCH_2O$	—	NOH	HBr	68[c]	66TL3069
18	—	MeO	MeO	—	MeO	MeO	OH	NOH	HBr	—[a,d]	69JOC1349
19	OH	—	OCH_2O		OH	MeO	—	NOH	HBr	—[a]	75JAP(K)75148396
20	MeO	—	OCH_2O		OH	MeO	—	NOH	HBr	—[a]	75JAP(K)75148396
21	MeO	—	MeO	MeO	OH	MeO	—	NOH	HBr	—[a]	75JAP(K)75148396
22	OH	—	MeO	MeO	OH	MeO	—	NOH	HBr	—[a]	75JAP(K)75148396
23	EtO	—	EtO	EtO	OH	MeO	—	NOH	HBr	—[a]	75JAP(K)75148396
24	—	OCH_2O			$PhCH_2NH$	MeO	—	NOH	HCl	—[a,e]	77JAP(K)7748695

[a] Yield not reported.
[b] Product was 10-hydroxy-2,3,9-trimethyldibenzo[*a*,*g*]quinolizinium bromide.
[c] Product was 10-hydroxy-9-methoxy-2,3-methylenedioxydibenzo[*a*,*g*]quinolizinium bromide.
[d] Although evidence was offered in support of the structure shown, later evidence ⟨70YZ82⟩ has raised serious doubts about the structure of the product obtained in example 18.
[e] Product isolated was the 2,3-methylenedioxy-9-amino-10-methoxy salt.

2.10.3.4.3 By electrophilic attack of a cyano group on a benzenoid ring

The acid-catalyzed cyclization of salts (**188**; Scheme 101) prepared from 2-cyanopyridine by quaternization with a benzyl halide provides the only method yet developed for the synthesis of 11-aminoacridzinium salts (**189**). The prototype quaternary salt (**188**; R = H) was cyclized in sulfuric acid in an overall yield of 25% ⟨73JOC4167⟩. A better yield (59%) was obtained when the point of electrophilic attack was activated by a *para* methoxy group.



(**187**) (**188**) (**189**) R = H, OMe

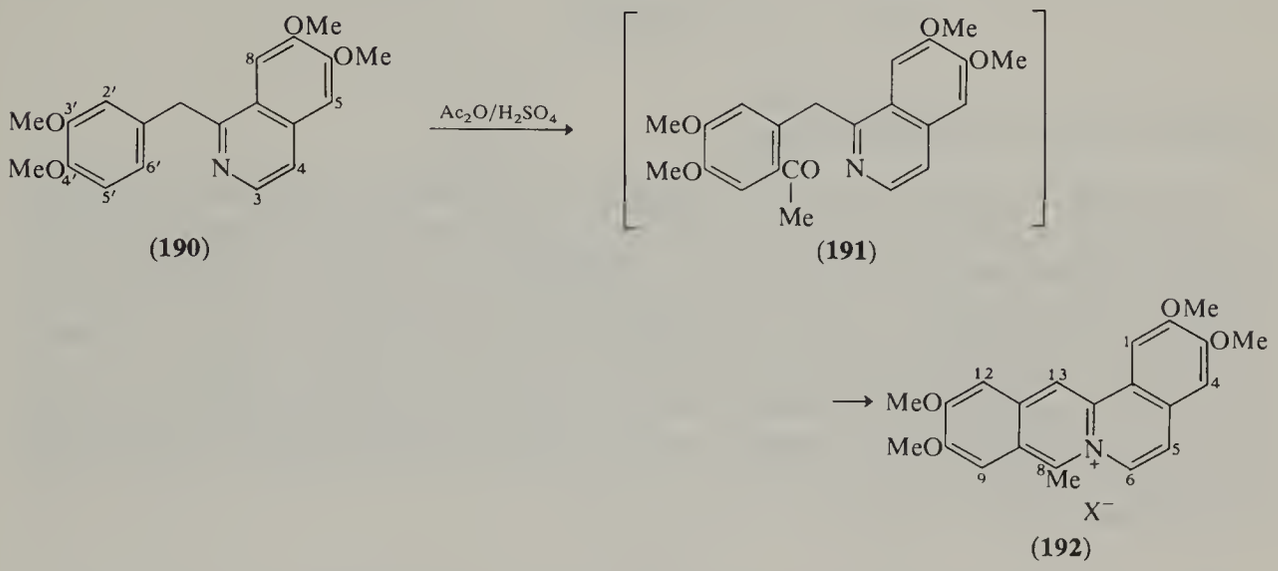
Scheme 101

2.10.3.5 Formation of Two Bonds

2.10.3.5.1 From [5+1] atom fragments

Although the quinolizinium ion itself does not appear to have been made by a [5+1] reaction, benzo analogs of the quinolizinium ion have been formed in this way, and the first recorded example of a compound having a quinolizinium nucleus, a dibenzo[*a*,*g*]quinolizinium ion, was the result of such a reaction. Schneider and Schroeter ⟨20CB(B)1459⟩ showed that when papaverine (**190**; Scheme 102) was treated with acetic anhydride containing some sulfuric acid, it was converted into a yellow crystalline fluorescent salt (**192**) which they named coralyne. The appreciated the fact that acetylation to give (**191**) was the first step and showed that (**191**), prepared by ring opening, would undergo the expected

cyclization. The chemistry of coralyne and some related compounds has been reviewed ⟨81JHC223⟩. It was later found ⟨60AF936⟩ that a coralyne-type cyclization would still occur if the methoxy groups on the benzyl group of (**190**) were at 2′,3′ instead of at 3′,4′, and also if the methoxy groups on the isoquinoline ring of (**190**) were at 5,6 instead of 6,7. The coralyne reaction succeeded if the methoxy groups at 6,7 were replaced by methylenedioxy, but failed if the methoxy groups at 3′,4′ were so replaced. Analogs with one or two substituents on the methylene bridge of (**190**) failed to give the reaction, as did eupaverine, which has an additional ethyl group at position 3. In the latter case, the product was 6′-acetoeupaverine.

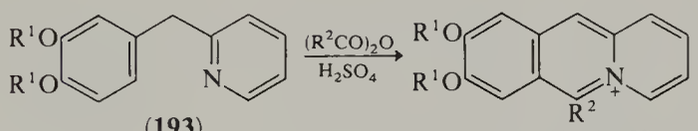


(**190**) (**191**) (**192**)

Scheme 102

When (**190**) was subjected to a Friedel–Crafts reaction with benzoyl chloride, the result was an analog of coralyne with a phenyl rather than a methyl group at position 8. Kametani *et al.* ⟨74YZ478⟩ have carried out a parallel study using the Vilsmeier–Haack reaction to produce norcoralyne.

The simplest system found to undergo a coralyne-type cyclization is that of the 2-(3,4-dialkoxybenzyl)pyridines (**193**; Scheme 103). Best results (74% yield) were obtained when $R^1 = Et$ and $R^2 = Me$, and the worst (25% yield) was with 2-(3,4-methylenedioxybenzyl)pyridine (**193**; $R^1 = —CH_2—$) which gave the expected salt (**194**) ⟨60JOC293⟩. The latter result is of interest in that it was shown by Awe *et al.* ⟨60AF936⟩ that a 1-(3,4-methylenedioxybenzyl)isoquinoline failed to cyclize under much the same conditions.

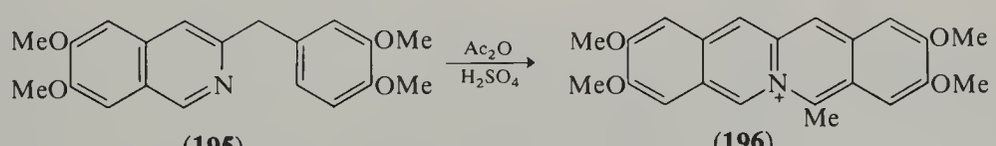


(**193**) (**194**)

$R^1 = MeO, EtO, —CH_2—$; $R^2 = Me, Et$

Scheme 103

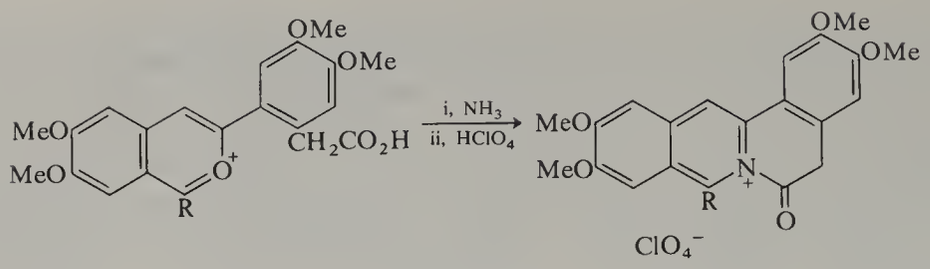
A coralyne-type cyclization has been used to prepare a dibenzo[*b*,*g*]quinolizinium derivative (**196**; Scheme 104) starting with 3-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (**195**) ⟨68AP33⟩.



(**195**) (**196**)

Scheme 104

Another type of [5 + 1] reaction leading to the synthesis of an (in effect) quinolizin-4-one (**198**, Scheme 105) involves the concurrent replacement of the oxygen atom of a 2-benzopyrylium salt (**197**) by nitrogen (from ammonia), and cyclization ⟨77CHE1183⟩.

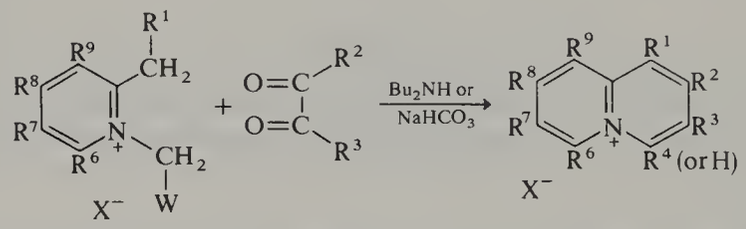


(**197**) R = Me, Et (**198**)

Scheme 105

2.10.3.5.2 From [4+2] atom fragments

The Westphal synthesis has made a number of substituted quinolizinium compounds available easily and economically. The synthesis requires basically a 1,2-dimethylpyridinium salt (**199**) having the methyl at position 1 substituted by an electron-withdrawing group (usually ethoxycarbonyl) to undergo a base-catalyzed condensation with an α-diketone, orthoquinone or (in one case) an α-ketoaldehyde. As a consequence of these requirements nearly all the quinolizinium compounds made by this synthesis have substituents at both the 2 and 3 positions. In most instances the electron-attracting group (usually ethoxycarbonyl) is lost during the condensation reaction. An important development has been the modification of the synthesis to make possible the introduction of functional groups (Table 12, examples 10–18).



(**199**) (**200**)

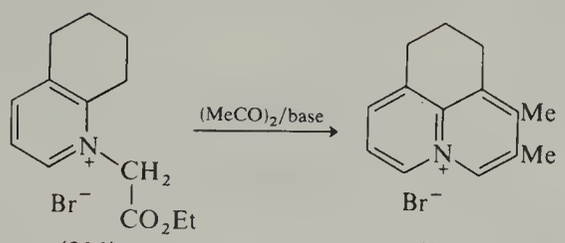
Scheme 106

Table 12 Quinolizinium Derivatives by the Westphal Synthesis (Scheme 106)

No.	R^1	R^2	R^3	R^4	R^6	R^7	R^8	R^9	*W*	*Base*	*Yield* (%)	*Ref.*
1	—	Me	Me	—	—	—	—	—	CO_2Et	i[c]	70	61AP37
2	—	Me	Me	—	—	—	—	—	COPh	i[c]	—[a]	63BRP916507
3	—	Me	Me	—	—	—	—	—	COMe	i[c]	—[a]	63BRP916507
4	—	2-furyl	2-furyl	—	—	—	—	—	CO_2Et	i[c]	80	61AP37
5	—	anisyl	anisyl	—	—	—	—	—	—	—	—[b]	63BRP916507
6	—	2-pyridyl	2-pyridyl	—	—	—	—	—	—	—	—[b]	63BRP916507
7	Me	2-furyl	2-furyl	—	—	—	—	—	—	—	—[b]	63BRP916507
8	—	2-furyl	2-furyl	—	Me	—	—	—	—	—	—[b]	63BRP916507
9	—	2-furyl	2-furyl	—	—	—	Me	—	—	—	—[b]	63BRP916507
10	—	Me	Me	CN	—	—	—	—	CN	—	—[b]	63BRP916507
11	OH	Ph	Ph	—	—	—	—	—	CO_2Et	i[c]	60	64CB3566
12	Me	Me	Me	—	—	—	—	—	CO_2Et	i[c]	61	68JCS(C)1082
13	—	Me	Me	—	—	—	—	$CONH_2$	CO_2Et	NH_3	54	68JCS(C)1082
14	—	Me	Me	—	—	—	NHAc	—	CO_2Et	i[c]	73	68JCS(C)1082
15	NHAc	Me	Me	—	—	—	—	—	CO_2Et	i[c]	54	68JCS(C)1082
16	NHAc	Et	Et	—	—	—	—	—	CO_2Et	i[c]	41	68JCS(C)1082
17	$N(Ac)CH_2Ph$	Me	Me	CO_2Et	—	—	—	—	CO_2Et	i[c]	21	68JCS(C)1082
18	NHAc	—	Me	—	—	—	—	—	CO_2Et	i[c]	42	68JCS(C)1082
19	—	Me	Me	CO_2Et	benzo		—	—	CO_2Et	ii[d]	39	61AP37
20	—	Me	Me	—	—	—	benzo		CO_2Et	i[c]	—[a]	63BRP916507

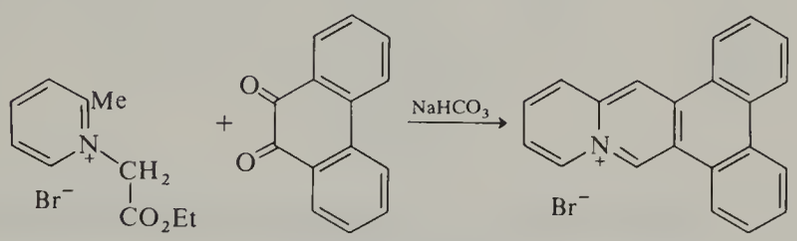
[a] Yield not reported.
[b] Details not available in abstract.
[c] Bu_2NH.
[d] $NaHCO_3$.

Two additional examples of the Westphal synthesis which do not lend themselves to tabular treatment are the condensation of 1-ethoxycarbonylmethyl-5,6,7,8-tetrahydroquinolinium bromide (**201**; Scheme 107) with diacetyl to yield a quinolizinium ion (**202**) having a 1,9-trimethylene bridge, and the condensation of 1-ethoxycarbonylmethyl-2-methylpyridinium bromide with phenanthroquinone (Scheme 108) to yield phenanthro[9,10-*b*]quinolizinium bromide.



(**201**) (**202**)

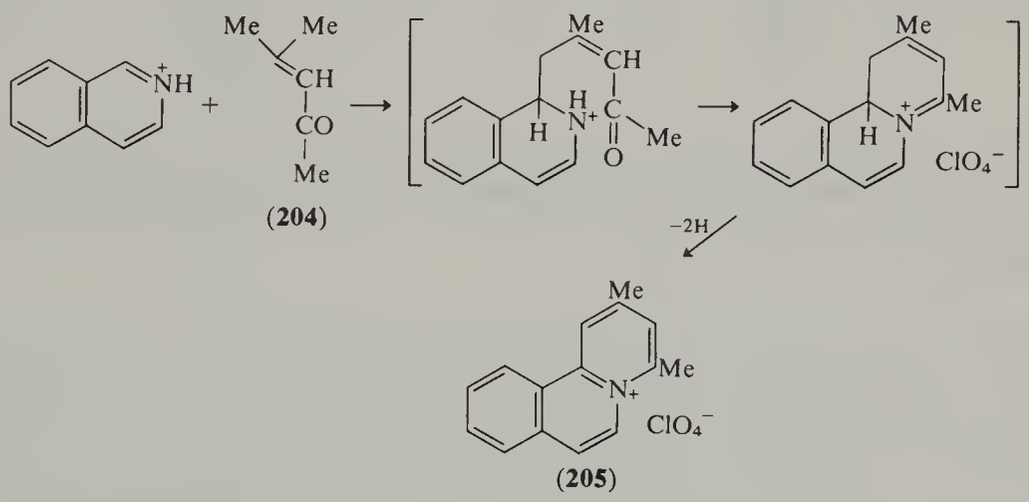
Scheme 107



(**203**) 68%

Scheme 108

The most readily available benzo[*a*]quinolizinium compound is the 2,4-dimethyl derivative, which is easily obtained ⟨75CC489⟩ by a new [4+2] reaction between isoquinoline perchlorate and mesityl oxide (**204**, Scheme 109). The sequence in which the new bonds form remains a matter for conjecture, but the rationalization shown has been presented.



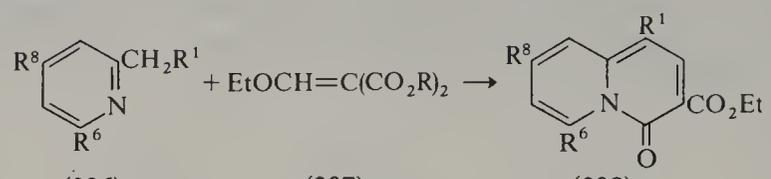
(**204**) (**205**)

Scheme 109

2.10.3.5.3 From [3+3] atom fragments

As pointed out earlier (Section 2.10.3.3.1, Scheme 88), quinolizinium derivatives may be formed by two related but different [3+3] reactions, one (the more important) leading to quinolizone derivatives, the other to quinolizinium ions bearing other functional groups. The reaction, at about 180 °C, of diethyl ethoxymethylenemalonate (**207**; Scheme 110) with a pyridine (or homolog) bearing at position 2 a methyl group having an electron-attracting group (usually alkoxycarbonyl) attached (**206**) has provided a useful route to quinolizone derivatives (**208**, Table 13). Thyagarajan *et al.* have not only introduced the use of ketones (**206**; $R^1 = COR$) as activating groups (see examples 4–7, Table 13) ⟨65T3305⟩, but have also modified the ethoxymethylene reagent (Scheme 111) by replacing (in effect) one of the ethoxycarbonyl groups with nitro. The reaction of ethyl α-nitro-β-ethoxyacrylate

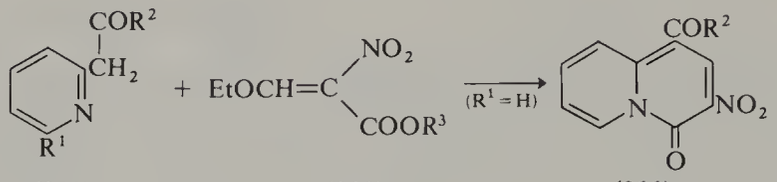
(**210**) with ethyl 2-pyridylacetate ⟨64T1051⟩ and with 2-pyridylacetone and 1-(2-pyridyl)butan-2-one (**209**; $R^1 = H$) gave the desired nitroquinolizone (**211**), but when the 6-methyl homologs (**209**, $R^1 = Me$) were tried, the products were indolizines.



(**206**) (**207**) (**208**)

$R^1 = CO_2Et$, CO_2Me, COMe, COEt, COPh

Scheme 110



(**209**) (**210**) (**211**)

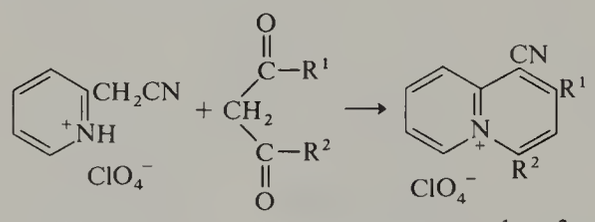
$R^2 = OEt$, Me, Et

Scheme 111

Table 13 Reaction of Diethyl Ethoxymethylenemalonate with 2-Methylpyridine Derivatives (Scheme 110)

No.	R^1	R^6	R^8	*Yield* (%)	*Ref.*
1	CO_2Et	—	—	35	51JA3681
2	CO_2Et	Me	—	80	54JOC499
3	CO_2Me	—	Me	42	76JCS(P1)341
4	COMe	—	—	50	65T945
5	COMe	Me	—	43	65T3305
6	COEt	Me	—	48	65T3305
7	COPh	Me	—	18	65T3305

The remaining [3+3] reaction proceeds directly to form derivatives of the quinolizinium cation ⟨75CHE467⟩. The perchlorate (**212**; Scheme 112) of 2-pyridylacetonitrile was allowed to react with malonaldehyde (as its diacetal), or with a β-diketone (**213**) to give 1-cyanoquinolizinium derivatives (**214**).



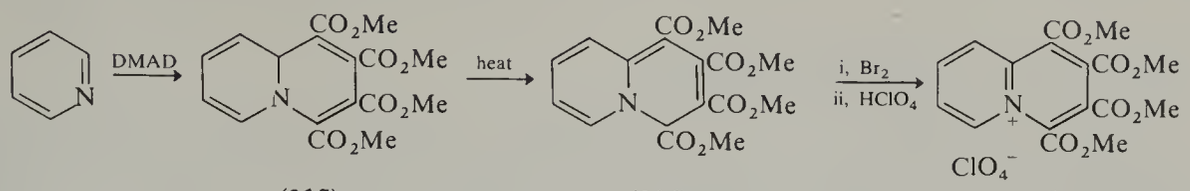
(**212**) (**213**) (**214**) a; $R^1 = R^2 = H$ (bisacetal) (8%)
b; $R^1 = R^2 = Me$ (46%)
c; $R^1 = COEt$, $R^2 = Me$ (77%)

Scheme 112

2.10.3.6 Formation of Three Bonds

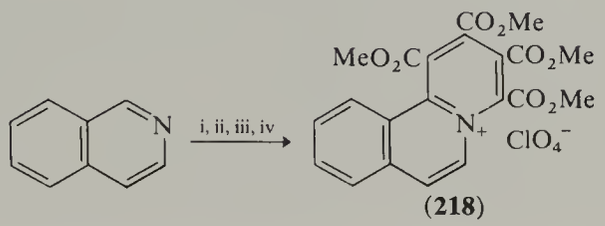
The preparation by Diels and Alder ⟨33LA(505)103⟩ of 1,2,3,4-tetramethoxycarbonylquinolizinium perchlorate is of significance in providing the first example of a simple quinolizinium derivative (as opposed to a benzo analog). The steps involved in the transformation (Scheme 113) were clarified later by Acheson and coworkers ⟨60JCS1691⟩, who showed also the resemblance between the spectrum of the perchlorate (**217**) and that of the quinolizinium ion. The addition of two moles of dimethyl acetylenedicarboxylate to pyridine gave a red 9a*H*-quinolizine derivative (**215**) which, on heating, gave a yellow 4*H*-quinolizine derivative (**216**). The latter was oxidized to the quinolizinium structure (**217**)

by action of bromine. In much the same way the first benzo[*a*]quinolizinium salt (**218**; Scheme 114) was obtained starting from isoquinoline ⟨36LA(525)73, 63AHC(1)157⟩.



(**215**) (**216**) (**217**)

Scheme 113



(**218**)

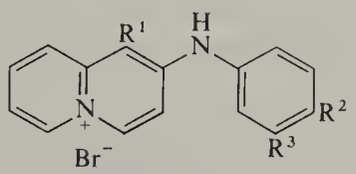
i, DMAD; ii, heat; iii, Br_2; iv, ClO_4^-

Scheme 114

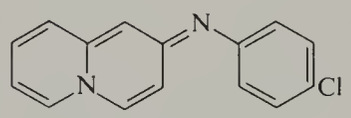
2.10.4 APPLICATIONS AND IMPORTANT COMPOUNDS

2.10.4.1 Quinolizinium Derivatives

Through the reaction of 2-bromoquinolizinium ion or its 1-acetoxy analog with suitable amines, Alaimo and coworkers have produced a large number of 2-aminoquinolizinium salts having useful medicinal activity. Most, but by no means all, of these active compounds are 2-arylaminoquinolizinium salts (**219** and **220**). Best anthelmintic activity was found in (**219**) when R^2 was alkoxy (<Bu) or dialkylamino (NMe_2 or NEt_2) and $R^3 = H$ ⟨70JMC554⟩.



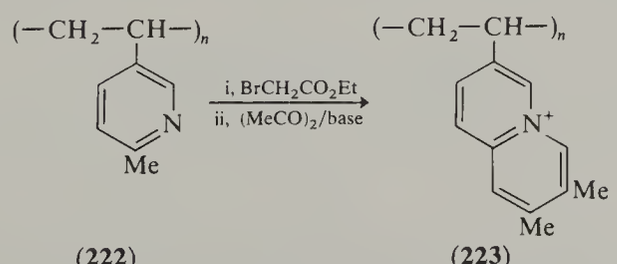
(**219**) $R^1 = H$
(**220**) $R^2 = OH$



(**221**)

The most extensive testing appears to have been for anti-inflammatory activity with useful activity being found in (**219**; $R^2 = R^3 = Cl$) ⟨78MI21000⟩ and (**219**; $R^2 = PhN{=}N-$, $R^3 = H$ or $R^2 = H$, $R^3 = CF_3$) ⟨75USP3899479⟩ as well as in (**220**; R^2 = alkoxy or phenoxy, $R^3 = H$, $R^2 = R^3$ = methoxy) ⟨77USP4020075⟩. Good antispasmodic activity was shown by (**219**; $R^2 = R^3 = Cl$) ⟨75JMC1145⟩. It was found that a potent antiulcerogenic agent, 2-(4-chlorophenylimino)-2*H*-quinolizine (**221**), could be prepared by treatment of the related quinolizinium salt with alkali ⟨78JPS1183⟩.

The quinolizinium ion has been reported to show low, but significant, anti-acetylcholinesterase activity ⟨63JMC456⟩.



(**222**) (**223**)

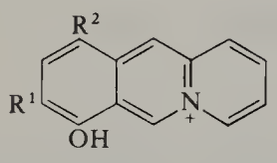
Scheme 115

An ingenious strategy for producing an exchange resin with quinolizinium groups attached (**223**; Scheme 115) has been patented ⟨77USP4046766⟩. A resin (**222**) formed by

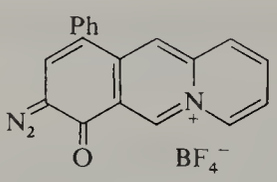
the polymerization of 2-methyl-5-vinylpyridine was treated with ethyl bromoacetate and then with biacetyl under the conditions of the Westphal synthesis.

2.10.4.2 Benzoquinolizinium Derivatives

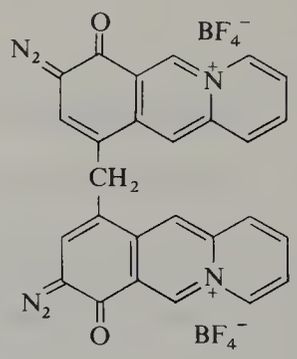
The patent literature gives evidence of interest in benzoquinolizinium compounds in connection with photography and photoreproduction processes. Shortly after the appearance of Chapman's communication on a new method for the synthesis of 2,4-dimethylbenzo[*a*]quinolizinium perchlorate (Section 2.10.3.5.2), a patent was issued to him concerning photographic elements containing benzo[*a*]quinolizinium methine dyes ⟨78USP4108667⟩. It has been claimed that acridizinium compounds having the general formula (**224**) (where R^1 or $R^2 = OH$) are photographic developers, and it has been shown how these and related compounds can be prepared by the usual aromatic cyclodehydration methods ⟨65BEP664166⟩. It is also claimed that the adduct (**34**) obtained by addition of benzyne across the *meso* position of the acridizinium ion is useful in xerography ⟨69FRP1576578⟩. Positive working photoresist compounds suitable for making lithographic printing plates have been prepared from two 8-diazo-7-oxoacridizinium derivatives (**225** and **226**) ⟨68MIP21001⟩.



(**224**)



(**225**)

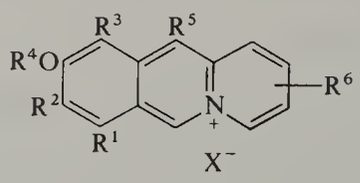


(**226**)

The photodimer (Scheme 27) of acridizinium ethylhexanesulfonate has been used as a non-destructively read-reversible optical memory material to control the intensity and wavelength of emission from a laser ⟨72MI21000⟩.

Thomas ⟨63JMC456⟩ has shown that the antiacetylcholinesterase activity of aromatic cations increases with the number of rings for the sequence *N*-methylpyridinium iodide, quinolizinium bromide, benzo[*b*]quinolizinium bromide. He reasons that the flat ring structure coupled with delocalization of the positive charge is favorable to coulombic interaction with the anionic center of the enzyme. Lower activity was shown with the only tetracyclic cation tested, naphtho[2,1-*b*]quinolizinium ion.

A basic patent ⟨68MIP21000⟩ has been issued for the manufacture of acridizinium compounds having the general formula (**227**), all prepared by the aromatic cyclodehydration method. The compounds are claimed to be cardiovascular agents, particularly for lowering blood pressure, as well as tranquilizers and antipyretic agents. In nearly all of the examples cited, either R^2 or R^3 was hydroxyl or a hydroxyl derivative. At least one agent, 7-methyl-8,9-dihydroxyacridizinium bromide (GPA-1734) (**227**; $R^1 = Me$, $R^2 = OH$, $R^3 = R^4 = R^5 = R^6 = H$), has been made available for laboratory testing.

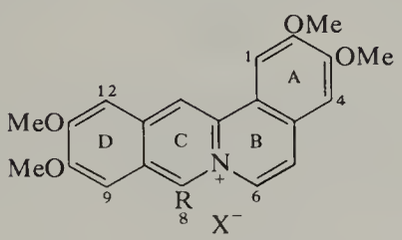


(**227**)

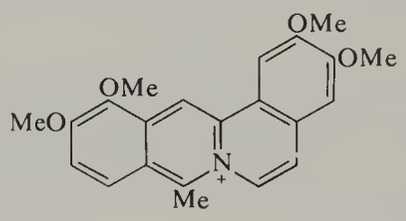
It is reported that GPA-1734 inhibits prolyl and lysyl hydroxylations by Fe chelation and that the formation of non-dialyzable labeled hydroxyproline was inhibited 70% at a concentration of 50 μM, yet incorporation of proline into total liver protein was unaffected at this concentration ⟨78BBA(538)328⟩. GPA-1734 is a potent inhibitor of basement membrane synthesis ⟨78MI21002⟩.

2.10.4.3 Dibenzoquinolizinium Derivatives

Coralyne (**228**; R = Me), a dibenzo[*a*,*g*]quinolizinium derivative, was not only the first quinolizinium derivative known, but has again become the most important. Over a half century after its first synthesis, Zee-Cheng and Cheng reported that it has important antileukemic activity ⟨72JPS969⟩. A study of related compounds ⟨74JMC347⟩ showed that the 8-ethyl analog of coralyne (**228**; R = Et) is slightly more active, while the propyl analog (**228**; R = Pr) is inactive. The product known ⟨61JOC2231⟩ as norcoralyne (**228**; R = H), despite its insolubility, showed significant activity. Replacement of one or both of the pair of adjacent methoxy groups at 2,3 and 10,11 by methylenedioxy groups resulted in decreased activity and increased toxicity. If the methoxy groups in ring A of coralyne (**228**; R = Me) were in effect moved from the 2,3- to the 3,4-positions to form neocoralyne there is little effect on antileukemic activity ⟨76JMC882⟩. Likewise, shifting (in effect) the methoxy groups in the D ring of coralyne from positions 10 and 11 to positions 11 and 12 to form isocoralyne (**229**) also effected little change in activity. Even a dibenzo[*b*,*g*]quinolizinium ion (**196**), a linear analog of coralyne, showed high activity. The coralyne isomer in which the methyl at C-8 is transferred to C-6 decreased the activity and the survival time of the host.

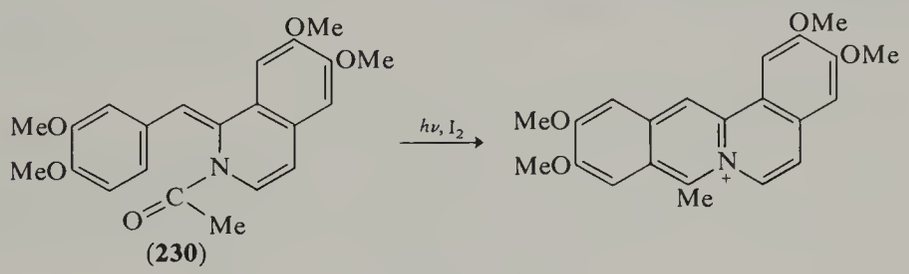


(**228**) R = H, Me, Et, Pr
X = $MeCO_2SO_3^-$, Cl^-



(**229**)

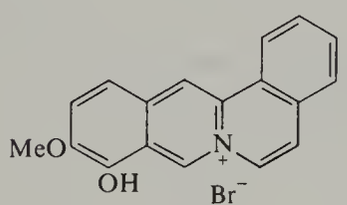
Most coralyne analogs have been prepared by a suitable modification of the coralyne reaction (Scheme 102) although a patent ⟨76JAP(K)7634200⟩ has described a novel photochemical cyclization of an amide (**230**) to yield coralyne (Scheme 116). Evidence concerning the possible mode of action of coralyne is included in a recent reveiw ⟨81JHC223⟩.



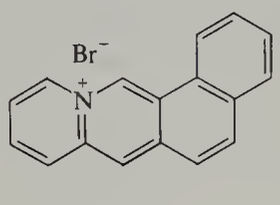
(**230**)

Scheme 116

Using the more versatile tool of aromatic cyclodehydration (Scheme 98), Sawa and Ikekawa have prepared a variety of dibenzo[*a*,*g*]quinolizinium derivatives for use in cancer chemotherapy. Their results are described in a large number of Kokai ⟨*e.g.* 75JAP(K)75154295⟩. From these, it is clear that the compounds of greatest interest bear a hydroxy group or hydroxy derivative at position 8. In a German patent ⟨75GEP2520524⟩ it was claimed that 8-hydroxy-9-methoxydibenzo[*a*,*g*]quinolizinium bromide (**231**) increased the survival time of mice infected with sarcoma 180 and leukemia 1210 by 100% and 240% respectively.



(**231**)



(**232**)

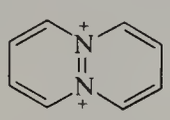
2.10.4.4 Naphthoquinolizinium Derivatives

A novel use for naphtho[1,2-*b*]quinolizinium (**232**) is as a spray which in effect prunes away all new growth from trees ⟨75USP3888656⟩.

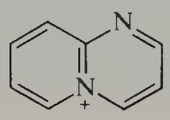
2.10.5 AZAQUINOLIZINIUM DERIVATIVES

2.10.5.1 Introduction and General

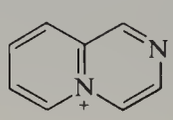
In theory, replacement of the carbon (and attached hydrogen) at positions 1, 2, 3 or 4 should lead to aromatic systems resembling the quinolizinium ion. Although systems which could be considered as diazaquinolizinium ions are already known ⟨71JOC2457⟩, they lie outside the scope of this brief review. Likewise excluded is the pyridazo[1,2-*a*]pyridazinium dication (**233**) which is not properly an aza but a 9a-azoniaquinolizinium dication ⟨68MI21000⟩. Continuing the emphasis on aromatic systems, no effort has been made to consider the literature ⟨61HC(15-2)1141⟩ on reduced ring systems except as they were derived from or converted into the aromatic species. It is convenient to use the 'azaquinolizinium' nomenclature here. With the more correct pyridodiazolium systems the numbering schemes lose correspondence with each other, making comparisons more difficult.



(233)



(234)



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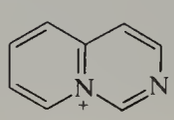

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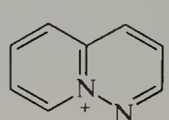


(237)

Of the four possible azaquinolizinium systems, only the 1-aza- (pyrido[1,2-*a*]pyrimidin-5-ium, **234**), the 2-aza- (pyrido[1,2-*a*]pyrazin-5-ium, **235**) and the 4-aza- (pyrido[1,2-*b*]pyridazin-9-ium, **237**) quinolizinium systems are known in at least a betaine form. No example of the fully aromatic 3-azaquinolizinium system (pyrido[1,2-*c*]pyrimidin-9-ium, **236**) has been found.

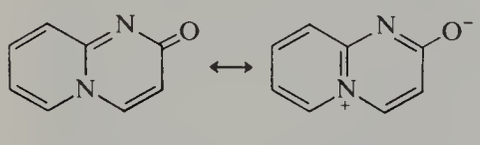
Galasso ⟨68MI21000⟩ has computed the electronic structure and absorption spectrum for each of the monoazaquinolizinium ions.

2.10.5.2 1-Azaquinolizinium Derivatives

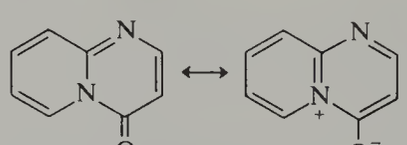
2.10.5.2.1 Structure and physical properties

Nesmeyanov *et al.* reported that the 1-azaquinolizinium ion shows UV absorption maxima at 336, 318, 312, 304, 274 and 228 nm ⟨57DOK(113)343⟩.

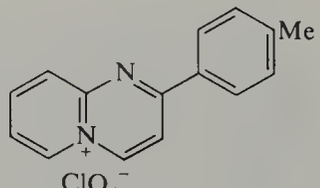
Adams *et al.* ⟨52JA5491⟩ were the first to compare the UV spectra of authentic samples of 1-azaquinolizin-2-one (**238**) and 1-azaquinolizin-4-one (**239**) and, using the spectra as models, were able to assign (or reassign) structures of several known 1-azaquinolizone derivatives ⟨61HC(15-2)1141⟩. The same study showed that the 1-azaquinolizin-2-one (**238**) showed more dipolar character (**238b**) than did its 4-isomer (**239**).



(238a) (238b)



(239a) (239b)



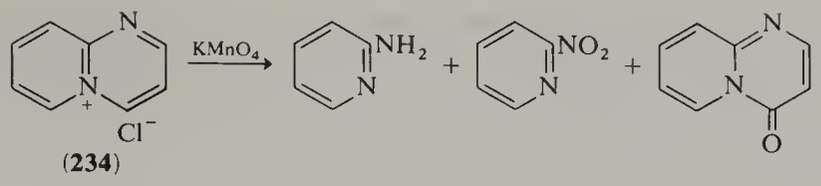
(240)

Many 1-azaquinolizinium compounds have been reported to be fluorescent and 2-(*p*-tolyl)-1-azaquinolizinium ion (**240**) and some analogs, when excited by irradiation at 340 nm, show a luminescent intensity comparable with that of quinine sulfate ⟨74JPR875⟩.

The ^{1}H NMR spectrum of 1-azaquinolizinium chloride (**234**) shows signals at δ 8.16 (m, H-3 and H-6), 8.66 (d, $J = 2$ Hz, H-8), 8.70 (dd, $J = 2$ and 6 Hz, H-7), 9.38 (dd, $J = 2$ and 6 Hz, H-2), 9.55 (dd, $J = 2$ and 4 Hz, H-7) and 9.71 p.p.m. (dd, $J = 2$ and 6 Hz, H-4) ⟨78CPB3167⟩.

2.10.5.2.2 Reactivity

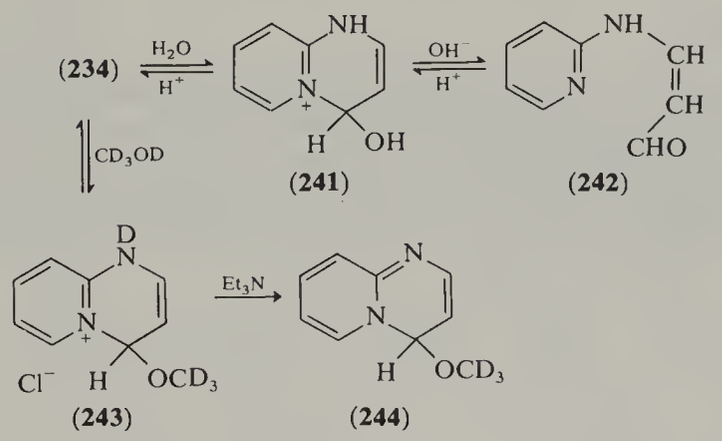
Oxidation of 1-azaquinolizinium chloride with permanganate afforded a mixture containing 2-aminopyridine, 2-nitropyridine and 1-azaquinolizin-4-one (Scheme 117) ⟨78CPB3167⟩.



(234)

Scheme 117

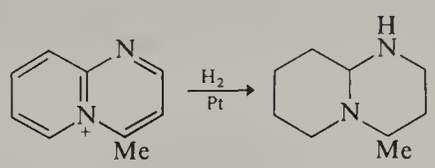
A careful ^{1}H NMR study by the same group has shown that the 1-azaquinolizinium ion in neutral aqueous solution undergoes hydration to yield (**241**), but the equilibrium is shifted to the aromatic species (**234**) if the solution is made 0.1 M in acid (Scheme 118). Bicarbonate causes ring opening to afford β-(2-pyridylamino)acrolein (**242**), which can be recyclized in acid. Deuteromethanol also adds to the 1-azaquinolizinium ring, in a transannular manner, and triethylamine converts the resulting salt (**243**) to 4-methoxy-1-aza-4*H*-quinolizine (**244**).



Scheme 118

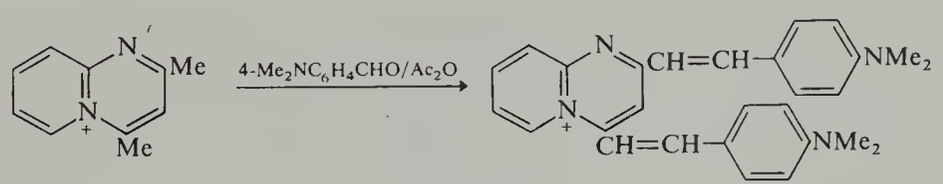
Catalytic reduction of the 1-azaquinolizinium system (Scheme 119) leads to the expected 1-azaquinolizidine ⟨57DOK(113)343⟩.

Methyl groups α or γ to the cationic nitrogen are active towards condensation as illustrated (Scheme 120) by the reaction of 2,4-dimethyl-1-azaquinolizinium ion with *p*-dimethylaminobenzaldehyde ⟨72UKZ262⟩.

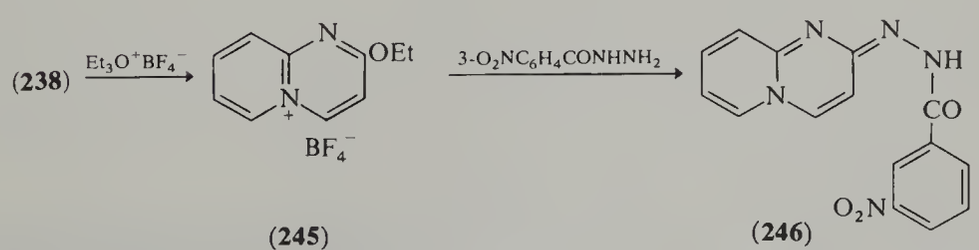


Scheme 119

2-Ethoxy-1-azaquinolizinium tetrafluoroborate (**245**), prepared by the action of triethyloxonium tetrafluoroborate on 1-azaquinolizin-2-one (**238**), undergoes nucleophilic displacement by *m*-nitrobenzoylhydrazine (Scheme 121) to afford a 1-aza-2*H*-quinolizine derivative (**246**), useful as a dye intermediate ⟨61LA(640)98⟩.

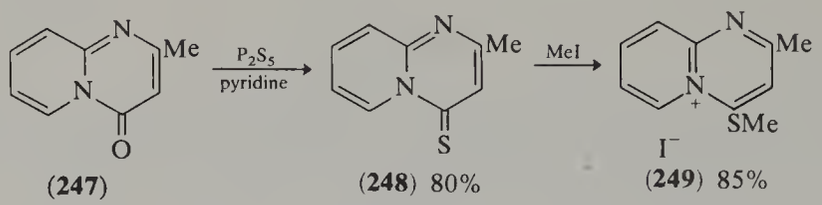


Scheme 120



Scheme 121

The reactions of 1-azaquinolizin-4-ones resemble those of quinolizin-4-ones ⟨73JHC821⟩. For example, the oxygen of 2-methyl-1-azaquinolizin-4-one (**247**) may be replaced by sulfur by the action of P_2S_5 (Scheme 122). The resulting thione (**248**) reacts effectively with methyl iodide to produce 2-methyl-4-methylthio-1-azaquinolizinium iodide (**249**).

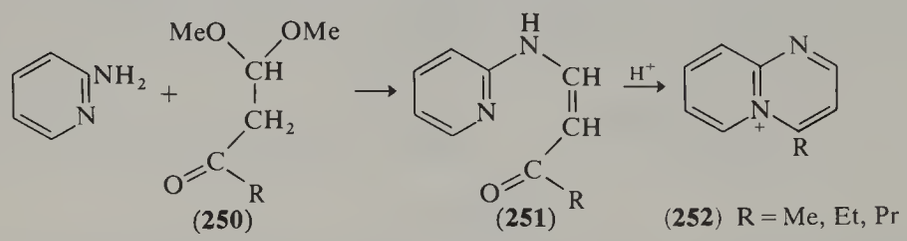


(**247**) (**248**) 80% (**249**) 85%

Scheme 122

2.10.5.2.3 Syntheses

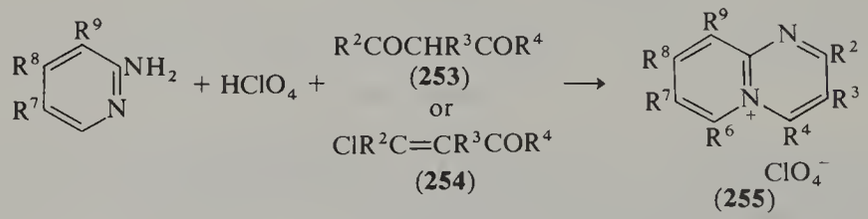
The first synthesis of a 1-azaquinolizinium salt (**252**) was accomplished by Nesmeyanov *et al.* ⟨57DOK(113)343⟩. They heated 2-aminopyridine with the acetal of an acylacetaldehyde (**250**) to form an intermediate (**251**) first thought to be an acylanil but now recognized ⟨73JCS(P1)1138, 74JPR469⟩ to have the double bond conjugated with the carbonyl group. The intermediate was cyclized by the action of hydrobromic acid (Scheme 123).



(**250**) (**251**) (**252**) R = Me, Et, Pr

Scheme 123

Soon it was found that good yields of many 1-azaquinolizinium salts could be obtained by adding either the ketoacetal (**250**) or a β-chlorovinyl ketone (**254**) to an acidic solution of 2-aminopyridine ⟨58DOK(118)297⟩. This simple one-pot reaction was extended by the use of additional ketoacetals as well as β-diketones (**253**) and malonaldehyde diacetal (Scheme 124). Table 14 illustrates the scope of this [3+3] addition mode of the 1-azaquinolizinium synthesis.



(**255**)

Scheme 124

In general the orientation is that to be expected if the 1,3-dicarbonyl compound was first formed and the more reactive carbonyl group was attacked by the primary amino group. The deviation of examples 14–16 (Table 14) from this rule probably has a steric explanation. The intermediate formed by the attack of the primary amine on the aldehyde group cyclized poorly because of the presence of the alkyl groups at positions 4 and 6. Despite the very low concentration of ketone–primary amine addition product in the equilibrium mixture, this intermediate provides access to a final product without having to surmount the large energy barrier to achievement of a planar structure observed when alkyl groups stand in *peri* opposition, as in 1,8-dimethylnaphthalene ⟨65JCS528⟩. The decrease in yield as the size of the group at position 6 is increased (examples 15, 16) suggests that even the acid-catalyzed attack of an aldehyde group might be subject to steric influence. Note in examples 18 and 19 that the β-chlorovinyl synthesis can be used to prepare 3,4-cyclopenteno or 3,4-cyclohexeno derivatives of the 1-azaquinolizinium ion.

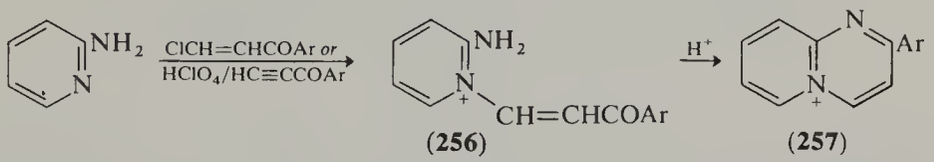
Fischer found that, in the absence of perchloric acid, 2-aminopyridine reacted with β-chlorovinyl aryl ketones to form quaternary salts (**256**, Scheme 125) which, when heated with perchloric acid, gave not the 4-substituted product obtained in the Nesmeyanov

Table 14 Mono- and Di-substituted 1-Azaquinolizinium Perchlorates (**255**) Obtained by [3 + 3] Reactions using a Dicarbonyl Derivative (**253**) or a β-Chlorovinyl Ketone (**254**) with a 2-Aminopyridine (Scheme 124)

No.	R^2	R^3	R^4	R^6	R^7	R^8	R^9	*Yield (%) from* (**253**)	(**254**)	*Ref.*
1	—	—	—	—	—	—	—	75	—	72UKZ262
2	—	—	Me	—	—	—	—	72	75	58DOK(118)297
3	—	—	Pr	—	—	—	—	60	82	58DOK(118)297
4	—	—	Ph	—	—	—	—	13	11	58DOK(118)297
5	—	—	—	Me	—	—	—	70	—	72UKZ262
6	—	—	—	—	Me	—	—	49	—	73JCS(P1)1138
7	—	—	—	—	Br	—	—	80	—	72UKZ262
8	—	—	—	—	—	Me	—	70	—	72UKZ262
9	—	—	—	—	—	—	Me	71	—	72UKZ262
10	Me	—	Me	—	—	—	—	96	—	72UKZ262
11	Me	—	Et	—	—	—	—	—[a]	—	75UKZ186
12	Me	—	$EtOCH_2$	—	—	—	—	—[a]	—	75UKZ186
13	Me	—	cyclopropyl	—	—	—	—	—[a]	—	75UKZ186
14	Me	—	—	Me	—	—	—	95	—[a]	73JCS(P1)1138, 75UKZ186
15	Me	—	—	Et	—	—	—	34	—	73JCS(P1)1138
16	Me	—	—	Pr	—	—	—	24	—	73JCS(P1)1138
17	—	Me	Me	—	—	—	—	—	67	73KGS242
18	—	$CH_2CH_2CH_2$		—	—	—	—	—	36	73KGS242
19	—	$CH_2(CH_2)_2CH_2$		—	—	—	—	—	65	73KGS242
20	—	—	Me	—	—	Me	—	—	79	73KGS242
21	—	—	Me	—	—	—	Me	—	81	73KGS242
22	—	—	—	—	Br	—	Br	69	—	72UKZ262

[a] Yield not given.

procedures (Table 14, example 4) but instead the previously unknown 2-aryl-1-azaquinolizinium salts (**257**) in yields of 54–77% ⟨74JPR474⟩. An effective alternative approach to one such quaternary intermediate (**256**; Ar = Ph) was by the reaction of ethynyl phenyl ketone with 2-aminopyridine in the presence of perchloric acid.

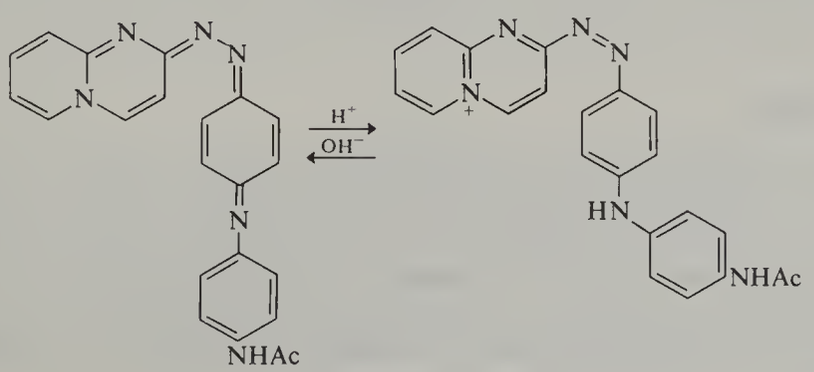


Scheme 125

Methods for the synthesis of the betaine 1-azaquinolizin-2-one (**238**) and 1-azaquinolizin-4-one (**239**) have been well reviewed ⟨61HC(15-2)1141⟩.

2.10.5.2.4 Uses

By use of an oxidation coupling reaction, Hünig *et al.* ⟨61LA(640)98⟩ have been able to prepare dyes which, in the acid form, are 2-substituted 1-azaquinolizinium salts (*e.g.* Scheme 126). Some 1-azaquinolizin-4-one derivatives have been reported to show hypoglycemic activity ⟨71IJC201⟩ while others are stated to have favorable analgesic properties ⟨79JHC457⟩.



Scheme 126

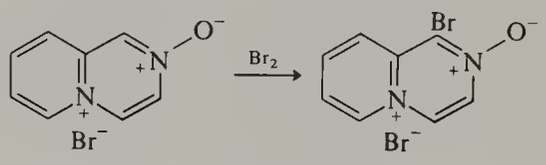
2.10.5.3 2-Azaquinolizinium Derivatives

2.10.5.3.1 Structure and physical properties

The 2-azaquinolizinium ion or pyrido[1,2-*a*]pyrazin-5-ium has been reported to show the following UV absorption maxima [λ/nm ($\log_{10}\varepsilon$)]: 232 (4.31), 276 (3.34), 287 (3.35), 310 (3.73), 322 (3.98), 336 (4.03) ⟨67JCS(C)2391⟩.

2.10.5.3.2 Reactivity

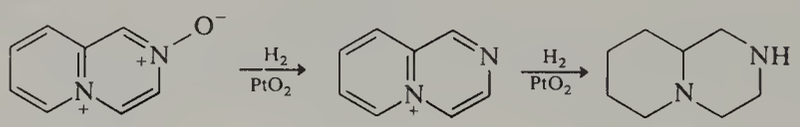
Although electrophilic substitution of the 2-azaquinolizinium ion has not been reported, the readily available (Section 2.10.5.3.3) *N*-oxide (**258**) is easily brominated (Scheme 127). Under the same conditions the 1-methyl-2-azaquinolizinium 2-oxide is not brominated, suggesting that relative to other positions in the oxide (**258**) the 1-position is especially reactive ⟨67JCS(C)2391⟩.



(**258**) (**259**) 92%

Scheme 127

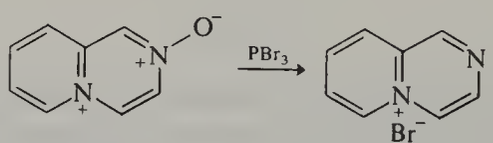
Reduction of the 2-azaquinolizinium ion evidently leads to 2-azaquinolizidine (**260**), for controlled hydrogenation of 2-azaquinolizinium 2-oxide (**258**) yields the 2-azaquinolizinium ion while complete hydrogenation of the oxide (**258**) yields 2-azaquinolizidine (**260**; Scheme 128) ⟨66JOC941⟩.



(**258**) (**235**) (**260**)

Scheme 128

A more efficient method for converting the oxide (**258**) to 2-azaquinolizinium bromide is by refluxing it in phosphorus tribromide (Scheme 129) ⟨67JCS(C)2391⟩. Deoxygenation by use of phosphorus trichloride or tribromide proved effective ⟨71JCS(C)861⟩ with a number of 2-azaquinolizinium 2-oxides substituted in positions 1 and 3, although the 1-methyl oxide offered some resistance.

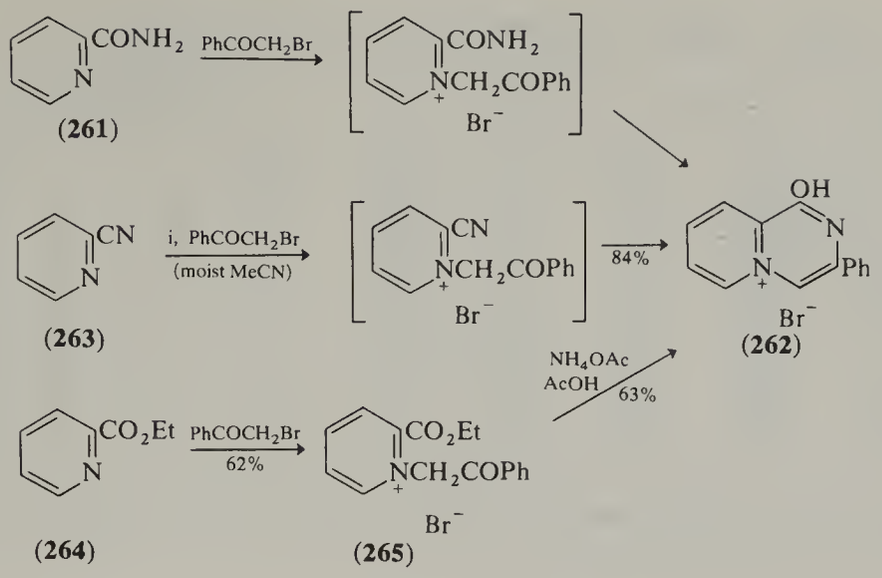


(**258**) (**235**) 58%

Scheme 129

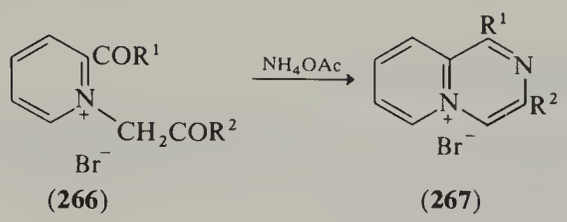
2.10.5.3.3 Syntheses

The first fully aromatic 2-azaquinolizinium salts were prepared by Kröhnke *et al.* ⟨64CB3566⟩, who examined three approaches to the 1-hydroxy-3-phenyl-2-azaquinolizinium ion (**262**; Scheme 130). The first involved the reaction of picolinamide (**261**) with phenacyl bromide which produced (**262**) in unspecified yield. Most effective was refluxing 2-cyanopyridine (**263**) in moist acetonitrile with phenacyl bromide. Finally, it was shown that 2-ethoxycarbonyl-1-phenacylpyridinium ion (**265**) could serve as a starting material if ammonium acetate were present in the solvent.



Scheme 130

If a ketone rather than an ester group were present at position 2 of the pyridinium salt (**266**, Scheme 131), ammonium acetate produced 2-azaquinolizinium salts with an alkyl or aryl group at position 1 (Table 15).

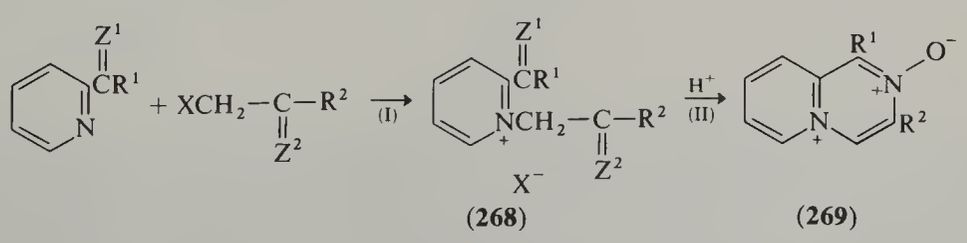


Scheme 131

Table 15 Synthesis of 1,3-Disubstituted 2-Azaquinolizinium Salts (**267**) by Reaction of Ammonium Acetate on 2-Acyl-1-acylmethyl-pyridinium Salts (**266**; Scheme 131)

R^1	R^2	*Yield* (%)
Me	Ph	96
Et	Ph	71
Pr	Ph	95
Ph	4-BrC_6H_4	65

A method conceptually related to Scheme 131 requires that one or both of the carbonyl groups shown in (**266**) be present as the oxime derivative, with cyclization leading to the 2-*N*-oxide (**269**; Scheme 132). In actual practice ⟨66JOC941⟩ it was found that two of the proposed intermediates (Table 16, examples 7 and 9) cyclized spontaneously under quaternization conditions to afford the aromatic 2-azaquinolizinium *N*-oxide derivative directly. In another example (Table 16, example 4) ⟨71JCS(C)861⟩ intramolecular addition occurred during quaternization, but the product, a 3-hydroxy-3,4-dihydro-2-azaquinolizinium derivative, did not lose water spontaneously to form the aromatic system until heated with acid.



Z^1 or Z^2 must be NOH [(I) and (II) refer to Table 16]

Scheme 132

Table 16 Synthesis of 2-Oxides of 2-Azaquinolizinium Salts (Scheme 132)

No.	R^1	Z^1	X	R^2	Z^2	Yield (%) Step I	Step II	Overall	Ref.
1	H	NOH	Cl	H	NOH	90	—[a]	—[a]	66JOC941
2	H	$O(CH_2)_2O$	Cl	H	NOH	83	80	66	66JOC941
3	Me	$O(CH_2)_2O$	Br	H	NOH	58	59	34	67JCS(C)2391
4	Et	$O(CH_2)_2O$	Br	H	NOH	51[b]	71	36	71JCS(C)861
5	Pr^i	NOH	Br	H	O	—[a]	—[a]	21	71JCS(C)861
6	Bu^t	NOH	Br	H	NOH	81	48	39	71JCS(C)861
7	H	NOH	Br	Me	O	—	—	54[c]	66JOC941
8	H	NOH	Br	Ph	O	45	85	38	66JOC941
9	Me	NOH	Br	Me	O	—	—	50[c]	66JOC941
10	Ph	NOH	Br	Ph	O	45	54	24	71JCS(C)861

[a] Not reported.
[b] The intermediate was not (**268**) but instead the 2-oxide of 1-ethyl-3-hydroxy-3,4-dihydro-2-azaquinolizinium bromide.
[c] Cyclization occurred during the quaternization step.

As a class, the 2-azaquinolizinium *N*-oxides are of less theoretical interest than their deoxygenation products. Fortunately, Glover *et al.* found a satisfactory deoxygenation procedure (Section 2.10.5.3.2) ⟨67JCS(C)2391⟩.

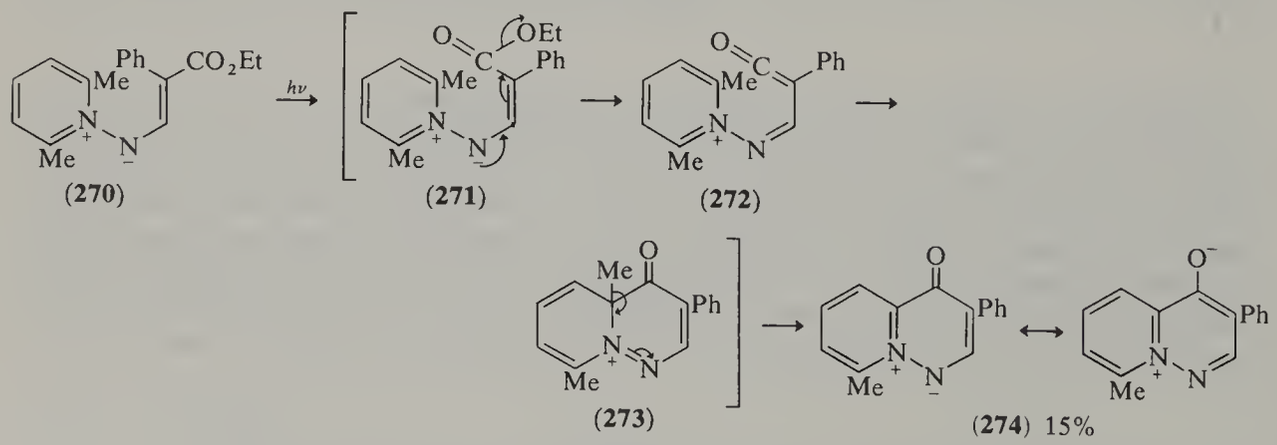
2.10.5.4 3-Azaquinolizinium Derivatives

Although there are a number of compounds which are formally related in ring structure to the. 3-azaquinolizinium system ⟨61HC(15-2)1203⟩, none is a fully aromatic 3-azaquinolizinium ion or a betaine thereof.

2.10.5.5 4-Azaquinolizinium derivatives

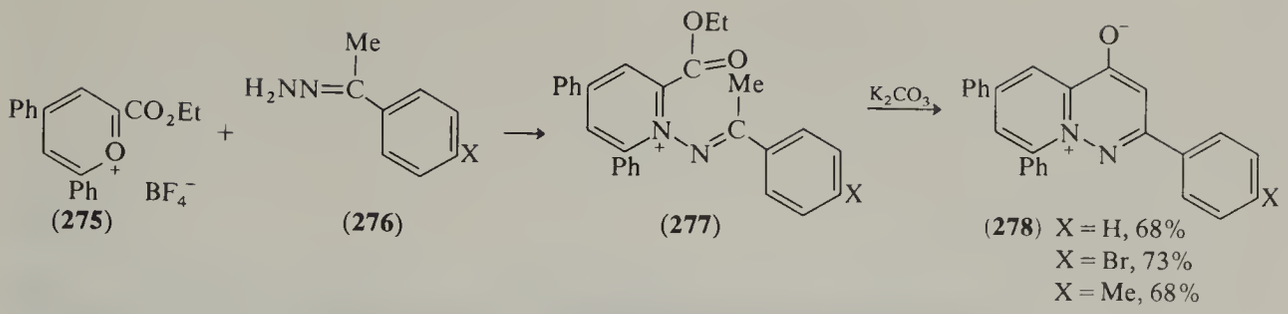
Although no simple 4-azaquinolizinium salts are known, the aromatic system is known through derivatives of 4-azaquinolizin-1-one, recently synthesized by two research groups.

Kakehi *et al.* ⟨76JOC1570⟩, in a study of an *N*-pyridinium *N*-ylide (**270**), found that on irradiation it afforded a 15% yield of 6-methyl-2-phenyl-4-azaquinolizin-1-one (**274**), which is a resonance hybrid of which one of the dipolar structures is that of the betaine of 1-hydroxy-6-methyl-2-phenyl-4-azaquinolizinium hydroxide (Scheme 133). The authors suggested a possible mechanism for (271 → 274).



Scheme 133

The more recent 4-azaquinolizin-1-one synthesis by Katritzky *et al.* ⟨81JCS(P1)1495⟩ appears more versatile. A 2-ethoxycarbonylpyrylium salt (**275**; Scheme 134) is allowed to react with the hydrazone of acetophenone or of a *p*-substituted acetophenone (**276**). The methyl group of the resulting 1-aminopyridine derivative (**277**) is acidic and, when treated with potassium carbonate, generates an anion which attacks the ethoxycarbonyl group to afford the 4-azaquinolizin-1-one derivative (**278**) in good yield.


Ph
CO2Et
O
Ph
BF4−
(275)
+
Me
H2NN=C
X
(276)
OEt
C=O
Me
Ph
N
N
C
X
(277)
K2CO3
O−
Ph
N
N
X
(278) X = H, 68%
X = Br, 73%
X = Me, 68%

Scheme 134

2.11

Naphthyridines, Pyridoquinolines, Anthyridines and Similar Compounds

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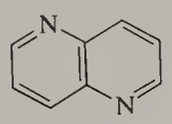
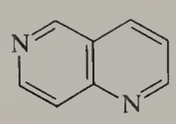
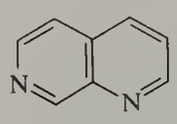
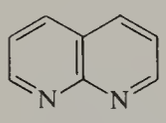
2.11.1 INTRODUCTION

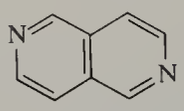
The naphthyridines consist of those diazanaphthalenes which have one nitrogen atom in each ring neither of which occupies a bridgehead position. Alternatively they can be named as pyridopyridines. The six possible isomers (**1**)–(**6**) are shown below.

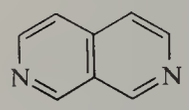

(**1**) 1,5-Naphthyridine


(**2**) 1,6-Naphthyridine


(**3**) 1,7-Naphthyridine


(**4**) 1,8-Naphthyridine


(**5**) 2,6-Naphthyridine


(**6**) 2,7-Naphthyridine

The first naphthyridine derivative was prepared in 1893 by Reissert ⟨1893CB2137⟩, who suggested the name, but the first unsubstituted naphthyridines, 1,5-naphthyridine ⟨27CB1081⟩ and 1,8-naphthyridine ⟨27CB1918⟩, were not obtained until 1927. The preparations of the 1,6- ⟨58CPB263⟩, the 1,7- ⟨58CPB401⟩ and the 2,7- ⟨58CPB269⟩ naphthyridines were reported in 1958, both the 1,6- and 1,7-naphthyridines were described independently in 1960 ⟨60JCS1790⟩, whilst the remaining isomer, 2,6-naphthyridine, was first reported in 1965 ⟨65TL1117, 65TL2737⟩. Increasing interest in the chemistry of naphthyridines is reflected in the number of previous reviews ⟨50CRV(47)275, B-61MI21100, 70AHC(11)123, 74MI21103, 83AHC(33)147⟩. Coverage of a lesser extent is given in ⟨B-78MI21100⟩ and ⟨B-79MI21100⟩ but reviews of different aspects of naphthyridine chemistry are also available; for example ⟨79KGS3⟩ covers the chemistry of compounds (**1**)–(**4**), ⟨80MI21102⟩ and ⟨82H(19)363⟩ are concerned with compound (**3**), ⟨70MI21102⟩ and ⟨80MI21103⟩ review the chemistry of compounds (**1**) and (**4**) respectively, and ⟨81MI21100⟩ is concerned with compounds (**5**) and (**6**). In addition there are reviews covering quaternization ⟨64AHC(3)46⟩, nucleophilic substitution ⟨65AHC(4)377, 83AHC(33)95⟩ and of annelated naphthyridines ⟨51HC(2), 72MI21104, 79MI21101, 80MI21104⟩.

2.11.2 STRUCTURE AND PHYSICAL PROPERTIES

2.11.2.1 Crystal Structure

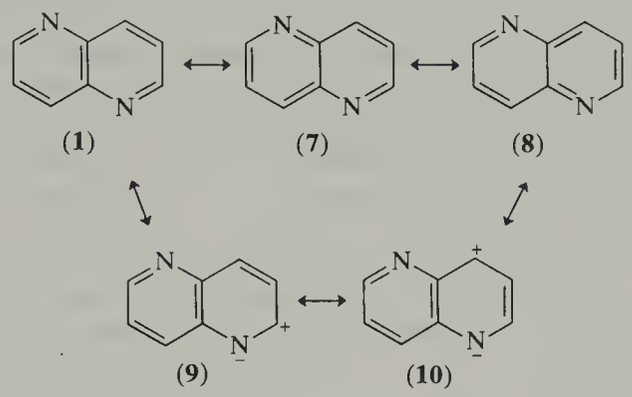
All of the parent naphthyridines are crystalline compounds (see Table 1) and consequently several X-ray crystallographic analyses have been reported ⟨57MI21001, 59G2328, 66MI21100, 72AX(B)350, 77AX(B)1867, 78AX(B)3134⟩ (for further details including a table see ⟨70AHC(11)123⟩). All of the isomers are planar with the exception of 1,8-naphthyridine, which is non-planar due to repulsion of the nitrogen lone pairs of electrons ⟨72AX(B)350⟩. However, the molecule becomes planar on chelation to a metal atom.

Comparison of the bond lengths with those of benzene, naphthalene and pyridine suggests that whilst there is certainly aromatic character some bond fixation occurs in the naphthyridines. It is probable that canonical structure (**1**) (of, for example, 1,5-naphthyridine) and to a lesser extent structures (**7**) and (**8**) are the major contributors to the ground state, but the charged structures (**9**) and (**10**) must also be included in order to account for the chemical properties of the naphthyridines.

Table 1 Some Properties of the Naphthyridines

Compound	*M.p.* (°C)	*Ref.*	*M.p. of picrate* (°C)	*Ref.*
1,5-Naphthyridine	75[a]	63JOC1753	200	27CB1081
1,6-Naphthyridine	35–36	70AHC(11)123	219–220	58CPB263
1,7-Naphthyridine	64	63JOC1753	195.5–196.5	66TL1233
			205–206	58CPB401
1,8-Naphthyridine	98–99	66TL1233	207–208	27CB1918
2,6-Naphthyridine	118–119	65TL1117	206	65TL2737
2,7-Naphthyridine	92–94	58CPB269	240	58CPB269

[a] B.p. 150–152 °C/54 mmHg.



2.11.2.2 Quantum Chemical Calculations

Several groups of workers have carried out quantum mechanical calculations on the naphthyridines during the past 30 years and have correlated the results with various chemical and physical properties. The total π-energies and the delocalization energies of the naphthyridines have been calculated and compared with those of naphthalene (Table 2) ⟨67TH21100, 68JOC1384⟩, which suggests that the naphthyridines have similar resonance energies. The distribution of π-electron densities in ground-state naphthyridines has been calculated using several sets of parameters ⟨68JOC1384, 49JCS971⟩. Calculation of the energy of the π-electron levels and of the electron densities using a first-order perturbation method gave results in good agreement with observed reactivity ⟨57MI21100⟩. Correlations between total π-electron densities and electrophilic ⟨68JOC1384⟩ and nucleophilic ⟨68JOC1384, 58JCS204, 79BCJ1498⟩ substitutions, and with hyperfine splitting constants ⟨66JCP(44)2139⟩ have shown some success.

Table 2 Total π-Energies and Delocalization Energies of the Naphthyridines[a]

Compound	E_π *total*	*Delocalization energy* (β)
Naphthalene	$10\alpha + 13.68\beta$	3.68
1,5-Naphthyridine	$10\alpha + 16.37\beta$	3.81
1,6-Naphthyridine	$10\alpha + 16.37\beta$	3.81
1,7-Naphthyridine	$10\alpha + 16.34\beta$	3.78
1,8-Naphthyridine	$10\alpha + 16.41\beta$	3.85
2,6-Naphthyridine	$10\alpha + 16.32\beta$	3.76
2,7-Naphthyridine	$10\alpha + 16.35\beta$	3.79

[a] $\alpha_N = \alpha_C + 1.1\beta$, $\beta_{CN} = 1.0\beta_{CC}$ (as described in ⟨68JOC1384⟩).

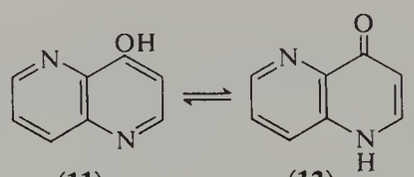
A simple additivity model has been developed and used to predict total ($\sigma + \pi$) electron density distributions in naphthyridines ⟨75MI21100⟩, and these values have been applied successfully to estimate ^{1}H NMR chemical shifts, which are in reasonable agreement with experimental values. π-Electron densities have also been obtained using MINDO/3 calculations ⟨B-82MI21100⟩, using CNDO/2 wave functions and perturbation theory ⟨75MI21104⟩, and using NDDO calculations ⟨79ZC111⟩. Pariser–Parr–Pople (PPP) calculations have been used to calculate transition energies and intensities of the $\pi \rightarrow \pi^*$ bands in the electronic spectra of naphthyridines, a good agreement with experimental values being obtained

⟨79MI21104, 75JSP(54)167⟩. Correlation between molecular orbital energies calculated using the MIEH method and photoelectron spectra of naphthyridines showed more recognizable 'lone pair' orbitals than did the extended Hückel method ⟨74MI21100⟩.

2.11.2.3 Spectral Data

2.11.2.3.1 Infrared spectra

A study of the IR spectra of naphthyridines ⟨66SA117⟩ concluded that a correlation between spectral band position and the position of adjacent hydrogen atoms cannot be made. Earlier workers ⟨58CPB404, 63JOC1753⟩ had attempted to correlate out-of-plane vibrations with the position of substitution, but the results of Armarego and co-workers ⟨66SA117⟩ show that there is a wide variation from one naphthyridine isomer to another, which is, however, less marked within a series of compounds of the same isomer. In the latter case a transferable valence force field has been developed for application to the out-of-plane vibrations of the parent substances ⟨77JSP(66)192⟩. An assignment of all the functional absorption bands of a series of 1,5-naphthyridines led to the conclusion that the spectrum of (**1**) was similar to that of a 5-substituted quinoline ⟨63BAP423⟩ and a combination of IR and Raman spectra of 1,6- and 1,8-naphthyridines has allowed the assignment of all the 42 fundamental vibrations of these two systems ⟨73JSP(46)401⟩. Comparison of the IR spectrum of 4-'hydroxy'-1,5-naphthyridine in solution with that in the solid state gives information on the position of the keto–enol tautomerism, the keto form (**12**) predominating in polar solvents and the enol form (**11**) in non-polar solvents ⟨67MI21101⟩. Similar investigations of the IR spectra of 8-'hydroxy'-1,7-naphthyridine ⟨57JCS4874⟩ and of 2-'hydroxy'-1,7-naphthyridine ⟨61JOC803⟩ led to the suggestions that these compounds exist mainly in the keto form in polar solvents.



(**11**) (**12**)

2.11.2.3.2 Electronic spectra

The UV spectral data for each of the six isomeric naphthyridines (**1**)–(**6**), measured in methanol as solvent, are shown in Table 3. They indicate that there are strong similarities in the spectra of (**1**) and (**4**) and those of (**2**) and (**3**), but the spectra of (**5**) and of (**6**) do not resemble those of any other isomer ⟨60JCS1790⟩. The main features of the spectra of (**1**), (**2**), (**3**) and (**4**) are three distinct bands similar to those in the spectra of quinoline and isoquinoline.

Table 3 UV Spectra of the Naphthyridines in Methanol

Compound	λ_{max}[nm]($log\ \varepsilon$)	*Ref.*
1,5-Naphthyridine	250 (3.65), 259 (3.63), 268 (3.51), 297 (3.75), 304 (3.79), 309 (3.78)	63JOC1753
1,6-Naphthyridine	220 (4.43), 248 (3.62), 303 (3.54), 314 (3.49)	58CPB263
1,7-Naphthyridine	219 (4.42), 262 (3.58), 302 (3.33), 313 (3.28)	63JOC1753
1,8-Naphthyridine	257 (3.60), 295 (3.65), 302 (3.79), 307 (3.80)	70AHC(11)123
2,6-Naphthyridine	247 (3.34), 255 (3.42), 264 (3.33), 318 (3.34), 330 (3.30)	65TL1117
2,7-Naphthyridine	274 (3.61), 292 (3.49), 298 (3.43), 305 (3.42)	58CPB269

Analysis of the ultraviolet spectra of 8-'hydroxy'-1,7-naphthyridine ⟨57JCS5010⟩ and of 4-'hydroxy'-1,5-naphthyridine ⟨67MI21101⟩ in alcoholic solvents indicates that the keto forms predominate.

The high-resolution He 584 Å PE spectra of the naphthyridines (**1**)–(**6**) have been measured ⟨72MI21100⟩, and show that the first ionization involves an n-orbital in the case of the 1,5- and the 1,8-naphthyridines but that a π-orbital is involved in the other four

instances (for further details see ⟨83AHC(33)147⟩). A later study of the PE spectra of the naphthyridines involving empirically corrected MIEHM energies gives similar results to those reported earlier ⟨74MI21100⟩. The results from an analysis of the electronic spectrum of 1,5-naphthyridine measured in both vapor and crystal states, together with a theoretical study, indicate that the first transition is forbidden ⟨81JSP(87)316, 331, 345⟩. The EPR spectrum of 1,6-naphthyridine in its lowest triplet state has been obtained for a solid solution in single crystals of durene. The nuclear hyperfine structure allows an estimate of 0.14 to be made for the spin density on the nitrogen atom in the 1-position ⟨75MI21102⟩.

The zerofield splitting parameters of phenanthrene and 26 of its aza analogues, including six diazaphenanthrenes (benzonaphthyridines) in their lowest triplet states, have been evaluated by EPR spectroscopy ⟨80MI21100⟩, and an ESR and luminescence spectral investigation of these same compounds reveals their photochemical instability in EPA at 77 K ⟨81T341⟩. The authors postulate the formation of a complex of the azaaromatic compound and a solvent radical as an intermediate for the energy transfer, which is only stable at low temperature. Examination of the high-resolution electronic spectral and luminescence properties of benzo[*h*]-[1,5]-, -[1,6]- and -[4,6]-naphthyridines shows the $\pi \rightarrow \pi^*$ state to be the lowest excited singlet state of benzo[*h*]-[1,6]- and -[4,6]-naphthyridines. In benzo[*h*][1,5]naphthyridine the S_1 ($n \rightarrow \pi^*$) state is strongly perturbed by the nearby S_2 ($\pi \rightarrow \pi^*$) state ⟨80JST(64)209⟩. An investigation of the rates of intersystem crossing and internal conversion in naphthyridines indicates that the latter competes as a non-radiative decay mechanism for the excited singlet state ⟨82JPC1976⟩.

The phosphorescence spectrum of 1,5-naphthyridine is similar to that of naphthalene ⟨59MI21100⟩. The polarized phosphorescence spectra of 1,5-naphthyridine and its d_6 isomer in durene and in durene-d_{14} mixed crystals have been obtained at 4 K. The lowest singlet state is at 27 123 and 27 200 cm^{-1} while the corresponding triplet state is at 23 215 and 23 288 cm^{-1} for the proto and deutero compounds respectively ⟨73MI21100⟩. The polarized spectra of these isomers in naphthalene have also been obtained at 4 K. The difference between the spectra in naphthalene and in durene is attributed to a decrease of the strong vibronic coupling which is thought to exist between the $n \rightarrow \pi^*$ state and the higher $\pi \rightarrow \pi^*$ states ⟨81JSP(87)345⟩.

2.11.2.3.3 Nuclear magnetic resonance spectra

The ^1H NMR spectra of all of the parent naphthyridines (**1**)–(**6**) can be interpreted by first order splitting rules including *meta*, *para* and cross-ring spin–spin coupling. The various chemical shifts are shown in Table 4. As it is now common practice to report ^1H NMR data of naphthyridine derivatives, which are far too numerous to list individually, further information can be obtained from the references given in the table as well as from references in the sections on reactivity (2.11.3) and synthesis (2.11.4).

Table 4 ^1H NMR Spectral Data of the Parent Naphthyridines in $CDCl_3$

	$\delta(^1H)$ (p.p.m.) ⟨83AHC(33)95⟩							
Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-7*	*H-8*
1,5-Naphthyridine	—	8.96	7.55	8.37	—	8.96	7.55	8.37
1,6-Naphthyridine	—	9.03	7.43	8.20	9.22	—	8.75	7.87
1,7-Naphthyridine	—	9.01	7.48	8.14	7.64	8.60	—	9.50
1,8-Naphthyridine	—	9.15	7.51	8.21	8.21	7.51	9.15	—
2,6-Naphthyridine	9.27	—	8.65	7.69	9.27	—	8.65	7.69
2,7-Naphthyridine	9.37	—	8.68	7.59	7.59	8.68	—	9.37

	Coupling constants (Hz) ⟨70AHC(11)123⟩									
Compound	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,8}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
1,5-Naphthyridine	4.1	1.8	8.0	0.6	—	—	—	4.1	1.8	8.0
1,6-Naphthyridine	4.1	1.9	8.2	0.9	—	—	0.9	—	—	6.0
1,7-Naphthyridine	4.2	1.6	8.4	0.9	5.6	—	0.9	—	—	—
1,8-Naphthyridine	4.2	2.0	8.0	—	8.0	2.0	—	4.2	—	—
2,6-Naphthyridine	—	—	6.0	—	—	—	—	—	—	6.0
2,7-Naphthyridine	—	—	6.0	—	6.0	—	—	—	—	—

Measurement of the ^1H spectra of some of the naphthyridines ⟨72MI21102, 72MI21103, 76JCS(P2)19⟩ partially oriented in liquid crystalline solvents shows that with the exception of 1,8-naphthyridine, which has been shown (see Section 2.11.2.1) to have the two pyridine rings non-coplanar, the others have hydrogen to hydrogen ratios identical to the corresponding hydrogens in pyridine, which suggests that bond distances are not affected significantly by fusion of the two pyridine rings. Europium induced shifts of the proton resonances of 1,6- (**2**), 1,7- (**3**) and 1,8-naphthyridines (**4**) indicate that in cases (**2**) and (**3**) complex formation appears to occur almost specifically on the 'isoquinoline-type' nitrogen atoms (N-6 and N-7 respectively) giving induced shifts even greater than those produced in isoquinolines. In 1,8-naphthyridine (**4**) the europium atom is probably situated midway between the two nitrogen atoms ⟨71OMR(3)575⟩. Europium-induced shifts have also been estimated from a knowledge of the coordinating abilities of the nitrogen atoms and their influence on the chemical shifts of the hydrogens in quinoline and in isoquinoline. These estimated shifts agreed nearly quantitatively with the observed values ⟨76BCJ1322⟩.

The ^{13}C spectral data of the naphthyridines (**1**)–(**6**), together with the ^{13}C chemical shifts for quinoline and isoquinoline are shown in Table 5. These ^{13}C chemical shifts are linearly dependent on the total charge density on the carbons as calculated by SCF-MO approximations ⟨73JCS(P2)1024, 74BCJ2083⟩. The use of ^{13}C NMR spectroscopy in ascertaining both the site of protonation and pK_a values is referred to in Section 2.11.2.4 ⟨76OMR(8)187, 77OMR(9)281⟩ and the site of methylation in Section 2.11.3.4.1 ⟨77OMR(10)165⟩. Both ^1H and ^{13}C NMR spectroscopy techniques have proved valuable in establishing the sites of addition of amide ion to compounds (**1**)–(**6**) ⟨81JOC2134⟩ (see also tables in ⟨83AHC(33)95⟩).

Table 5 ^{13}C NMR Spectral Data of Parent Naphthyridines in $CDCl_3$ ⟨83AHC(33)95, 147⟩

	$\delta(^{13}C)$ (p.p.m.)									
Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	*C-10*
1,5-Naphthyridine	—	151.0	124.1	137.2	—	151.0	124.1	137.2	144.0	144.0
1,6-Naphthyridine	—	154.9	122.7	135.8	153.0	—	146.9	122.2	150.5	123.8
1,7-Naphthyridine	—	152.1	125.2	134.7	119.9	144.0	—	154.5	143.7	131.3
1,8-Naphthyridine	—	153.8	122.3	137.3	137.3	122.3	153.8	—	156.6	123.1
2,6-Naphthyridine	152.0	—	144.9	119.3	152.0	—	144.9	119.3	130.3	130.3
2,7-Naphthyridine	152.9	—	147.1	119.1	119.1	147.1	—	152.9	123.9	138.5
Quinoline	—	150.9	121.5	136.0	128.3	126.8	129.7	130.1	149.0	128.7
Isoquinoline	153.1	—	143.8	120.8	126.8	130.5	127.5	127.9	129.0	136.0

2.11.2.3.4 Electron spin resonance spectroscopy

ESR spectroscopy measurements in various solvents have provided information on the spin density distributions in the radical anions of naphthyridines (**1**)–(**6**) ⟨71MI21100, 71MI21101, 71MI21102, 74MI21102, 77IJC(A)371, 78MI21102⟩.

2.11.2.3.5 Mass spectra

All four parent 1,*x*-naphthyridines (**1**)–(**4**) give essentially identical mass spectra ⟨67JHC547⟩ in which the three most abundant fragment ions are found at *m/e* 104, *m/e* 103 and *m/e* 76, formed by expulsion of C_2H_2 and HCN from the parent ion-radical, and from *m/e* 103 by loss of a second molecule of HCN, respectively. The mass spectra of some derivatives of the 1,*x*-naphthyridines have also been reported: methyl ⟨67JHC547⟩, amino ⟨76JHC961, 78MI21107⟩, hydroxy ⟨76OMS231⟩, bromo ⟨78MI21107⟩ and nitro ⟨82H(19)363⟩.

2.11.2.4 Ionization Properties

The parent naphthyridines have basic strengths lower than those of quinoline (4.94) and of isoquinoline (5.40) (*cf.* Table 6), which has been attributed to the relayed inductive effect of one doubly bound nitrogen atom to the other. The greater basic strengths of the 1,6- and 1,7-isomers as compared to the 1,5- and 1,8-compounds appear to indicate that

protonation occurs on N-6 and on N-7, respectively, rather than on N-1 (compare the pK_a value of quinoline with that of isoquinoline) ⟨60JCS1790⟩. This is in agreement with spectroscopic data ⟨68JHC561, 76OMR(8)187, 77OMR(9)71, 77OMR(9)281, 77OMR(10)165⟩. A discussion of the structural information that can be inferred from a knowledge of pK_a values of substituted naphthyridines can be found in ⟨70AHC(11)123⟩.

Table 6 Ionization Constants of 1,*x*-Naphthyridines ⟨60JHC1790⟩

Compound	pK_a
1,5-Naphthyridine	2.91
1,6-Naphthyridine	3.78
1,7-Naphthyridine	3.63
1,8-Naphthyridine	3.39

2.11.2.5 Electrochemical Studies

Electrochemical reduction of the naphthyridines (**1**)–(**6**) has been described in both acidic ⟨76MI21100, 78MI21101⟩ and neutral media ⟨82RTC141⟩. In the former case the first reduction step produces a radical cation of variable stability (depending on the parent heterocycle) which undergoes a hydrogen transfer from nitrogen to carbon producing an unstable radical which then reacts with the original radical cation to give a dimer. The process is an acid- or base-catalyzed first order reaction ⟨78MI21101⟩. Reduction in DMF by means of 'transmission spectroelectrochemical methods' produces dianions which react with the parent neutral molecules ⟨82RTC141⟩.

2.11.3 REACTIVITY

2.11.3.1 Substitution Reactions

2.11.3.1.1 General considerations

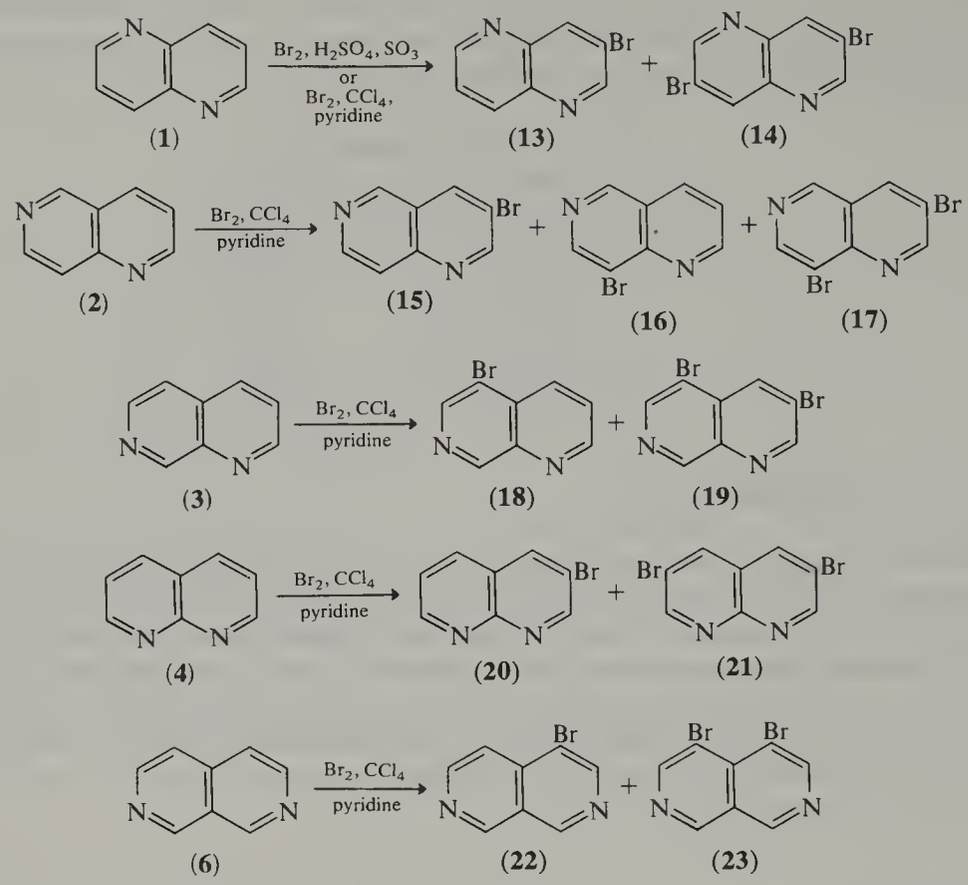
The naphthyridines have 10 delocalized π-electrons located in five molecular orbitals, each of which is distorted by the presence of the nitrogen atoms causing an electron drift in that direction. This distortion causes the positions *ortho* and *para* to the nitrogen atoms to have lower π-electron densities than the *meta* positions, which remain, in general, similar to the equivalent positions in naphthalene. As can be expected, electrophiles react primarily at the nitrogen atom(s) to give a cationic species which is then deactivated towards further electrophilic attack at a ring carbon, which will, however, occur at a position *meta* to a ring nitrogen atom. Similarly, nucleophilic attack will occur preferentially at *ortho* and *para* positions. These conclusions are in general agreement with molecular orbital calculations (see Section 2.11.2.2).

2.11.3.1.2 Electrophilic substitution

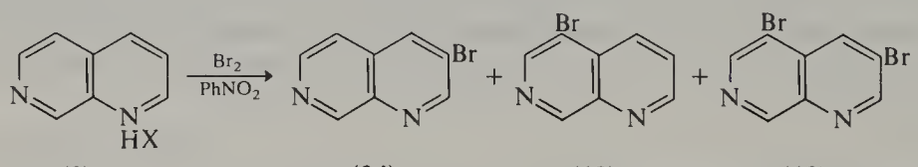
(*i*) *Bromination*

The reaction of 1,5-naphthyridine (**1**) with bromine in chloroform does not yield any brominated products ⟨54JCS1879⟩. However, treatment of (**1**) with bromine in oleum was found to give a mixture of the 3-bromo- (**13**) and the 3,7-dibromo-1,5-naphthyridines (**14**) in 10% and 35% yield respectively ⟨65JOC1607, 67LA(707)242⟩. With bromine in pyridine the yields were 27% of (**13**) and 10% of (**14**) ⟨68JOC1384⟩, and application of this procedure to 1,6-naphthyridine (**2**) gave a mixture of 3-bromo- (**15**), 8-bromo- (**16**) and 3,8-dibromo-1,6-naphthyridine (**17**). Similarly, 1,7-naphthyridine (**3**) gave 5-bromo- (**18**) and 3,5-dibromo-1,7-naphthyridine (**19**), and 1,8-naphthyridine (**4**) gave 3-bromo- (**20**) and 3,6-dibromo-1,8-naphthyridine (**21**). Compounds (**20**) and (**21**) were obtained in only 5% and 0.5% yield, respectively, which can perhaps be accounted for by the strong complexing properties of (**4**) (see Section 2.11.3.7). Treatment of 2,7-naphthyridine (**6**) under these

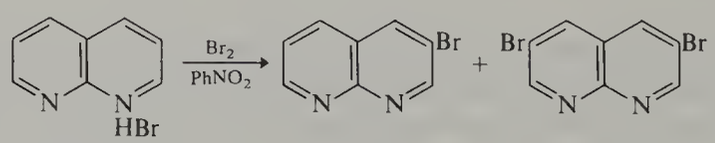
conditions gives a mixture of the 4-bromo- (**22**) and the 4,5-dibromo-naphthyridines (**23**) ⟨70JHC419⟩.



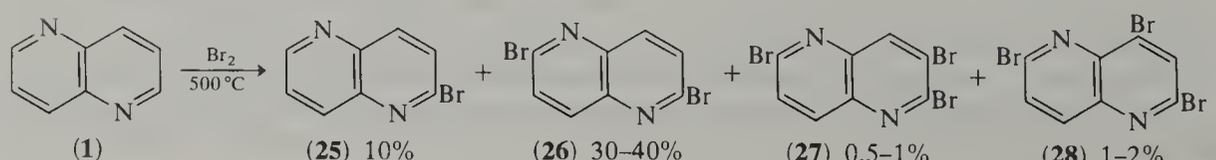
An alternative bromination procedure involving treatment of the naphthyridine hydrohalide with bromine in nitrobenzene has been applied to the 1,7- and 1,8-isomers ⟨76JHC961⟩. In the case of compound (**3**) treatment of the hydrobromide in nitrobenzene with 1.1 equivalents of bromine gave the 3-bromo-1,7-naphthyridine (**24**) in addition to (**18**) and (**19**), in the yields shown, whilst using an excess of bromine (2.5 equiv.) (**3**) gave almost exclusively the dibromo compound (**19**) in 75% yield. A significant difference in the product ratio is observed when the hydrochloride salt is brominated with 1.1 equivalents of bromine, and the products are also contaminated with some chloronaphthyridines. Bromination of 1,8-naphthyridine (**4**) by this latter method affords a 1 : 1 ratio of compounds (**20**) and (**21**) when 1.1 equivalents of bromine are used, and increasing this value to 2.5 equivalents gives the dibromo compound (**21**) in 73% yield. Thus this second procedure is vastly superior for the dibromination of 1,8-naphthyridine ⟨75USP308389, 72JCS(P1)705⟩. A possible difference



(**3**)	(**24**)	(**18**)	(**19**)
X = Br	13.5%	8.1%	45.6%
X = Cl	1.5%	30.9%	6.4%

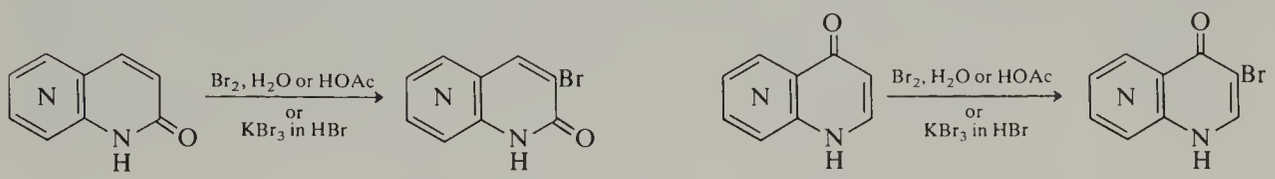


(**4**)	(**20**)	(**21**)
1.1 eq. Br_2	32%	30%
2.5 eq. Br_2	<1%	73%

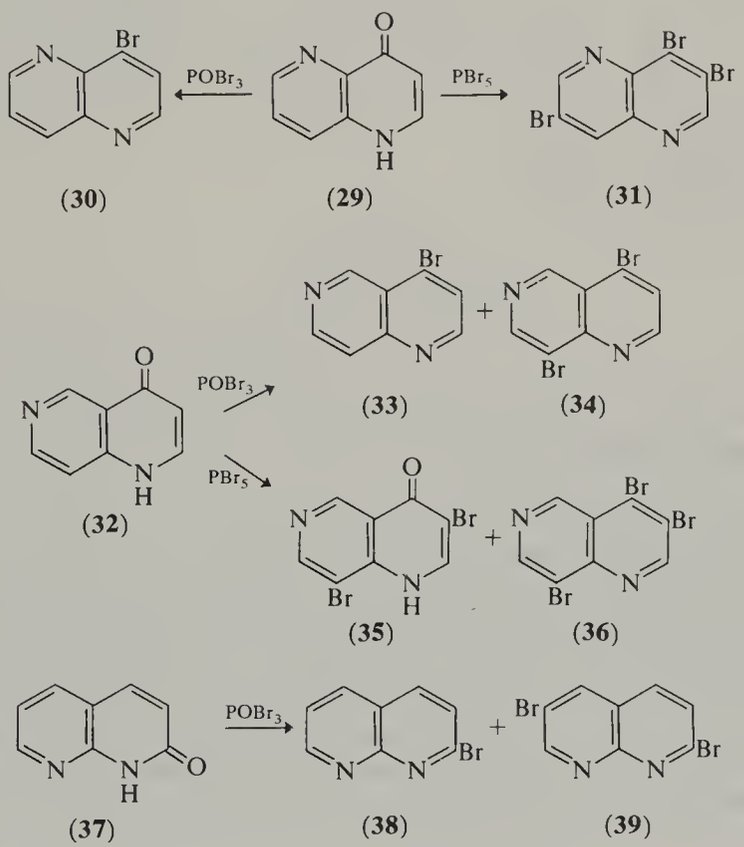


in mechanism of these alternative procedures may be that in the former instance the starting material may be a quaternary *N*-bromo derivative whilst in the latter case it is possibly a quaternary *N*-H derivative. This awaits further study. Bromination of 1,5-naphthyridine (**1**) in the gas phase at 500 °C gives a mixture of products (**25**), (**26**), (**27**) and (**28**) in the yields indicated. That the reaction probably proceeds *via* a radical mechanism accounts for the fact that none of the expected electrophilic bromination products is obtained ⟨73MI21103⟩.

The presence of electron-donating substituents facilitates electrophilic substitution, and hence bromination of either 2- or 4-oxonaphthyridine proceeds under much milder conditions than in the above examples ⟨70AHC(11)123, 73MI21104, 74RTC144, 75MI21105, 78JHC731⟩. The corresponding 3-chloro derivatives are obtained when $KClO_3$ in HCl is used as a chlorinating agent ⟨63JCS4237, 75JOC660⟩.



Treatment of 2- or 4-oxonaphthyridine with $POBr_3$ or PBr_5 leads to mono-, di- and sometimes tri-bromination; for example, 1,5-naphthyridin-4-one (**29**) gives (**30**) or (**31**) depending upon the reaction conditions, 1,6-naphthyridin-4-one (**32**) reacts with $POBr_3$ to give a mixture of (**33**) and (**34**), and with PBr_5 to give (**35**) and (**36**), and 1,8-naphthyridin-2-one (**37**) reacts with $POBr_3$ to give a mixture of (**38**) and (**39**) ⟨73MI21104, 74MI21104, 75JOC660, 76JHC43, 79MI21103⟩. The second bromine in these compounds is always introduced at the site of electrophilic substitution of the non-oxygenated ring.

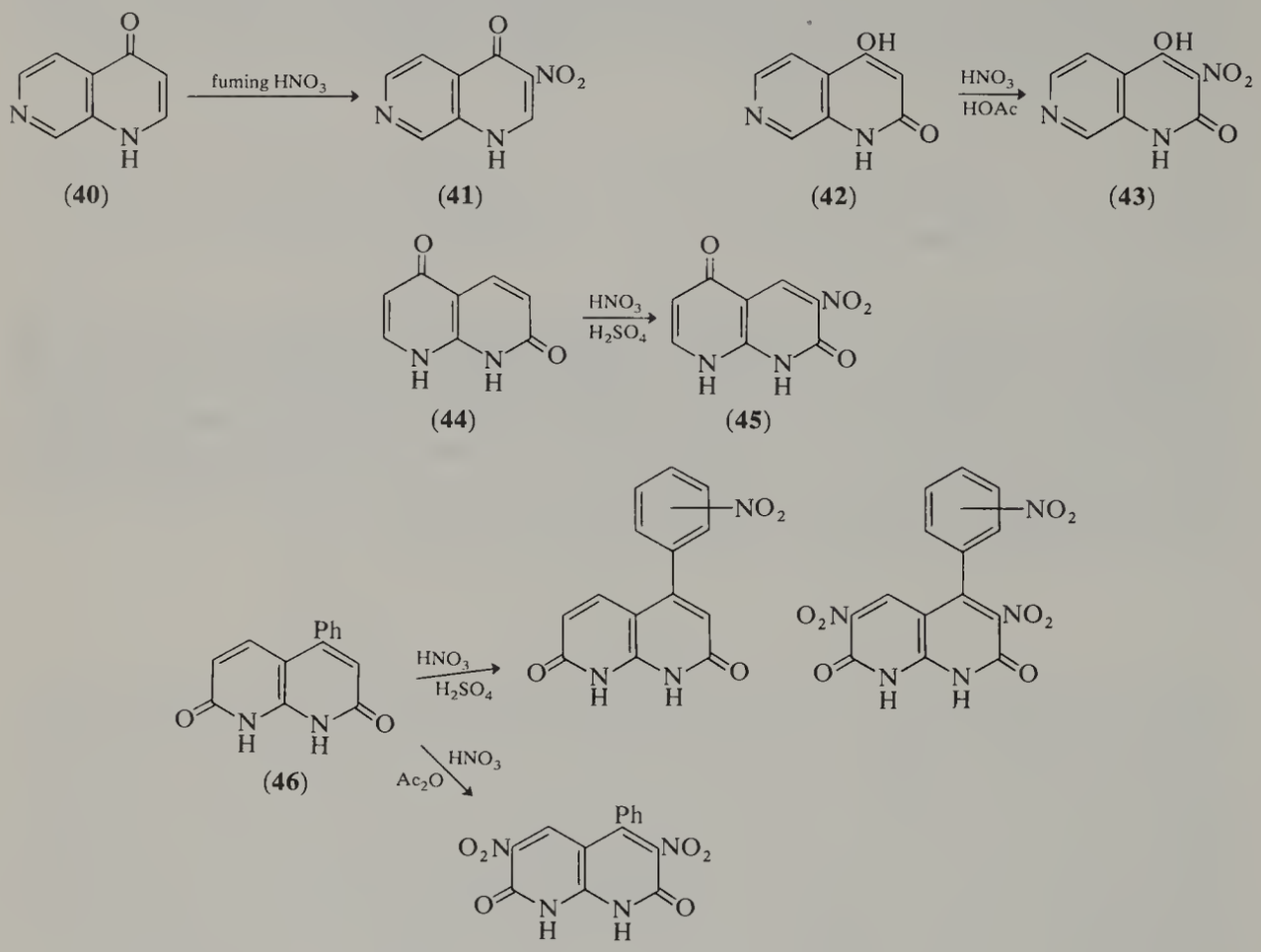


Bromination of 1,5-naphthyridine *N*(1)-oxide gives a mixture of 3,6-dibromo-1,5-naphthyridine and its 1-oxide. The side formation of some 3,7-dibromo-1,5-naphthyridine is probably a result of bromination taking place after the removal of the *N*-oxide group ⟨75JOC3068⟩. 1,8-Naphthyridine *N*-oxide gives a mixture of the corresponding 3,6-dibromo products.

(*ii*) *Nitration*

Nitration of naphthyridines occurs only when electron-donating groups are present in the 2- or (and) 4-position. Thus 1,7-naphthyridine-4(1*H*)-one (**40**) can be mononitrated to give the 3-nitro compound (**41**) in 74% yield ⟨60JCS1794⟩ whilst the presence of two

electron-donating groups allows the nitration to proceed very easily; for example, 4-hydroxy-1,7-naphthyridin-2-one (**42**) affords the 3-nitro derivative (**43**) in 78% yield ⟨75JMC726⟩, and the 2,5-dioxo compound (**44**) gives the 3-nitro derivative (**45**) ⟨72G253⟩. Where alternative sites of nitration exist, as in compound (**46**), the nitration product is dependent upon the reaction conditions ⟨72G253, 40MI21100⟩. In the presence of sulfuric acid substitution initially takes place in the phenyl ring, further nitration occurring in the 3- and 6-positions of the naphthyridine ring, whilst in acetic anhydride nitration takes place exclusively in the naphthyridine rings, giving the 3,6-dinitro compound.

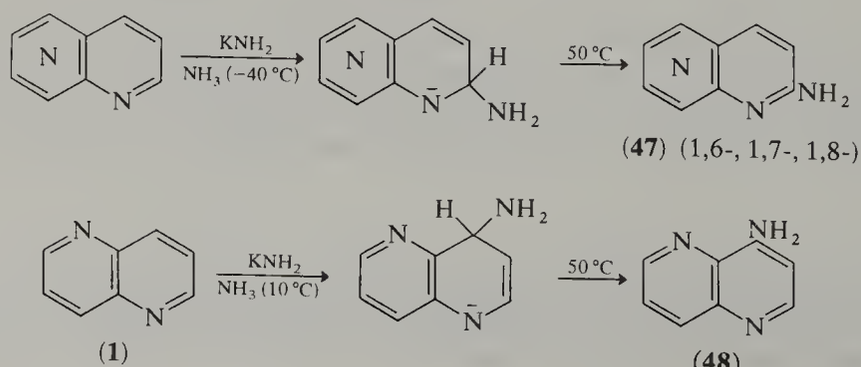


(**40**) (**41**) (**42**) (**43**) (**44**) (**45**) (**46**)

2.11.3.1.3 Nucleophilic substitution

(*i*) *Displacement of hydrogen*

The naphthyridine ring system, being very π-deficient, is highly vulnerable towards nucleophilic attack, and consequently there has been extensive investigation of reactions involving nitrogen nucleophiles to give aminonaphthyridines ⟨83AHC(33)95⟩. The amination at −40 °C of naphthyridines (**2**), (**3**) and (**4**) gives the 2-amino derivatives (**47**), whereas the 1,5-isomer (**1**) gives the 4-amino-1,5-naphthyridine (**48**) ⟨70JHC589, 70AHC(11)123⟩. It appears, in all four cases, that carrying out the reaction at −40 °C produces σ-adducts formed by addition of the amide ion to C-2 as illustrated, but in the case of naphthyridine (**1**), raising the temperature to 10 °C results in the conversion of the C-2 into a C-4 adduct,

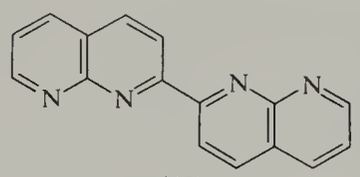


(**47**) (1,6-, 1,7-, 1,8-)

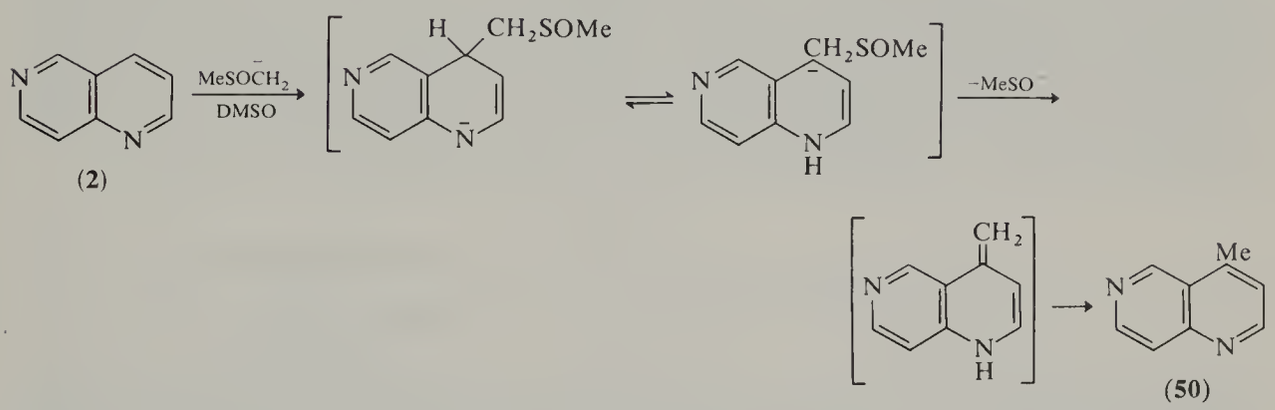
(**1**) (**48**)

which eventually gives (**48**) ⟨81JOC2134⟩. At 50 °C the yields of products may be as high as 80% ⟨74MI21105⟩. The intermediate adducts in these aminations have been identified by NMR spectroscopic analysis. In the case of 1,7-naphthyridine a mixture of a C-2 and a C-8 adduct is formed at −10 °C ⟨81JOC2134⟩, a result which agrees with electron density calculations ⟨79BCJ1498, 79MI21104⟩. However, on amination at room temperature, only the 8-amino compound is obtained. Both the naphthyridines (**5**) and (**6**) give σ-adducts at C-1 at −40 °C, which form the 1-aminonaphthyridines at higher temperatures (10–50 °C) ⟨81JHC1349⟩.

The naphthyridines (**1**)–(**4**) react with phenyllithium to give the corresponding 2-phenyl derivatives ⟨74CPB495, 76CPB1813⟩. 1,8-Naphthyridine reacts with butyllithium to give the 2-butyl derivative, but the reaction of butyllithium with dithiane followed by the addition of (**4**) generates the bis-naphthyridine (**49**) ⟨78ZC382⟩. With methylsulfinyl carbanion in DMSO, 1,*x*-naphthyridines give dimethyl derivatives, *e.g.* naphthyridine (**3**) gives 4,8-dimethyl-1,7-naphthyridine. Similar products are obtained from (**1**) and (**4**), but naphthyridine (**2**) gives only 4-methyl-1,6-naphthyridine (**50**) ⟨71CPB1751⟩. A probable mechanism is shown below.



(**49**)

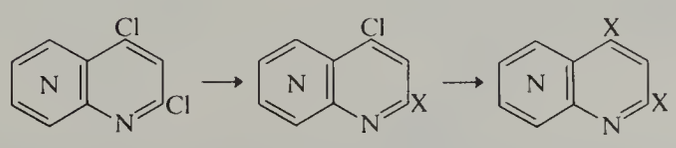


(**2**)

(**50**)

(ii) Nucleophilic displacement of halogens

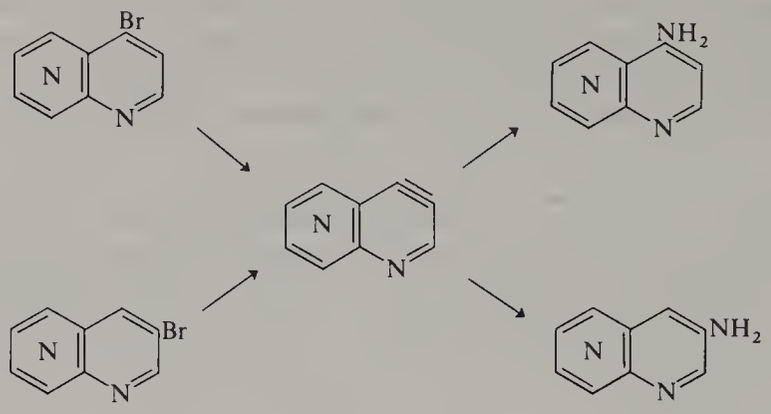
As is well known, halogen atoms in the 2- and 4-positions in the pyridine nucleus are readily replaced by nucleophiles, and a detailed study of the mechanistic aspects of this reaction has been carried out ⟨74MI21101⟩. There are many recorded examples of normal *ipso* substitution of halogens in these positions in naphthyridines (**1**)–(**4**) ⟨*cf.* 83AHC(33)95⟩. The reaction conditions are usually either (1) heating the halogenonaphthyridine with an ethanolic solution of ammonia in a sealed vessel, or (2) passing gaseous ammonia through a solution of the halogenonaphthyridine in phenol at higher temperatures. In the case of 2,4-dihalogeno-1,*x*-naphthyridines, the halogen in position 2 undergoes nucleophilic substitution more readily than that in the 4-position. This selectivity is in agreement with approximate MO calculations ⟨58JCS204⟩. As would be expected the halogen atom in the 4-position of 3,4-dihalogeno-1,6-naphthyridines is selectively replaced by tosylhydrazine, but this is not so in the corresponding 1,7-naphthyridines. This has been interpreted as being due to the different position of the nitrogen atom in the adjacent ring. In the former example the effects of both nitrogen atoms are concerted, which is not so in the latter ⟨74RTC144⟩.



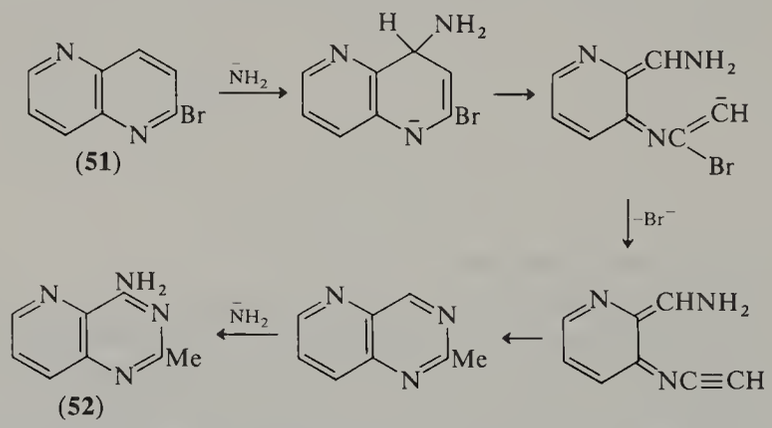
X = OH, NH_2, $NHNH_2$

The reaction of halogenated 1,*x*-naphthyridines with potassium amide in liquid ammonia has been extensively investigated ⟨83AHC(33)95⟩. Both 3- and 4-bromonaphthyridines derived from compounds (**1**)–(**4**) react to give mixtures of 3- and 4-amino derivatives. It is assumed

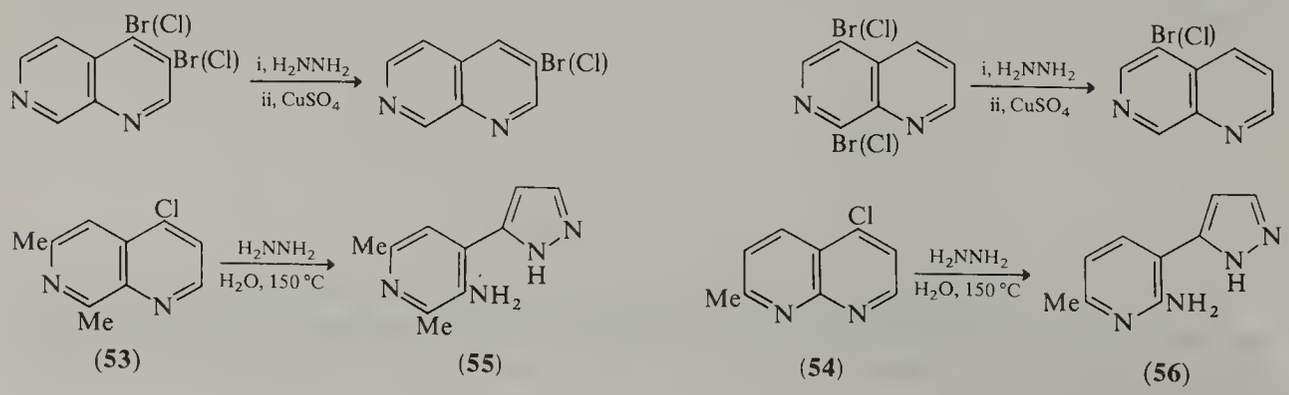
that 3,4-dehydronaphthyridines are intermediates in these reactions, but as the ratios of the products from the two different starting materials are different it is possible that an addition–elimination mechanism may also apply ⟨63RTC997, 74RTC143, 76RTC233, 76MI21101⟩.



The reaction of 2-bromo-1,5-naphthyridine (**51**) with KNH_2/NH_3 gives 2-amino-1,5-naphthyridine (77%), 4-amino-1,5-naphthyridine (1%), 1,5-naphthyridine and 2-methyl-4-amino-1,3,5-triazanaphthalene (**52**; 11%) ⟨63RTC997, 73MI21101⟩. The ring transformation has been explained by the intermediary formation of a C-4 adduct, for which there has as yet been no NMR evidence (the only σ-adduct whose existence has been proved is that at C-6 ⟨82JOC1673⟩). This C-4 adduct is then postulated to undergo a dehydrobromination leading to bond fission between C-3 and C-4 followed by recyclization to give the triazanaphthalene (**52**). Similar transformations have been observed in the reactions of 2,3-dibromo-1,5-naphthyridine ⟨73RTC970⟩, 2,6-dibromo-1,5-naphthyridine ⟨73MI21101⟩, 2,7-dibromo-1,5-naphthyridine ⟨73RTC970⟩, 2,4-dibromo-1,6-naphthyridine ⟨78MI21104⟩ and 2-bromo (or chloro) -1,7-naphthyridine ⟨77RTC151⟩ with KNH_2/NH_3. For a more detailed account of these amide substitutions the review ⟨83AHC(33)95⟩ should be consulted.

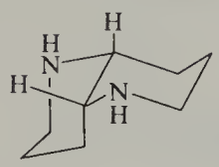


Replacement of a halogen by a hydrogen atom is conveniently accomplished by initial reaction with hydrazine to give the hydrazino compound followed by oxidation, usually with copper(II) sulfate (see Section 2.11.4). Two examples are shown below ⟨76JHC961, 72JOC3101, 76RTC233, 78JHC731⟩. In the first, some 1,7-naphthyridine was also isolated, showing that nucleophilic replacement by hydrazine can also occur to some extent at C-3. An alternative reaction with hydrazine occurs with 4-chloro-1,7- (**53**) and 4-chloro-1,8-naphthyridines (**54**), when the halogenated ring is cleaved to give the pyrazolylpyridine derivatives (**55**) and (**56**) ⟨70CC565, 72JCS(P1)1106, 75JCS(P1)1109⟩.

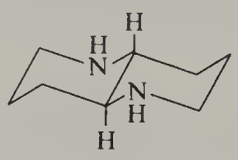


2.11.3.2 Reduction of Naphthyridines

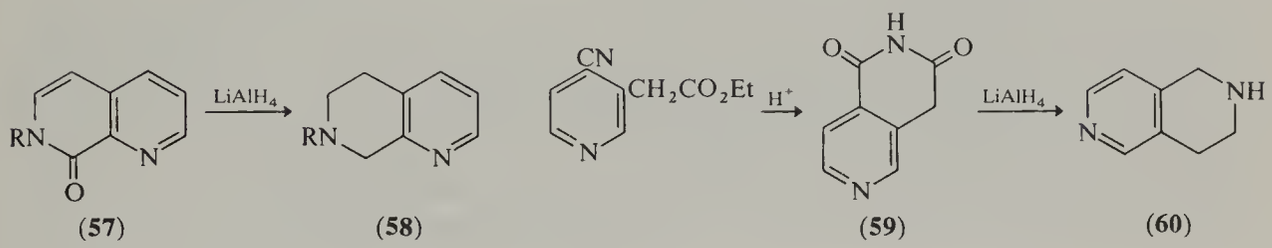
Hydrogenation of naphthyridines over PtO_2 or Pd leads primarily to tetrahydro products, whilst reduction with sodium and alcohol gives the fully hydrogenated compounds, the latter method affording the *trans* isomers only ⟨67JCS(C)377⟩. If hydrogenation is carried out over PtO_2 in acetic acid, both the *cis* and *trans* isomers are obtained ⟨67JCS(C)377⟩, the structures having been assigned by comparison of their ^1H NMR spectra with those of the *cis* and the *trans* decahydroquinolines and decahydroisoquinolines. An alternative method of hydrogenation utilizes halogenated naphthyridines which on treatment with $H_2/PtO_2/CaCO_3$ in a weakly basic alcoholic solution give excellent yields of the reduced products. For further details of individual compounds the review ⟨70AHC(11)123⟩ should be consulted. Lithium aluminum hydride converts the oxo compound (**57**) into the 5,6,7,8-tetrahydro-1,7-naphthyridine (**58**) ⟨60CPB427⟩ and the dioxo compound (**59**) into 1,2,3,4-tetrahydro-2,6-naphthyridine (**60**) ⟨72AC(R)239⟩.



cis-Decahydro-1,5-naphthyridine



trans-Decahydro-1,5-naphthyridine

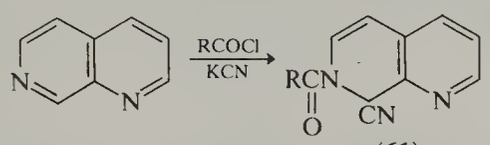


(**57**) (**58**) (**59**) (**60**)

2.11.3.3 Addition Reactions

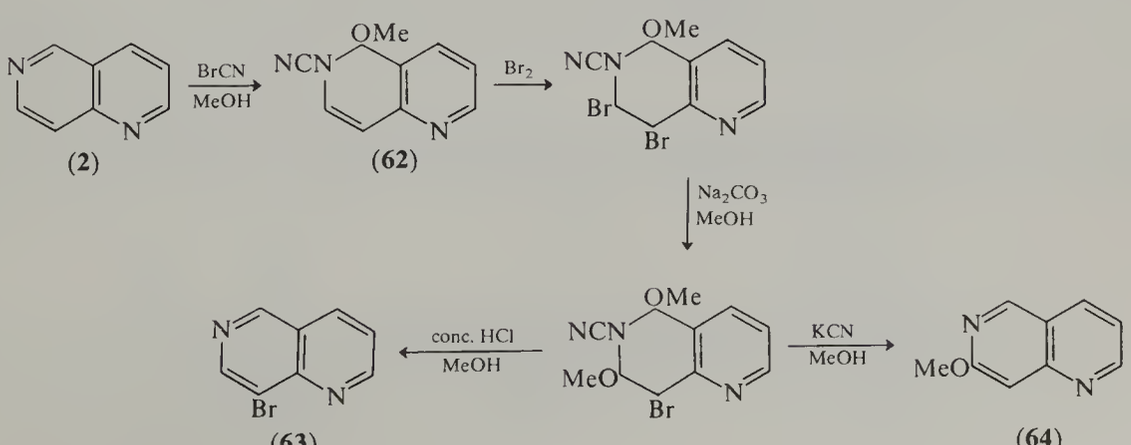
2.11.3.3.1 The Reissert reaction

The reaction of naphthyridines with acyl halides and potassium cyanide has been reported only for naphthyridines (**2**) ⟨69CPB2614, 70CPB1026⟩ and (**3**) ⟨76CPB1813⟩. The yields of Reissert compounds (**61**) are poor except when diphenylcarbamoyl chloride is used ⟨70CPB1026⟩, but can be improved using phase-transfer catalysts ⟨79YZ982⟩. The reaction of 1,6-naphthyridine (**2**) with cyanogen bromide in methanol gives an N-cyano compound (**62**) which has been converted into either 8-bromo-1,6-naphthyridine (**63**) or 7-methoxy-1,6-naphthyridine (**64**) ⟨78YZ1361⟩. Acid hydrolysis of the Reissert compound from (**2**), benzoyl chloride and cyanide gives 1,6-naphthyridine-5-carboxamide (**65**) together with the carboxylic acid (**66**) ⟨79YZ1225⟩.

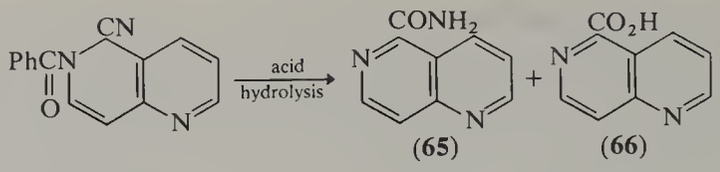


(**3**) (**61**)

R = Me, Et, Pr



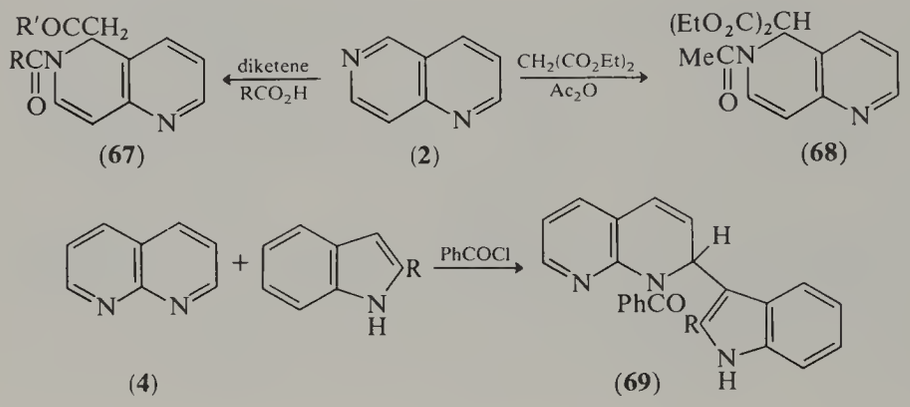
(**2**) (**62**) (**63**) (**64**)



2.11.3.3.2 Other additions

1,6-Naphthyridine (**2**) reacts with diketene and acetic or formic acids to give the addition compound (**67**; R = H, Me, R^1 = Me) ⟨81CPB1049⟩, with acetic anhydride to give (**67**; R = Me, R^1 = OH) ⟨79JHC527⟩ and with diethyl malonate and acetic anhydride to give the product (**68**) ⟨81CPB1056⟩. These resemble similar reactions that occur with isoquinolines, but not with quinolines.

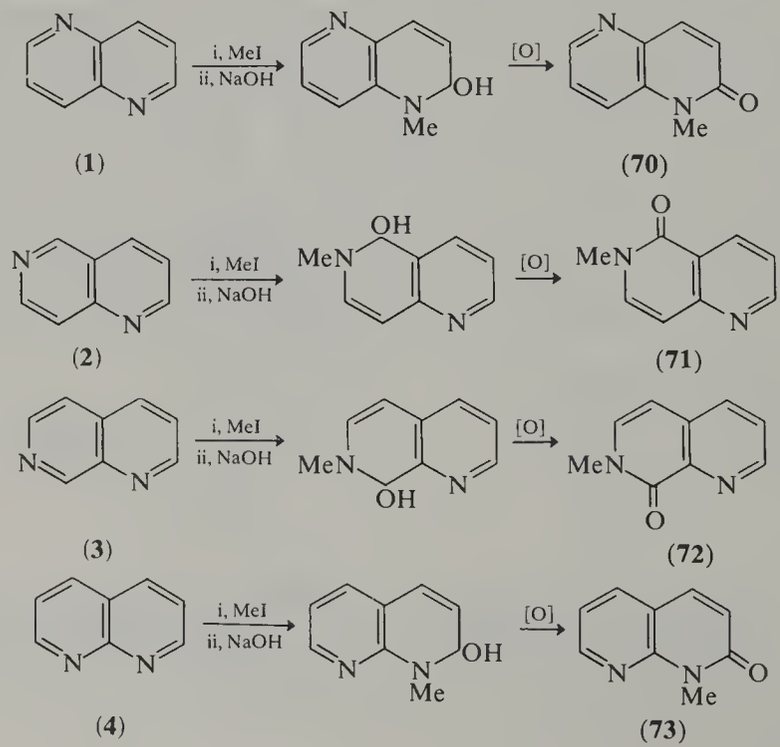
The reaction between 1,8-naphthyridine, indoles and benzoyl chloride gives the addition compound (**69**) ⟨78KGS132⟩.



2.11.3.4 Reactions on Nitrogen

2.11.3.4.1 N-*Alkylation*

Methyl iodide with the naphthyridines (**1**)–(**4**) gives the *N*-monomethiodides; it is the 'isoquinolinic' nitrogens N-6 and N-7 that are methylated in 1,6- and 1,7-naphthyridines respectively, as confirmed by ^{13}C NMR studies ⟨77OMR(10)165⟩. Treatment of these quaternary salts with alkaline $K_3Fe(CN)_6$ gives the expected cyclic amides (**70**)–(**73**) *via* the intermediate pseudo bases ⟨63JOC1753, 68JHC561, 69CC56, 71CPB1751, 74JCS(P1)1833, 72CJC917⟩.

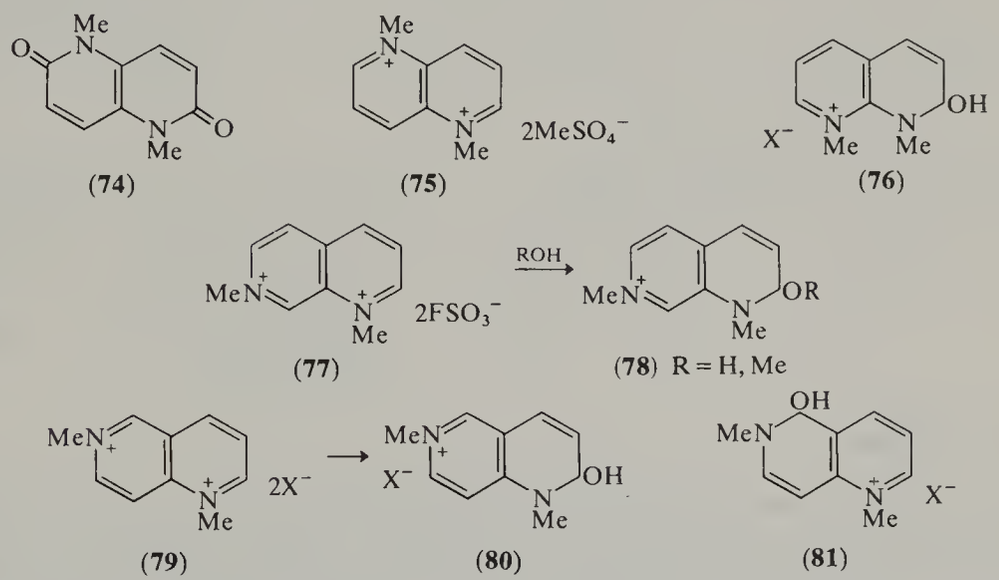


The kinetics of quaternization of naphthyridines ⟨69CC56⟩ and the structures of the intermediate pseudo bases have been extensively investigated ⟨67CC1183, 73CJC476, 74JCS(P1)1833, 72CJC917, 74CJC962, 73JCS(P1)2885, 73CI(L)275, 73CC579⟩. The second order rate constants for methiodide formation of some naphthyridines (with those of quinoline and isoquinoline for comparison) are shown in Table 7, and clearly show (1) that the additional nitrogen (N-5) in 1,5-naphthyridine relative to quinoline brings about a decrease in charge density at N-1, (2) that the alkylation rate constant of 1,6-naphthyridine is the sum of the separate constants for reaction at each nitrogen, and (3) that the much greater rate of alkylation of 1,8-naphthyridine relative to 1,5-naphthyridine reflects the steric interaction of the methyl group with the *peri* lone pair of electrons in the 1,8-naphthyridine ⟨74JCS(P1)1833, 72CJC917⟩.

Table 7 Second Order Rate Constants for Methiodide Formation in Acetonitrile (24.8 ± 0.1 °C) ⟨69CC56⟩

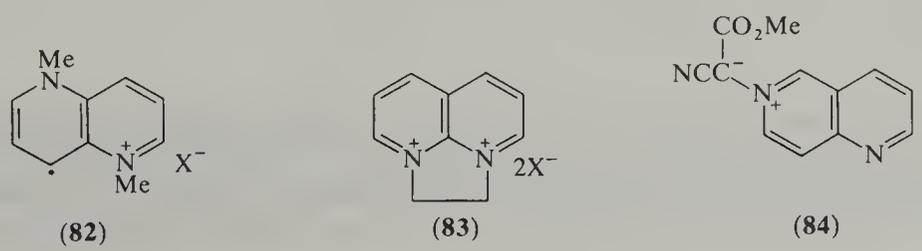
Compound	*Rate* (10^{-4} l mol^{-1} s^{-1})
Quinoline	0.517
Isoquinoline	4.23
1,5-Naphthyridine	0.232
1,6-Naphthyridine	1.66
1,8-Naphthyridine	4.25

Dimethylnaphthyridinediones, *e.g.* (**74**), may be formed by successive methylation and oxidation ⟨67CC1183⟩. Diquaternary salts, *e.g.* (**75**), have been prepared by reaction of naphthyridines with dimethyl sulfate ⟨67CC1183⟩ and with methyl fluorosulfonate ⟨73CJC476⟩, but the *N,N'*-dimethylnaphthyridinium salts differ significantly in their properties, for example, the diquaternary salt of 1,5-naphthyridine is relatively stable in neutral solution whereas that of 1,8-naphthyridine exists in equilibrium with its monopseudo base (**76**) ⟨73CJC476, 74CJC962⟩. Dimethyl-1,7-naphthyridinium difluorosulfonate (**77**) is highly reactive to nucleophilic attack at position 2, giving (**78**).

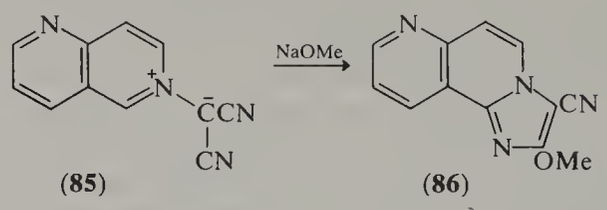


It is interesting that only mono- and not di-pseudo bases are obtained, and that with 1,6-naphthyridine, pseudo base formation occurs at the 'quinolinoid' site, the diquaternary salt (**79**) yielding (**80**) and not (**81**). However naphthyridinediones are formed on reaction with alkaline $K_3Fe(CN)_6$ ⟨72CJC917, 74CJC962⟩.

The 1,5-naphthyridine salt (**75**) is reduced readily in a one-electron transfer process to a reasonably stable green radical cation (**82**), whereas the salt (**83**) does not form a radical under similar conditions ⟨73JCS(P1)2885⟩. Stable ylides (**84**) and (**85**) are obtained from the



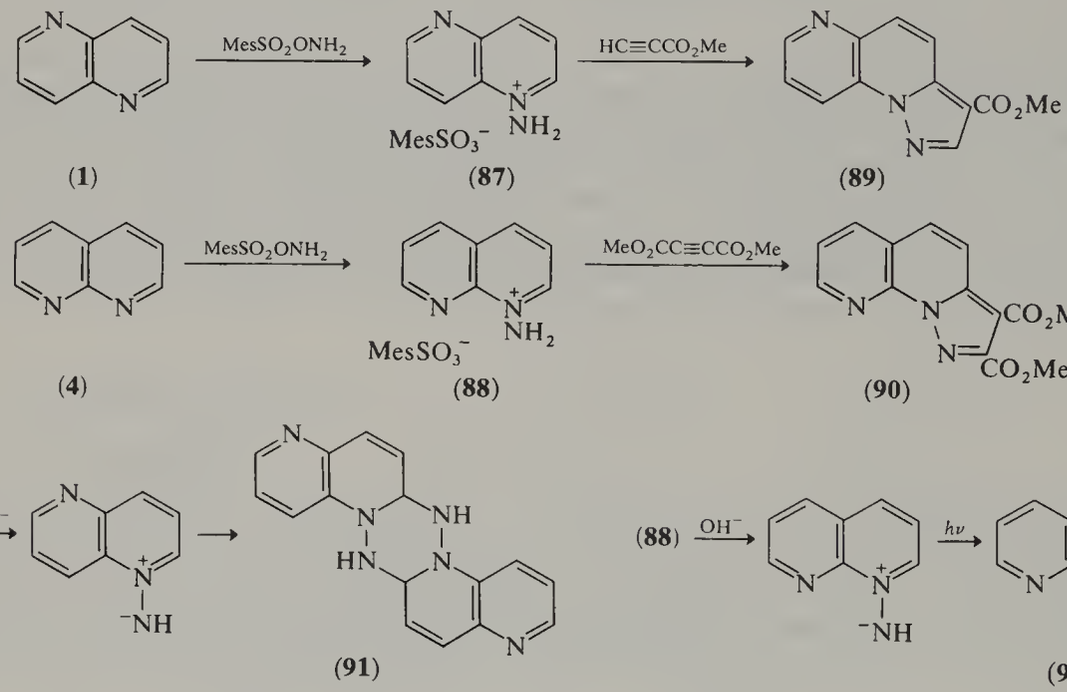
reaction of 1,6-naphthyridine with methyl bromocyanoacetate and tetracyanoethylene respectively; treatment of (**85**) with sodium methoxide (or with methanolic HCl) leads to cyclization and formation of (**86**) ⟨70CPB2489⟩.



(**85**) (**86**)

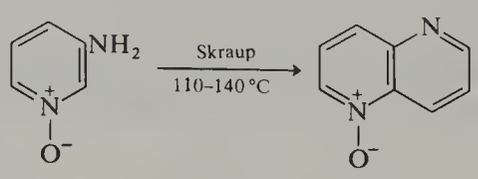
2.11.3.4.2 N-*Amino derivatives*

The 1,*x*-naphthyridines react with *O*-mesitylenesulfonylhydroxylamine to give salts of the *N*-amino derivatives, *e.g.* (**87**), (**88**) ⟨72TL4133⟩, which are readily benzoylated ⟨74JHC675⟩. These compounds react with acetylenecarboxylic acid esters to give tricyclic compounds such as (**89**) and (**90**) ⟨75JHC119⟩, and with alkali they form *N*-ylides which dimerize to give, for example, (**91**), or they may undergo ring expansion on irradiation to give (**92**) ⟨78H(9)621, 79CPB2183⟩.



2.11.3.4.3 N-*Oxides*

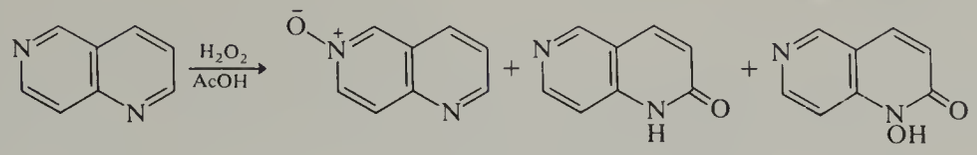
All of the naphthyridines except for the 2,6-isomer (**5**) give mono- and di-*N*-oxides on treatment with organic peracids ⟨54JCS1879, 49JCS1157, 70JHC291, 72KGS1237⟩. In addition naphthyridine *N*-oxides may be formed in Skraup syntheses with aminopyridine *N*-oxides, dependent on the reaction temperature ⟨68MI21100⟩. For example at 110–140 °C, 3-aminopyridine *N*-oxide gives 1,5-naphthyridine *N*-oxide (**93**) whereas at 150 °C the Skraup reaction product is 1,5-naphthyridine.



(**93**)

Oxidation of 1,6-naphthyridine (**2**) with peracetic acid gives a mixture of the *N*(6)-oxide (**94**), the 2-oxo derivative (**95**) and the 1-*N*-hydroxy-2-oxo derivative (**96**) whereas in the presence of sodium tungstate the product is the 1,6-dioxide ⟨69CPB1045⟩. 1,7-Naphthyridine (**3**) reacts with perbenzoic acid in $CHCl_3$ at room temperature to give predominantly the

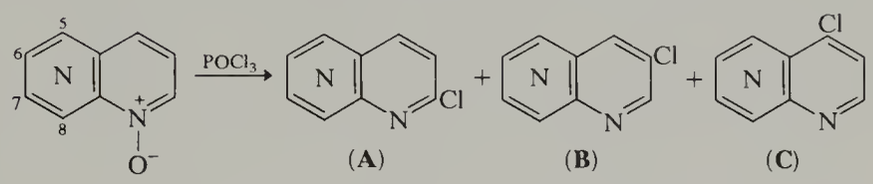
7-*N*-oxide, but gives the 1,7-dioxide in boiling $CHCl_3$ ⟨70JHC291⟩, the yield of the latter being much improved when the oxidation of (**3**) is carried out with $NaWO_4/H_2O_2$ ⟨72JHC3101⟩.



(**2**) (**94**) (**95**) (**96**)

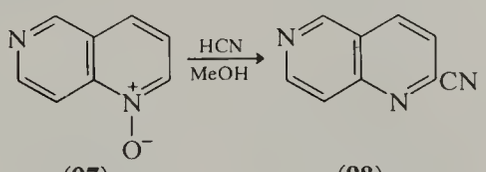
The treatment of 1,*x*-naphthyridine 1-*N*-oxides with phosphorus oxychloride (the Meisenheimer reaction) has been shown to give mixtures of isomeric 2-, 3- and 4-chloronaphthyridines (see Table 8) ⟨71JOC1720, 71JOC1331, 72JOC3101, 72JHC1151⟩. It appears that the 2-chloro compound may be formed in an intramolecular process whilst an intermolecular reaction may yield the 4-chloro isomer, with the 3-chloro compound possibly being formed in a modified electrophilic substitution process ⟨72JOC3101, 72JHC1151⟩. 1,6-Naphthyridine 6-*N*-oxide reacts under similar conditions to give 5-chloro-1,6-naphthyridine ⟨69CPB1045⟩, whereas the 1,6-di-*N*-oxide gives a mixture of 2,5-, 3,5- and 4,5-dichloro-, and 5-chloro-1,6-naphthyridines, with the 2,5- and 3,5-dichloro isomers predominating ⟨72JHC1151⟩. Naphthyridine *N*-oxides will undergo the Reissert reaction with HCN in methanol; for example, 1,6-naphthyridine 1-*N*-oxide (**97**) forms 2-cyano-1,6-naphthyridine (**98**) whereas the isomeric 6-*N*-oxide gives 5-cyano-1,6-naphthyridine ⟨69CPB2614⟩. The corresponding 1,6-naphthyridine di-*N*-oxide (**99**) gives, as would be expected, a mixture of cyanonaphthyridines under Reissert conditions ⟨70CPB861, 70CPB1026, 72JOC3588⟩; for example, with HCN in the presence of $K_3Fe(CN)_6$ compounds (**100**), (**101**) and (**102**) are obtained.

Table 8 Meisenheimer Reaction Products of some 1,*x*-Naphthyridine 1-Oxides ⟨71JOC1720, 72JOC3101⟩

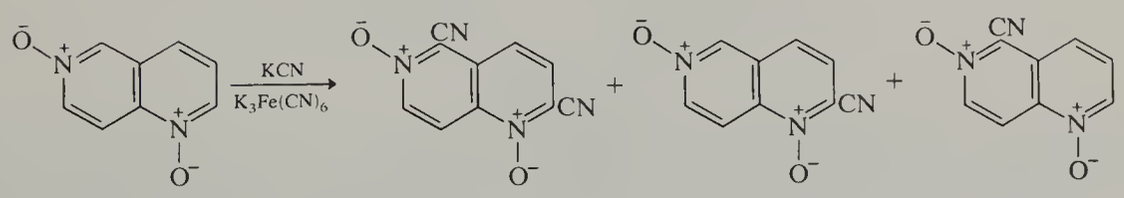


(**A**) (**B**) (**C**)

	Relative percentage yield		
Naphthyridine 1-oxide	(***A***)	(***B***)	(***C***)
1,5-Naphthyridine	42	3	54
1,6-Naphthyridine	12	20	66
1,7-Naphthyridine	56	3	35
1,8-Naphthyridine	36	7	57



(**97**) (**98**)



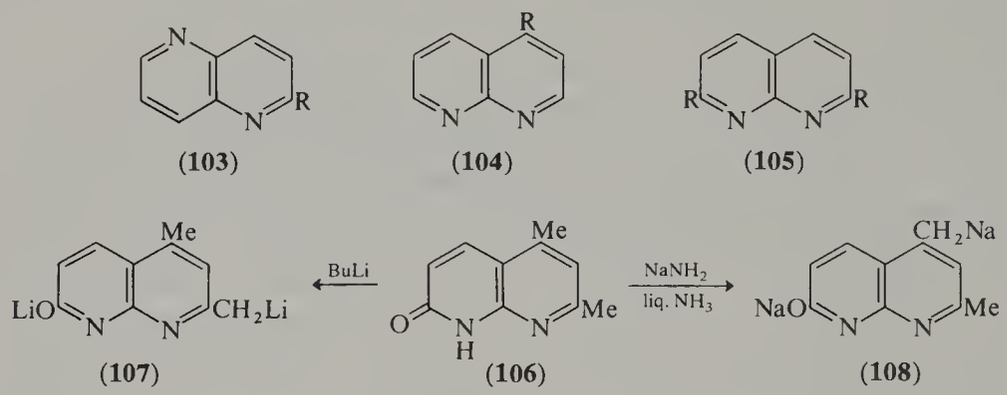
(**99**) (**100**) (**101**) (**102**)

2.11.3.5 Reactions of Methylnaphthyridines

Treatment of 2-methyl-1,5-naphthyridine (**103**; R = Me) with selenium dioxide gave the carboxylic acid (**103**; R = CO_2H) whereas the analogous oxidation of the *N*,*N*′-dioxide of

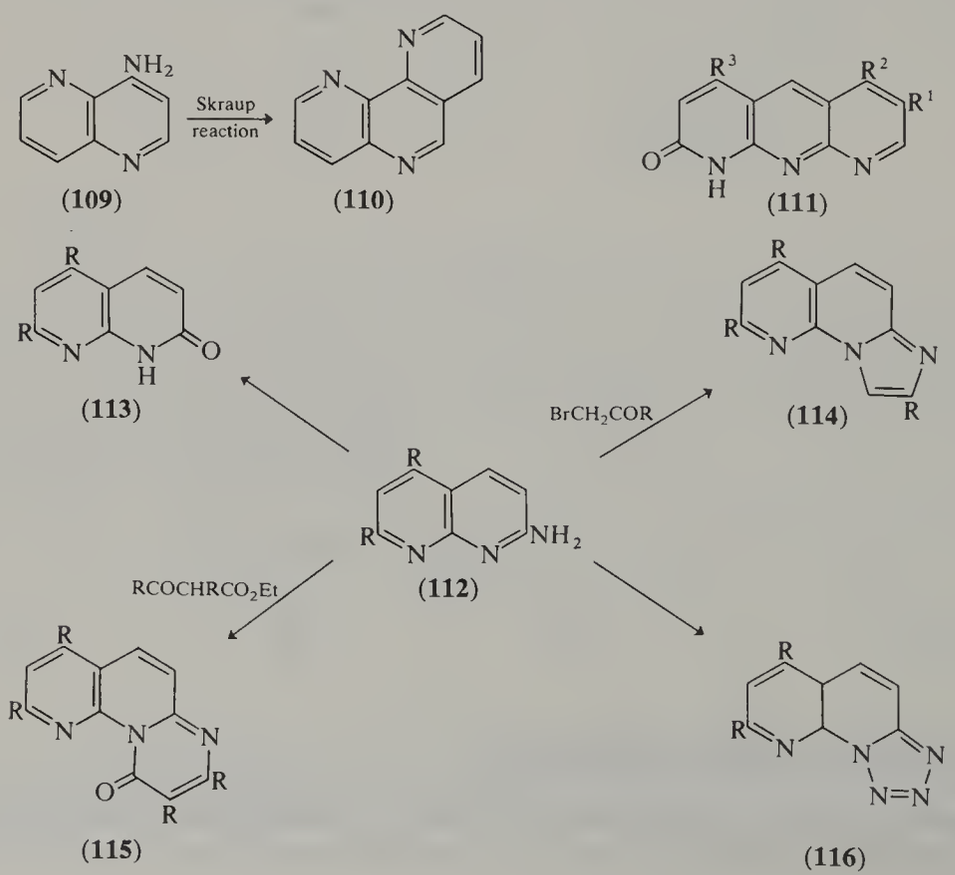
(**103**; R = Me) led only to the aldehyde ⟨73KGS1279⟩. However, similar oxidations with this reagent of 4-methyl-1,8-naphthyridine (**104**; R = Me) ⟨74MI21105⟩ and of 2,7-dimethyl-1,8-naphthyridine (**105**; R = Me) ⟨78ZC20⟩ gave the corresponding aldehydes (**104**; R = CHO) and (**105**; R = CHO).

The activated methyl groups of 5,7-dimethyl-1,8-naphthyridin-2-one (**106**) can be selectively metallated, reaction with two equivalents of butyllithium giving (**107**), while with two equivalents of sodamide in liquid ammonia (**108**) is obtained. Both (**107**) and (**108**) gave appropriate products on treatment with electrophiles ⟨81JOM(213)405⟩. A possible explanation of this result involves a coordination mechanism for the formation of (**107**) and an acid–base mechanism giving (**108**).



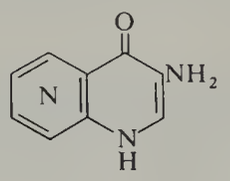
2.11.3.6 Reactions of Aminonaphthyridines

Attempts to prepare tricyclic homologues of the naphthyridines have been partially successful. 4-Amino-1,5-naphthyridine (**109**) reacts under Skraup conditions to give 4,5,9-triazaphenanthrene (**110**), and 1,8,9-triazaanthracene derivatives (**111**) can be isolated from the mixtures of products obtained by treatment of 2-amino-1,8-naphthyridin-7-one and its derivatives with ethyl ethoxymethylenemalonate, acetylacetone and alkyl β-oxoglutarates ⟨72JHC801⟩ (see also earlier papers in that series). However, 2-amino-1,8-naphthyridine (**112**; R = H) reacts under Skraup conditions to give the 2-oxo derivative (**113**; R = H) instead of a 1,8,9-triazaanthracene, and 2-amino-1,6-naphthyridine behaves similarly ⟨75MI21103⟩. Under non-hydrolytic conditions, naphthyridines (**112**; R = Alk, Ar, H) cyclize

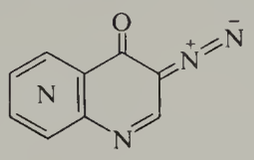


readily with α-bromoketones to give the imidazo[1,2-*a*][1,8]naphthyridines (**114**; R as before) ⟨71JCS(C)2985⟩, and with ethyl acetoacetate and related compounds they yield pyrimido[1,2-*a*][1,8]naphthyridines (**115**). Conversion of naphthyridines (**112**) into the tetrazoles (**116**) *via* the intermediate 2-azido-1,8-naphthyridines has been extensively investigated ⟨67G42, 70JHC1037, 71AC(R)318⟩.

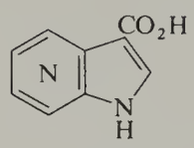
The conversion of 3-amino-4-oxo-1,*x*-naphthyridines (**117**) into the corresponding 3-diazo-4-oxo compounds (**118**) followed by photolysis results in the formation of azaindoles (**119**) *via* nitrogen evolution and ring contraction ⟨56LA(599)233, 60JCS1794⟩.



(**117**)



(**118**)

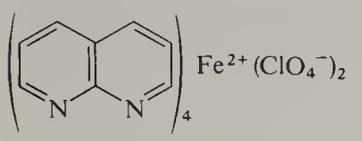


(**119**)

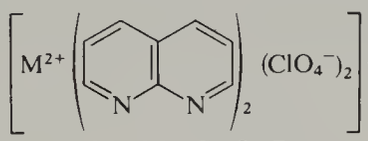
2.11.3.7 Metal Complexes of Naphthyridines

There has been considerable interest in the behavior of 1,8-naphthyridine as a ligand. Among the first metal complexes investigated were the Fe(II) perchlorates (**120**) ⟨70MI21100, 70CC389⟩ and the corresponding complexes of Mn(II), Ni(II), Cu(II), Zn(II), Pd(II) and Cd(II) ⟨74JCS(D)1949, 70MI21101⟩.

In the crystalline state four 1,8-naphthyridine molecules form an eight-coordinate complex with M(II) in which one of the naphthyridines is more tightly bonded than the other three ⟨70CC389⟩, but in solution this complex dissociates into a tris-1,8-naphthyridine–M(II) species ⟨76IC2615⟩. Other complexes of 1,8-naphthyridine and some of its methyl derivatives include four-coordinate (**121**) ⟨76IC2774⟩ and 10-coordinate (**122**) complexes ⟨72MI21101⟩. Some intensely colored four-coordinate complexes of compound (**4**) and ruthenium (**123**) possibly owe their color to metal-to-ligand charge transfer transitions ⟨77JA6581⟩. The seven-coordinate complex (**123a**) involves three coordinated bidentate naphthyridines and one perchlorate bonded to the metal through one of the oxygen atoms ⟨74JCS(D)1949⟩.

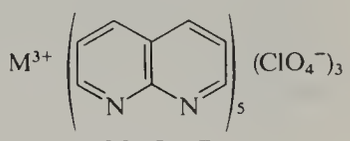


(**120**)



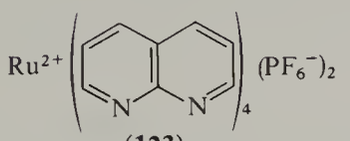
M = Mg, Ca, Sr, Be

(**121**)

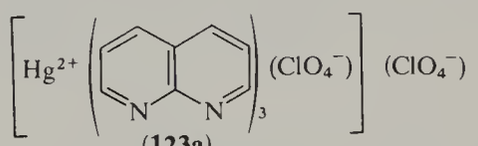


M = La–Pr

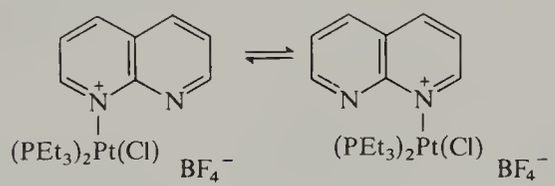
(**122**)



(**123**)



(**123a**)



(**124**)

The ^{1}H NMR spectrum of the platinum 1,8-naphthyridine complex (**124**) shows the naphthyridine protons to be equivalent above −30 °C, suggesting fluxional behavior ⟨77IC261⟩. Other examples of this phenomenon have also been observed ⟨73JA4855⟩.

1,5-Naphthyridine will form complexes of the type ML_2 with Cu(II), Co(II) and Ni(II) but not with Cd(II), Pd(II), Ba(II) or Zn(II) ⟨66MI21101⟩. 1,5-Naphthyridine 1,5-dioxide forms coordination compounds with Cu(II) salts ⟨76IC2916⟩, and metal complexes of 1,7-naphthyridin-8-ones with Cu(II), Ni(II), Fe(II) and Fe(III) have also been prepared ⟨54JCS505⟩. A more detailed account of metal ion–naphthyridine complex formation is given in a recent review ⟨83AHC(33)147⟩.

2.11.4 SYNTHESIS

2.11.4.1 Introduction

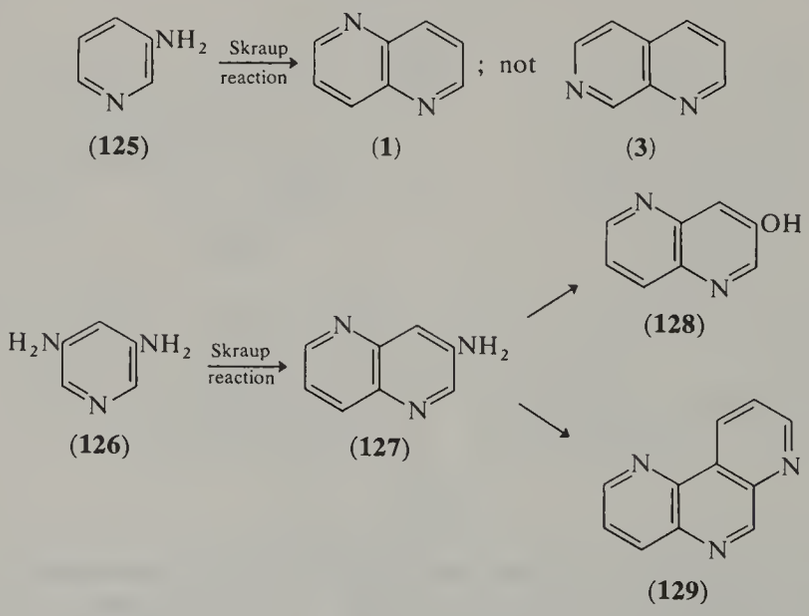
The majority of the methods for obtaining the naphthyridines (**1**)–(**4**) are similar to the methods employed for the preparation of quinolines, and aminopyridines are therefore the required starting compounds. Thus, 1,5-naphthyridines (**1**) may be obtained, sometimes together with the isomeric 1,7-naphthyridines (**3**), starting from 3-aminopyridine, 1,6-naphthyridines (**2**) are synthesized from 4-aminopyridines, and the 1,8-naphthyridines (**4**) are best obtained from 2-aminopyridine or its derivatives.

The remaining naphthyridines, (**5**) and (**6**), have received less attention than the above; many of the preparative methods for these compounds entail starting with either 4-cyanopyridines or their 3-cyano isomers, respectively, or with their carboxamide analogues.

2.11.4.2 Synthesis of 1,5-Naphthyridines

2.11.4.2.1 The Skraup reaction

This method was used for the first preparation of the parent compound, starting from 3-aminopyridine (**125**) ⟨27CB1081⟩. Various modifications of the reaction resulted in improved yields (over 60%) ⟨50JOC1224, 54JCS1879, 63JOC1753⟩, yields of up to 90% being obtained using a variety of oxidizing agents ⟨71CPB1857⟩. A number of methylated 1,5-naphthyridines have been obtained using the Doebner–Miller and related modifications (a list of these is given in ⟨70AHC(11)123⟩). Ring closure takes place exclusively in the 2-position as a result of the mesomeric effect being exerted more strongly in this position rather than in the 4-position ⟨60JCS1790, 63JOC1753⟩. However, if the 2-position is occupied by an oxo ⟨52JCS4985⟩ or an amino group ⟨68JOC1384⟩, ring closure takes place in the 4-position, giving a 1,7-naphthyridine derivative. 3-Aminopyridine *N*-oxide affords the parent 1,5-naphthyridine ⟨54JOC2008⟩. This method has been used to synthesize 2-oxo- ⟨26GEP507637⟩, 4-oxo- ⟨56JCS212⟩, 2-amino- ⟨42YZ257⟩ and 3-bromo-1,5-naphthyridines ⟨67MI21102⟩. The Skraup reaction on 3,5-diaminopyridine (**126**) gives a mixture of three products, (**127**), (**128**) and (**129**), compound (**127**) being the logical precursor of the other two ⟨67MI21102⟩. However 2,5-diaminopyridine gave 2-amino-1,5-naphthyridine as the sole isolated product ⟨42YZ257⟩.



(**125**) (**1**) (**3**)

(**128**)

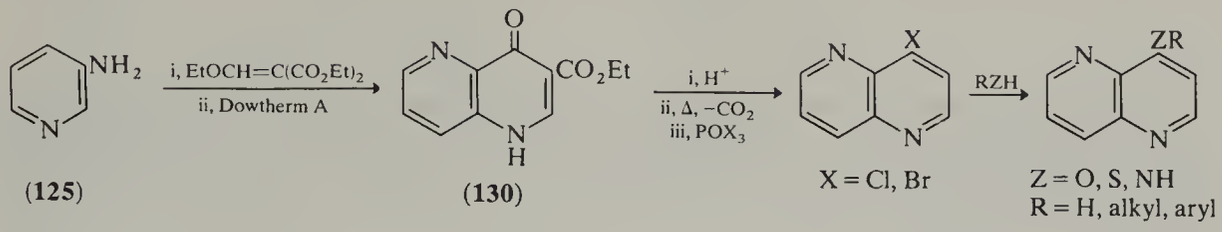
(**126**) (**127**)

(**129**)

2.11.4.2.2 EMME synthesis

A second general method ⟨46JA1317, 46JA1204⟩ for the synthesis of 1,5-naphthyridines consists in the condensation of 3-aminopyridine (**125**) with diethyl ethoxymethylenemalonate (EMME) followed by heating in Dowtherm to give 3-ethoxycarbonyl-1,5-

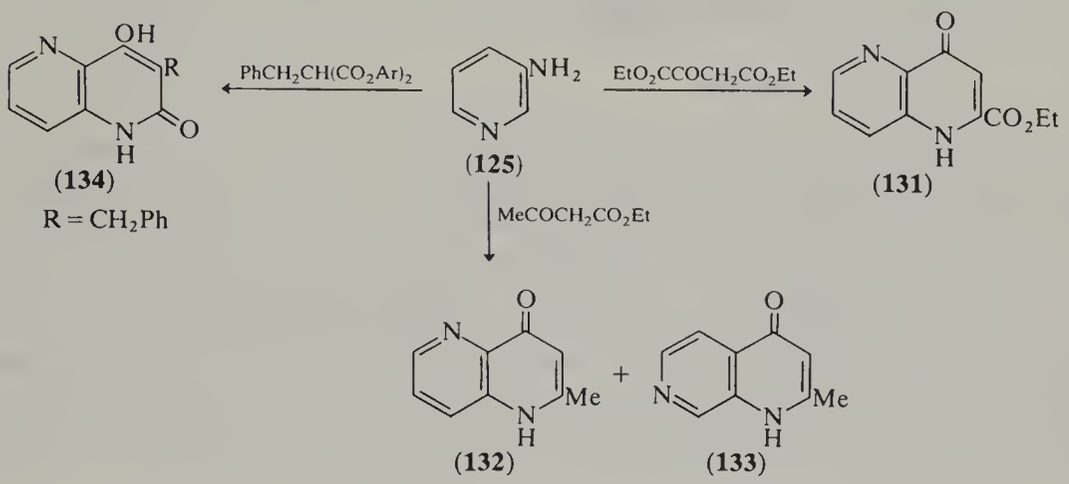
naphthyridin-4-one (**130**), a useful intermediate in the formation of 3- and 4-substituted 1,5-naphthyridines, as shown.



(**125**) (**130**) X = Cl, Br Z = O, S, NH R = H, alkyl, aryl

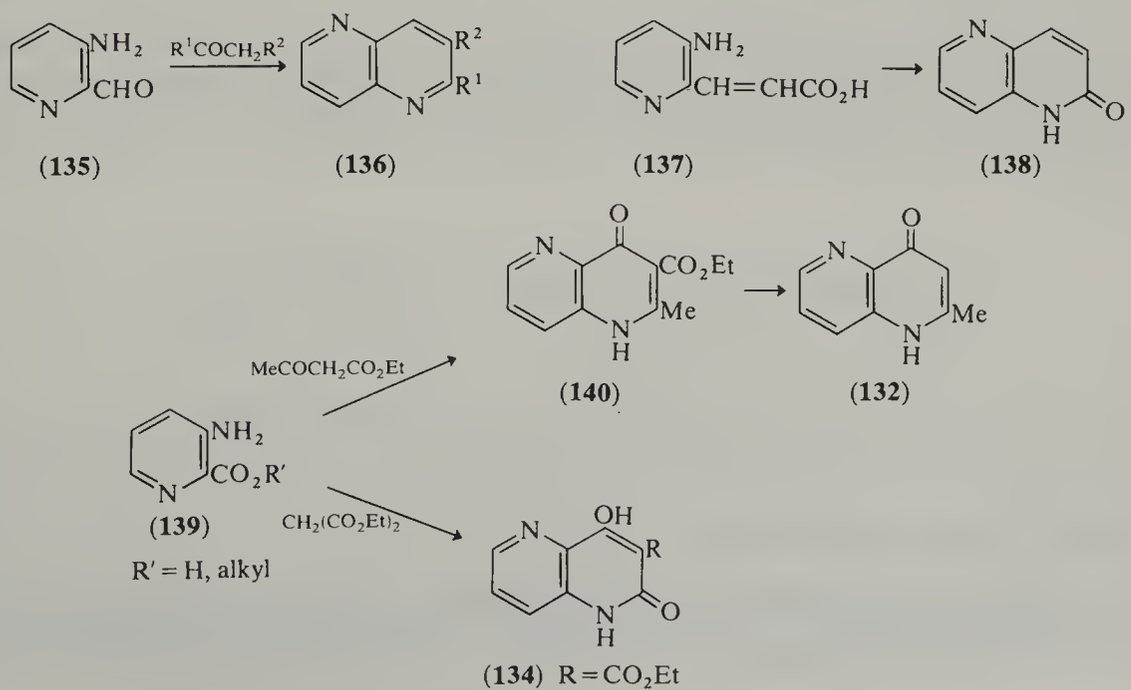
2.11.4.2.3 Miscellaneous syntheses

3-Aminopyridine (**125**) reacts with ethyl oxalylacetate to give 2-ethoxycarbonyl-1,5-naphthyridin-4-one (**131**) ⟨74MI21103⟩; with ethyl acetoacetate under Conrad–Limpach conditions it gives a mixture of the naphthyridines (**132**) and (**133**) in the ratio of 4:1 ⟨76RTC220⟩, and with bis(2,4-dichlorophenyl) benzylmalonate it gives 3-benzyl-4-hydroxy-1,5-naphthyridin-2-one (**134**; R = CH_2Ph) ⟨61M1184⟩.

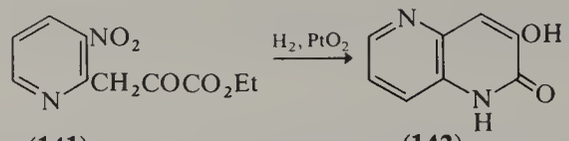


(**134**) R = CH_2Ph (**125**) (**131**) (**132**) (**133**)

The application of the Friedländer reaction to 3-aminopyridine-2-carbaldehyde (**135**) gives good yields of the 2,3-disubstituted 1,5-naphthyridines (**136**) ⟨75CR(C)(280)381⟩. The intramolecular cyclization of β-(3-aminopyridinyl)acrylic acid (**137**) results in the formation of 1,5-naphthyridin-2-one (**138**) ⟨66JHC357⟩, whilst the condensation of 3-aminopyridine-2-carboxylic acid or its esters (**139**) with active methylene compounds yields 4-oxo (**132**) and 4-hydroxy-2-oxo compounds (**134**; R = H) after hydrolysis and decarboxylation of the intermediates (**140**) and (**134**; R = CO_2Et). Reductive cyclization of the 3-nitropyridine derivative (**141**) gives the 1,5-naphthyridine (**142**) ⟨71JOC450⟩.

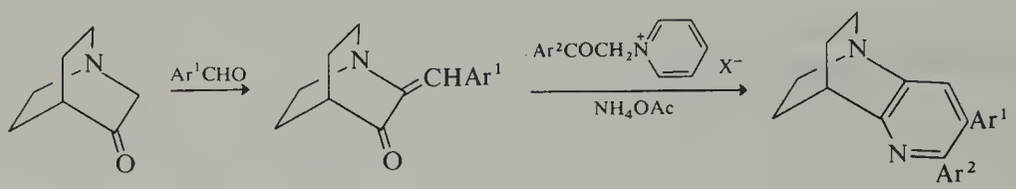


(**135**) (**136**) (**137**) (**138**) (**140**) (**132**) (**139**) R′ = H, alkyl (**134**) R = CO_2Et



(141) (142)

A novel approach to the synthesis of a 1,5-naphthyridine starts from quinuclidin-3-one (**143**), which is first converted to the 2-arylidene derivative and then reacted with phenacylpyridinium bromides and ammonium acetate to give 1,4-ethano-3,4-dihydro-2*H*-1,5-naphthyridines (**144**) ⟨82S27⟩.

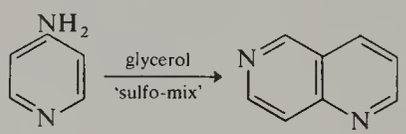


(143) (144)

2.11.4.3 Synthesis of 1,6-Naphthyridines

2.11.4.3.1 The Skraup reaction

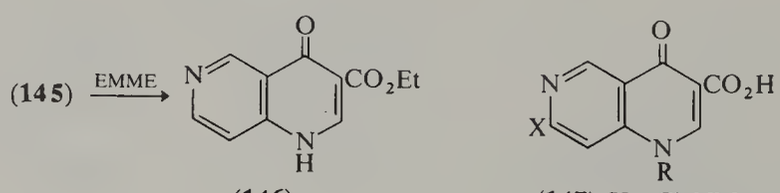
Early attempts to synthesize 1,6-naphthyridines by this method starting from 4-aminopyridine (**145**) proved unsuccessful ⟨27CB1081, 27MI21100⟩. Reinvestigation of the reaction utilizing the 'sulfo-mix' (a mixture obtained by heating nitrobenzene with oleum ⟨43JOC544⟩) procedure resulted in the formation of the parent compound (**2**) in 40% yield ⟨67CC3⟩, and further modification of the reaction conditions have significantly increased this yield ⟨71CPB1857⟩. Application of the Skraup reaction to 4-aminopyridine *N*-oxide and to some of its methyl derivatives gives the parent 1,6-naphthyridine 6-oxide and the corresponding methylated products ⟨56CPB178, 60YZ562⟩. 2-, 3- and 4-methyl-substituted 1,6-naphthyridines have been obtained starting from crotonaldehyde ⟨66JOC3055⟩, methacrolein ⟨67JHC284⟩ and methyl vinyl ketone ⟨66JOC3055⟩ respectively.



(145) (2)

2.11.4.3.2 EMME synthesis

The condensation of 4-aminopyridine (**145**) with diethyl ethoxymethylenemalonate (EMME) gives 3-ethoxycarbonyl-1,6-naphthyridin-4-one (**146**) from which compound (**2**) was obtained by standard procedures ⟨50JOC1224, 60JCS1790, 58LA(612)153, 65JHC393⟩. A recent application of this synthesis is for the preparation of nalidixic acid analogues (**147**) ⟨82CPB2399⟩.

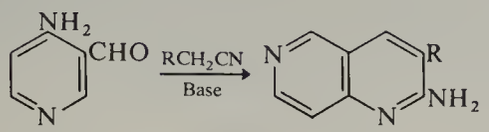


(146) (147) X = Cl, NMe_2; R = alkyl

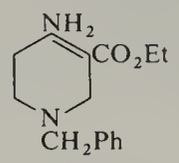
2.11.4.3.3 Miscellaneous syntheses

The condensation of 4-aminonicotinaldehyde (**148**) with active methylene compounds (the Friedländer synthesis) gives good yields of 1,6-naphthyridines (**149**) ⟨72JHC703, 74JHC151, 73JMC849, 75CR(C)(280)381⟩. The hexahydro-1,6-naphthyridine derivative (**150**) has

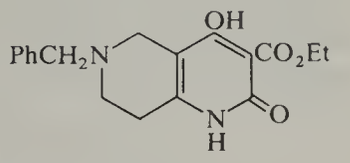
been obtained from the reaction between the tetrahydropyridine (**151**) and diethyl malonate ⟨78H(11)267⟩.



(**148**) (**149**)

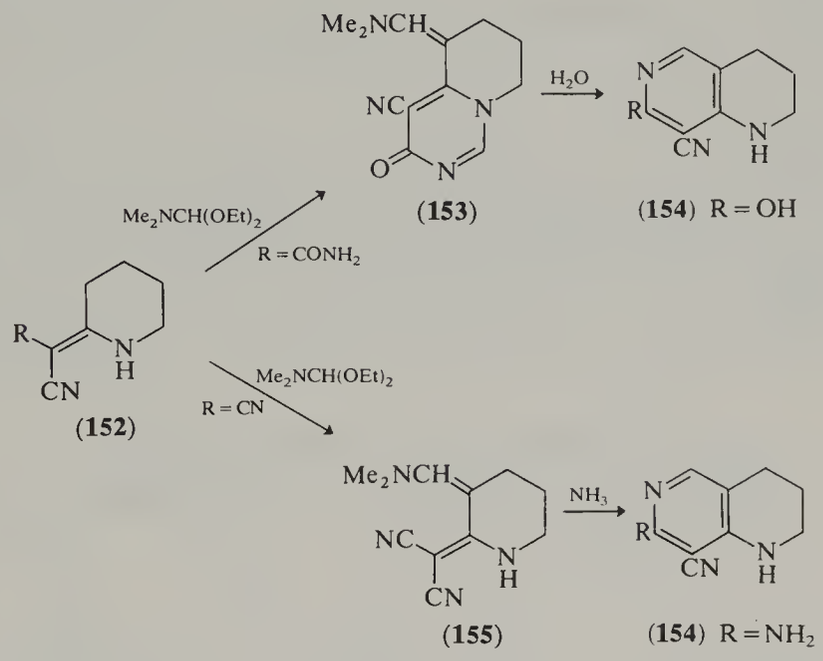


(**151**)



(**150**)

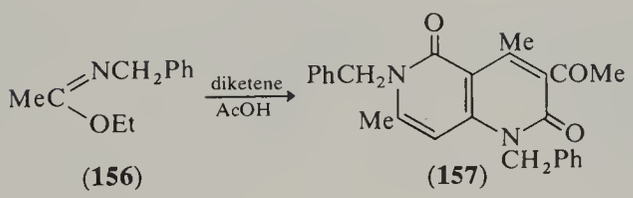
Two novel methods of formation of 1,2,3,4-tetrahydro-1,6-naphthyridines require enamines as starting materials. Condensation of the enaminoamide (**152**; R = $CONH_2$) with dimethylformamide diethyl acetal gave the pyrido[1,2-*c*]pyrimidine derivative (**153**) which on refluxing in aqueous solution rearranged to the 1,6-naphthyridine derivative (**154**; R = OH) ⟨80KGS416, 80KGS1120⟩. However, the closely related enamine (**152**; R = CN) reacted with the acetal to give compound (**155**) which cyclized with ammonia to give (**154**; R = NH_2) directly ⟨82KGS518⟩. The mechanism of the condensation between ethyl *N*-benzylacetimidate (**156**) and diketene to give the 1,6-naphthyridine derivative (**157**) is still rather obscure ⟨75CPB2629⟩. Cyclization of the enamine intermediate obtained by condensation of 3-cyano-2-methylpyridine (**158**) with dimethylformamide dimethyl acetal gives 1,6-naphthyridin-5-one (**159**) in 47% yield ⟨78JOC4878⟩. This method has also been used to obtain 1,7- and 2,7-naphthyridines.



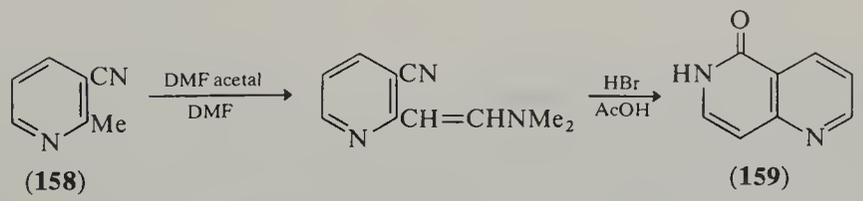
(**153**) (**154**) R = OH

(**152**)

(**155**) (**154**) R = NH_2



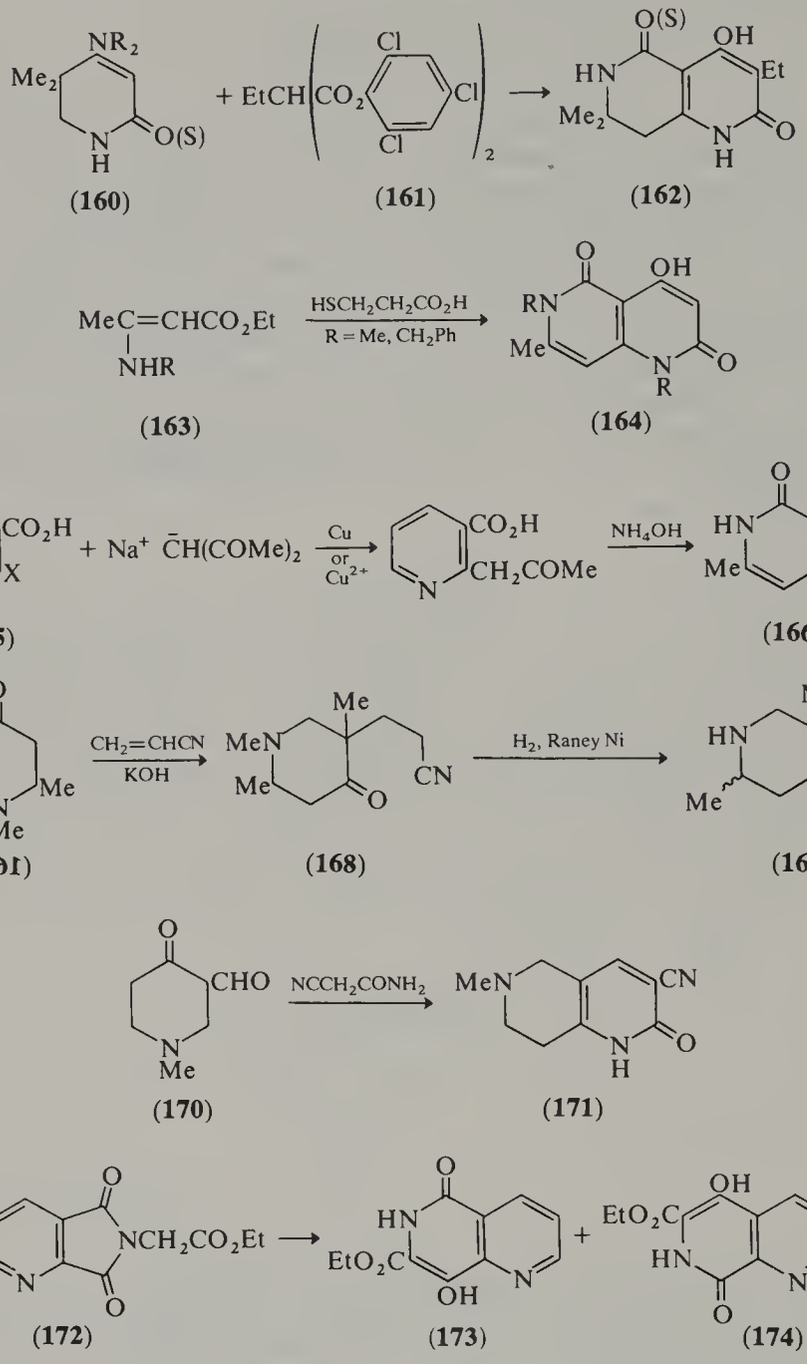
(**156**) (**157**)



(**158**) (**159**)

The reaction between 4-dialkylamino-3,4-dehydropiperidin-2-ones (and thiones) (**160**) and bis(2,4,6-trichlorophenyl) ethylmalonate (**161**) gives the 1,6-naphthyridines (**162**), together with three other products ⟨82M573⟩, and the condensation between ethyl 3-alkylaminocrotonates (**163**) in the presence of 3-mercaptopropanoic acid gives the compounds (**164**) in low yield ⟨82H(19)1263⟩. 2-Halogenonicotinic acids (**165**) react with compounds containing an active methylene group, followed by treatment with ammonia, to give 5,7-disubstituted 1,6-naphthyridines (**166**) ⟨72JCS(P1)705⟩. The reaction between the *N*-methyl-4-piperidone (**167**) and acrylonitrile gives an intermediate (**168**) that on reduction

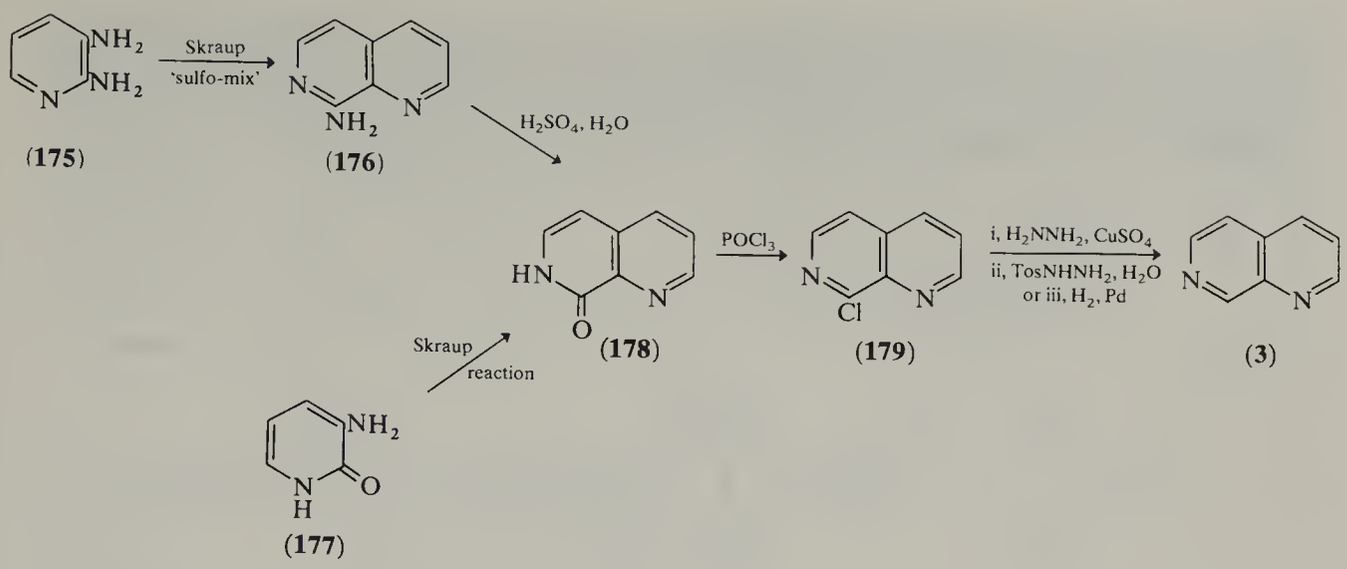
cyclizes to the perhydro-1,6-naphthyridine (**169**) (of unspecified stereochemistry) ⟨54JGU319⟩, whilst the *N*-methyl-3-formyl-4-piperidone (**170**) condenses with cyanoacetamide to afford the hexahydro-1,6-naphthyridine (**171**) ⟨67AK(26)489⟩. The base-catalyzed rearrangement of the quinolinic acid imide (**172**) gives a mixture of the 1,6-naphthyridine (**173**; 50%) and the 1,7-naphthyridine (**174**; 20%) ⟨52JCS4985⟩.



2.11.4.4 Synthesis of 1,7-Naphthyridines

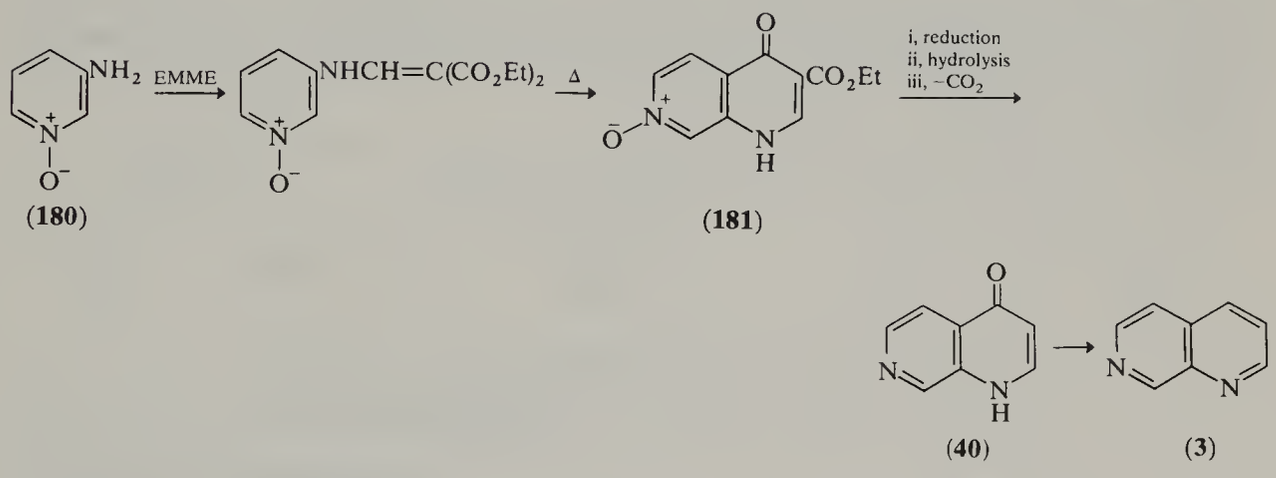
2.11.4.4.1 The Skraup reaction

As stated earlier (see Section 2.11.4.2.1) the Skraup reaction on 3-aminopyridines gives the 1,5-naphthyridines unless the 2-position of the pyridine ring is blocked by an electron-donating group; for example, 2,3-diaminopyridine (**175**) gives 8-amino-1,7-naphthyridine (**176**) ⟨68JOC1384, 77RTC151⟩, and 3-amino-2-pyridone (**177**) yields 1,7-naphthyridin-8-one (**178**) ⟨52JCS4985, 63JOC1753⟩. Compound (**178**) can also be obtained in high yields (81%) by acid hydrolysis of (**176**) ⟨78JHC731⟩. The oxo group in (**178**) can be replaced readily by a chlorine atom to give (**179**) which may then be converted to the parent 1,7-naphthyridine (**3**) by several methods ⟨63JOC1753, 66JCS(B)750, 76CPB1813⟩.



2.11.4.4.2 EMME synthesis

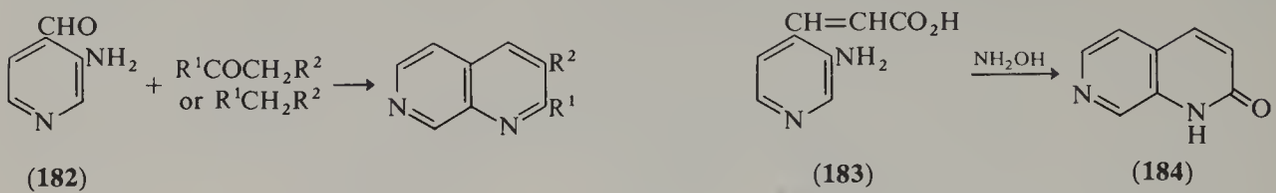
1,7-Naphthyridine derivatives may be obtained from the reaction between 3-aminopyridine *N*-oxide (**180**) and diethyl ethoxymethylenemalonate (EMME) in refluxing Dowtherm A ⟨54JOC2008⟩, the product being 3-ethoxycarbonyl-4-oxo-1,4-dihydro-1,7-naphthyridine 7-oxide (**181**). The *N*-oxide function in (**180**) makes position 4 more nucleophilic and the ethoxycarbonyl group therefore reacts at this rather than at the 2-position, which would have resulted in the formation of the 1,5-naphthyridine derivative. Deoxygenation of (**181**) followed by hydrolysis and decarboxylation gives (**40**) which may be converted to 1,7-naphthyridine (**3**) by procedures similar to those used for the conversion (**179**) → (**3**) ⟨54JOC2008⟩. Many 1,7-naphthyridine derivatives have been prepared by this method, starting either from the *N*-oxides of various 3-aminopyridines or from 3-aminopyridines containing a blocking group in the 2-position ⟨*cf.* 66BRP1022214, 69USP3429887, 70USP3517014⟩.



2.11.4.4.3 Miscellaneous syntheses

The Conrad–Limpach reaction on 3-aminopyridine gives a mixture of compounds (**132**) and (**133**) (see Section 2.11.4.2.3), but the reaction with 3-amino-2-methylpyridine gives a derivative of compound (**3**) only ⟨73MI21102⟩. The Friedländer quinoline synthesis has been widely applied to the synthesis of 2- and 3-amino- and to 2,3-disubstituted 1,7-naphthyridines. 3-Aminoisonicotinaldehyde (**182**) may be reacted with aldehydes, ketones or other active methylene compounds ⟨75CR(C)(280)381, 76JHC387⟩, or alternatively the keto compound may react with the Schiff's base of 3-aminoisonicotinaldehyde ⟨55JA2438, 57JOC138⟩, a modification which may however give widely varying yields depending on the ketone substituents. A second modification of the above reactions uses 3-(3-amino-4-pyridyl)acrylic acid (**183**) as the starting material. Reaction of (**183**) with hydroxylamine gave 1,7-naphthyridin-2-one (**184**) in 30% yield ⟨55JA2438⟩. The condensation of ethyl

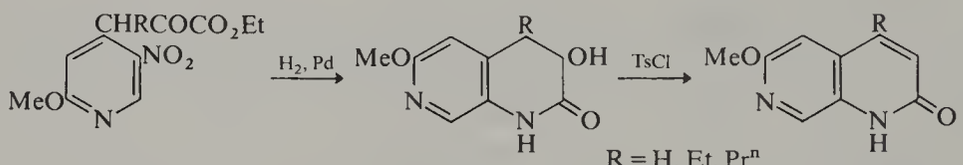
3-aminoisonicotinate (**185**) and diethyl malonate furnishes ethyl 4-hydroxy-1,2-dihydro-2-oxo-1,7-naphthyridine-3-carboxylate (**186**) which gives compound (**42**) after hydrolysis and decarboxylation ⟨74MI21104⟩. Compound (**42**) may also be obtained directly on treatment of (**185**) with ethyl acetate and sodium hydride ⟨75JMC726, 77BRP1490998⟩.



(**182**) (**183**) (**184**)

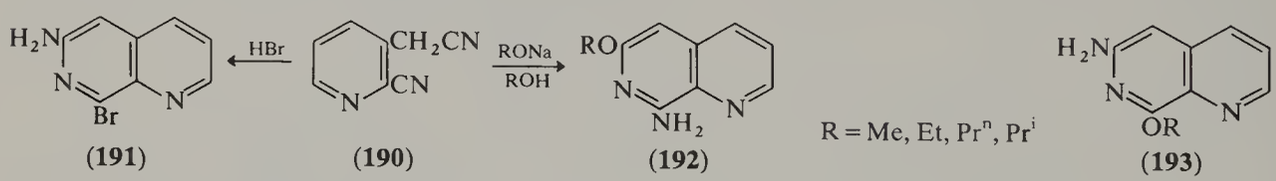
(**42**) (**185**) (**186**)

The reductive cyclization of ethyl (2-methoxy-5-nitro-4-pyridyl)pyruvates (**187**) with H_2/Pd followed by treatment of the intermediates (**188**) with toluenesulfonyl chloride gave the 6-methoxy-1,7-naphthyridin-2-ones (**189**) ⟨65JA3530, 73JOC1824⟩.

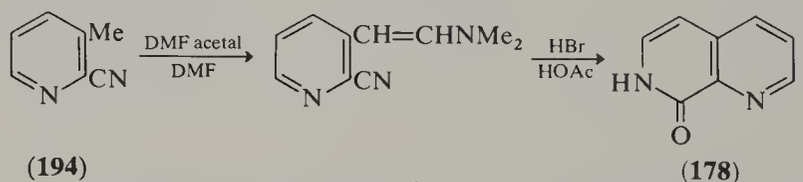


(**187**) (**188**) (**189**)

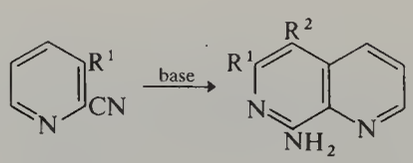
A number of syntheses of 1,7-naphthyridines starting from 2-cyanopyridine derivatives have been described. The reaction of (2-cyano-3-pyridyl)acetonitrile (**190**) with hydrobromic acid gave 6-amino-8-bromo-1,7-naphthyridine (**191**) ⟨66TL1233⟩, and treatment of (**190**) with sodium alkoxides gave mixtures of the 1,7-naphthyridines (**192**) and (**193**) ⟨75TL173, 75G1001⟩. The procedure mentioned earlier for cyclization of the enamines derived from cyanomethylpyridines (see Section 2.11.4.3.3) was carried out on 2-cyano-3-methylpyridine (**194**), but the yield of product (**178**) was only 5% ⟨78JOC4878⟩. A number of 5- and 6-substituted 8-amino-1,7-naphthyridines (**195**) have been obtained by a base-catalyzed condensation of 2-cyano-3-R^1-pyridines (**196**) either with themselves or with other nitriles ⟨75USP3928367, 76BEP835770, 77USP4017550⟩.



(**191**) (**190**) (**192**) (**193**)



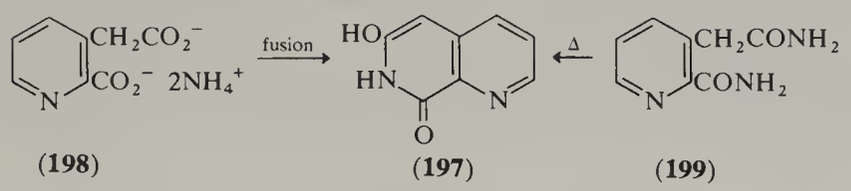
(**194**) (**178**)



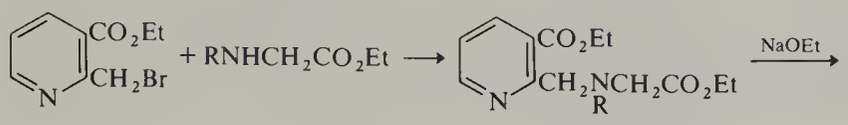
(**196**) (**195**) R^1, R^2 = alkyl, aryl, hetaryl

6-Hydroxy-1,7-naphthyridin-8-one (**197**) has been obtained by fusion of the ammonium salt of β-homoquinolinic acid (**198**) ⟨55JA2438⟩, and also by heating an alcoholic solution of the corresponding diamide (**199**) ⟨56HCA2106⟩. A novel method of formation of 5-hydroxy-1,7-naphthyridine (**200**) involves the condensation of ethyl (2 bromomethyl)nicotinate (**201**) with the amino acid derivative (**202**) to give (**203**), which on heating cyclizes to (**204**). Hydrolysis and decarboxylation of (**204**) give (**200**) ⟨79LA443⟩. Reaction of the lactone (**205**) with various primary amines affords the tetrahydro-1,7-naphthyridines (**206**)

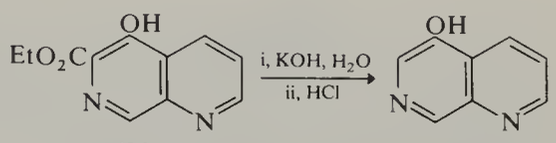
⟨62JAP624149⟩ and a wide variety of 1-*N*-alkylperhydro-1,7-naphthyridines (**207**) have been obtained by reaction of the ether (**208**) with various alkylamines ⟨66KGS427⟩. A convenient synthesis of 5-hydroxy-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine (**211**) starts from the 3-substituted amino isonicotinaldehyde (**209**) which undergoes a Wittig reaction followed by reduction to give (**210**), a compound that cyclizes readily in acid solution to (**211**) ⟨82CPB1257⟩.



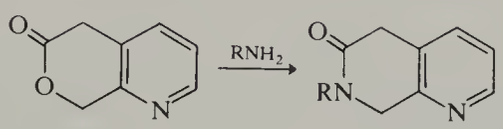
(**198**) (**197**) (**199**)



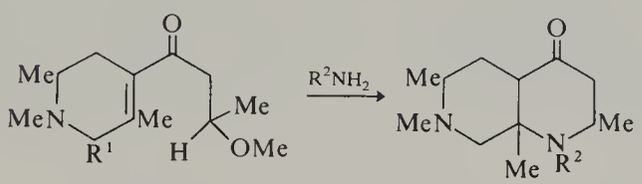
(**201**) (**202**) (**203**)



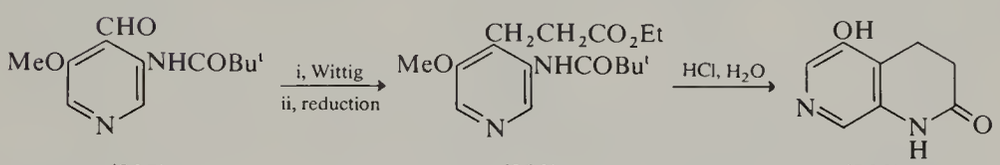
(**204**) (**200**)



(**205**) (**206**)



(**208**) (**207**) R^1, R^2 = H, Me, Et, Pr^i, Bu, *p*-$MeOC_6H_4$

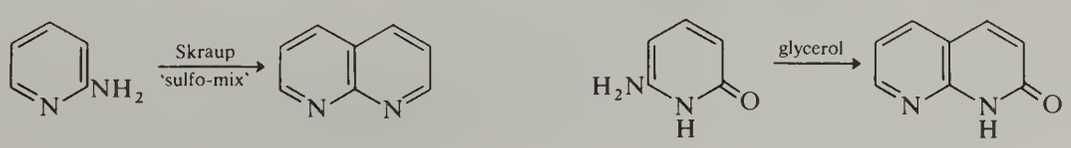


(**209**) (**210**) (**211**)

2.11.4.5 Synthesis of 1,8-Naphthyridines

2.11.4.5.1 The Skraup reaction

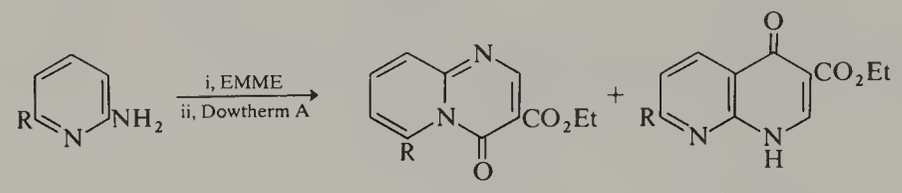
Attempts to synthesize 1,8-naphthyridines starting from 2-aminopyridine (**212**) were initially unsuccessful (*cf.* Section 2.11.4.3.1) but utilization of the 'sulfo-mix' procedure resulted in good yields of the parent 1,8-naphthyridine (**4**), and many of its mono-, di- and tri-methyl homologues have been obtained starting from (**212**), 2-aminopicolines and 2-aminolutidines and condensation with glycerol, crotonaldehyde, 2-methylacrolein or methyl vinyl ketone ⟨67JHC284, 67JOC832, 71CPB1857, 74YZ1328⟩. The reaction of 6-aminopyridin-2-one (**213**) with glycerol gives 1,8-naphthyridin-2-one (**37**) ⟨76S691⟩.



(**212**) (**4**) (**213**) (**37**)

2.11.4.5.2 EMME synthesis

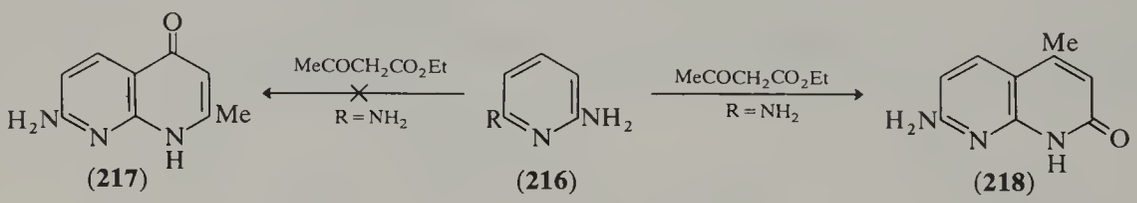
The condensation of 2-aminopyridine (**212**) with diethyl ethoxymethylenemalonate followed by heating in Dowtherm A gives only the pyrido[1,2-*a*]pyrimidine (**214**; R = H). However, when the 2-aminopyridine contains an electron-releasing 6-substituent (Me, OEt, NH_2) 1,8-naphthyridines (**215**) are obtained ⟨46JA1317, 48JA3348, 52JA5491⟩. It was initially thought that (**215**) was formed directly from the aminopyridine derivative ⟨48JA3348⟩, but recent work has shown that heating (**214**) in Dowtherm at 250 °C yields (**215**), the rearrangement taking place in a 1 → 3, N → C acyl migration ⟨75TL1019, 77JCS(P1)789⟩. This reaction has also been used to obtain 1,2,3,4-tetrahydro-1,8-naphthyridines ⟨79H(12)1407⟩, benzo-1,8-naphthyridines ⟨79JHC137⟩ and anthyridines ⟨77JCS(P1)789⟩.



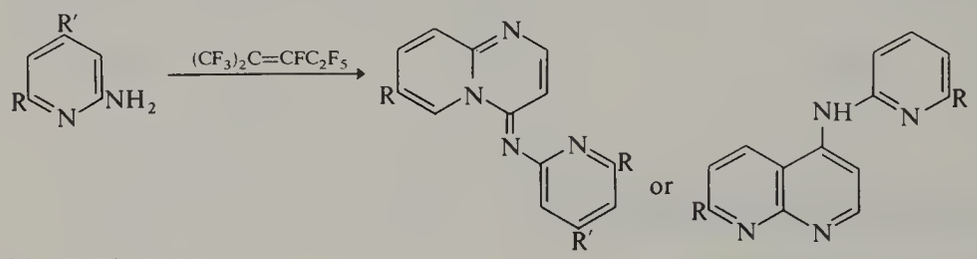
(**216**) [R = H: (**212**)] (**214**) (**215**)

2.11.4.5.3 Miscellaneous syntheses

A detailed discussion of the synthesis of 1,8-naphthyridine derivatives by means of adaptations of other quinoline-type syntheses should be consulted ⟨49JOC453⟩. The reaction between 2,6-diaminopyridine (**216**; $R = NH_2$) and ethyl acetoacetate under Conrad–Limpach reaction conditions does not yield the expected, and initially reported, 2-methyl-7-amino-1,8-naphthyridin-4-one (**217**) ⟨49JOC453⟩, but actually gives the isomeric 4-methyl-7-amino-1,8-naphthyridin-2-one (**218**) ⟨65JOC1607, 64AC(R)677, 66G103⟩. A number of studies have been reported of the reactions between 2,6-diaminopyridine (**216**; $R = NH_2$) and a large number of dicarbonyl compounds ⟨62AC(R)279, 62AC(R)340, 64AC(R)883, 66G1443, 66G1456, 67G1061, 76JHC41, 77TL2087⟩.



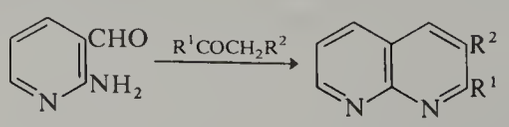
(**217**) (**216**) (**218**)



(**219**) R, R′ = H, Me (**220**)

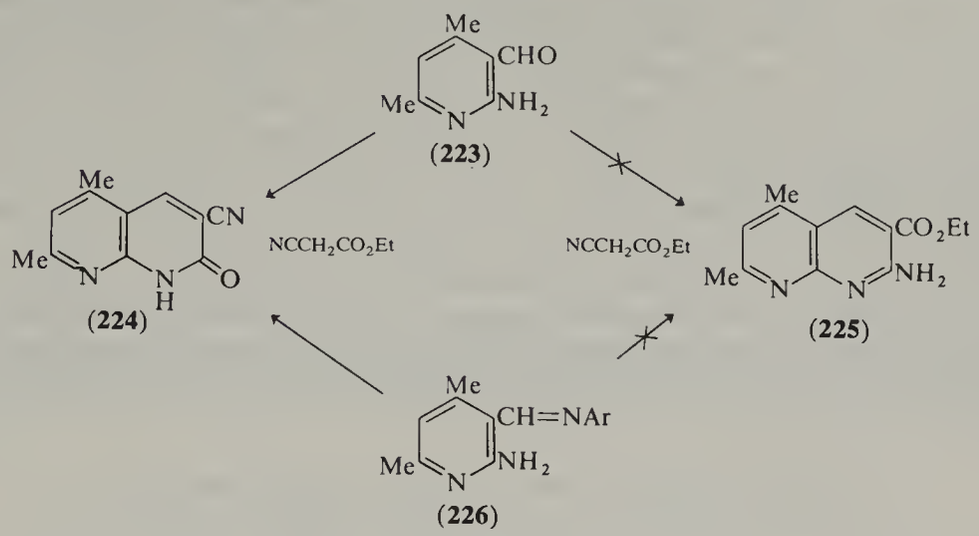
The reaction between 2-aminopyridine and 2-amino-4-methylpyridine with perfluoro-2-methylpent-2-ene gave pyrido[1,2-*a*]pyrimidines, but 2-amino-6-methylpyridine gave the naphthyridine (**220**) ⟨74CC134⟩.

The Friedländer condensation of 2-aminonicotinaldehyde (**221**) with ketones and other active methylene compounds gives, as expected, good yields of the 2-substituted or 2,3-disubstituted 1,8-naphthyridines (**222**) ⟨66JCS(C)315, 67JCS(C)1564, 71JCS(C)2991⟩. 2-Amino-

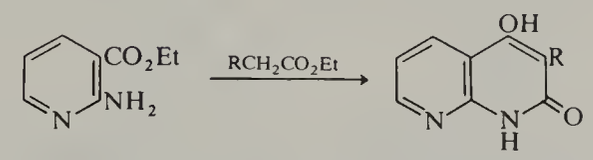


(**221**) (**222**) R^1 = H, Me, OH, NH_2
R^2 = H, Ph, COMe, CO_2Et, COPh, NO_2, CN, $CONH_2$

4,6-dimethylnicotinaldehyde (**223**) reacts with ethyl cyanoacetate to give mainly (**224**) rather than (**225**); the anil (**226**) reacts similarly ⟨71JCS(C)2991, 76JHC43⟩.

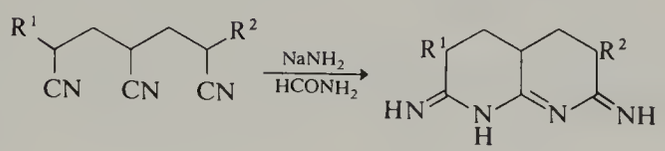


The condensation of ethyl 2-aminonicotinate (**227**) with diethyl malonate gives 3-ethoxycarbonyl-4-hydroxy-1,8-naphthyridin-2-one (**228**) ⟨58JCS204, 74MI21104⟩, with ethyl acetate it gives (**229**; R = H) ⟨74MI21105⟩ and with ethyl phenylacetates (**229**; R = Ar) ⟨78CB2813⟩. The tetrahydro derivative of (**227**) similarly gives the corresponding tetrahydro-1,8-naphthyridine ⟨78CB2813⟩.

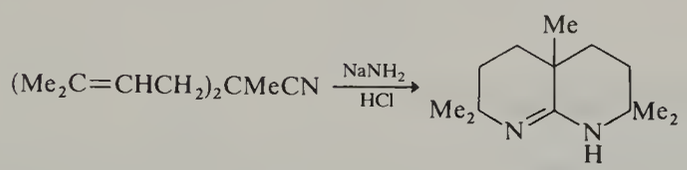


(**227**)

(**228**) R = CO_2Et
(**229**) R = H, Ar



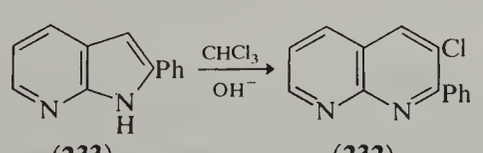
(**230**)



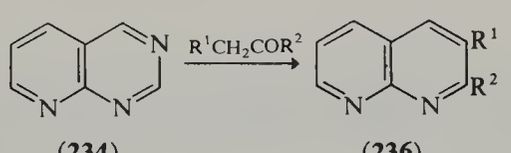
(**231**)

The reduced naphthyridines (**230**) and (**231**) have been obtained by treatment of nitriles with sodamide ⟨62BCJ1438, 64JAP6419176, 78HCA2851⟩.

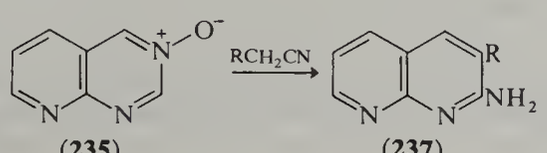
2-Phenyl-3-chloro-1,8-naphthyridine (**232**) has been obtained by the ring expansion of 2-phenyl-7-azaindole (**233**) in a carbene insertion reaction ⟨69JCS(C)1505⟩. Pyrido[2,3-*d*]pyrimidine (**234**) and its *N*-oxide (**235**) have been converted into 1,8-naphthyridines (**236**) and (**237**) by reaction with ketones and other active methylene compounds, by a series of reactions involving addition, ring opening, elimination and finally cyclization ⟨73CPB2643, 75CPB2939, 78CPB3242⟩.



(**233**) (**232**)



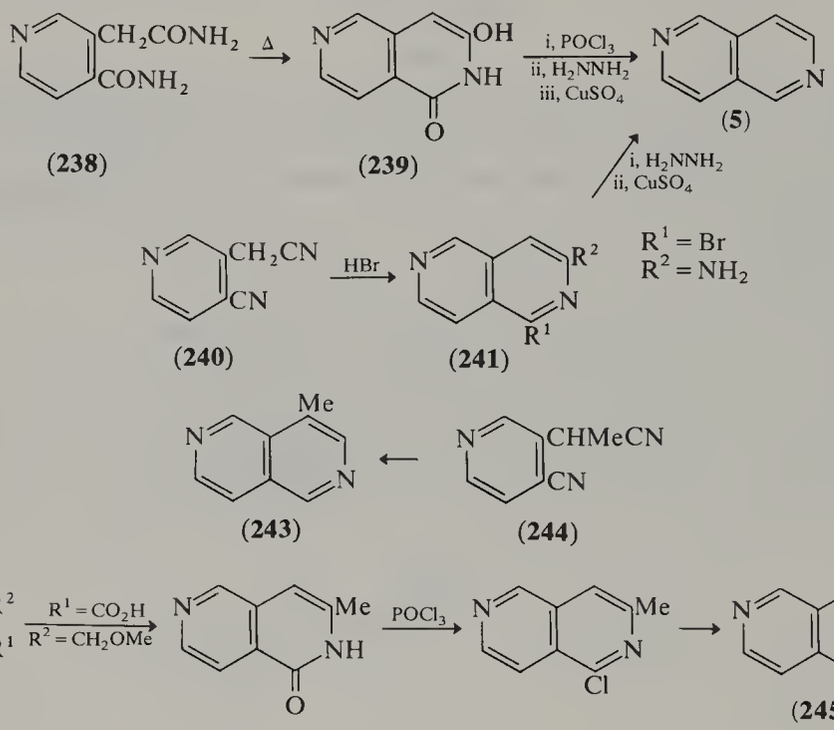
(**234**) (**236**)



(**235**) (**237**)

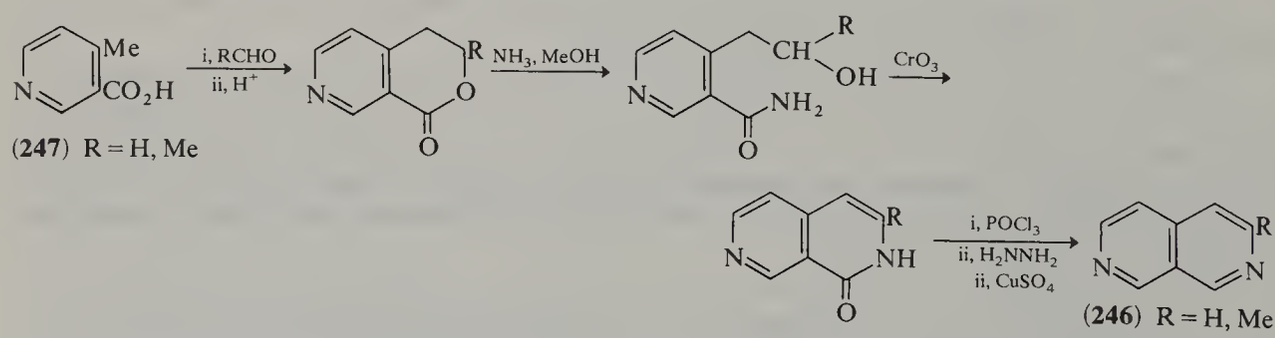
2.11.4.6 Synthesis of 2,6-Naphthyridines

The parent 2,6-naphthyridine (**5**) was first obtained through a series of reactions in which compound (**238**) was the key intermediate. This cyclized thermally to (**239**) which was then converted to (**5**) in a conventional series of steps ⟨65TL1117⟩. The dinitrile (**240**) can also be cyclized to give 3-amino-1-bromo-2,6-naphthyridine (**241**; $R^1 = Br$, $R^2 = NH_2$) which has also been converted into (**5**) ⟨65TL2737⟩. Compound (**240**) will also cyclize on treatment with alkoxides to give mixtures of the isomeric 2,6-naphthyridines (**241**; $R^1 = OR$, $R^2 = NH_2$) and (**241**; $R^1 = NH_2$, $R^2 = OR$) ⟨75TL173, 75G1001⟩. Compound (**239**) has also been obtained by cyclization of the isomeric cyanoesters (**242**; $R^1 = CO_2Et$, $R^2 = CH_2CN$) and (**242**; $R^1 = CN$, $R^2 = CH_2CO_2Et$) under acidic conditions. The synthesis of 4-methyl-2,6-naphthyridine (**243**), which has been isolated from a number of *Antirrhinum* species ⟨70TL4773⟩, has been accomplished by modification of the above reactions, starting from (**244**) ⟨74CJC843⟩, and 3-methyl-2,6-naphthyridine (**245**) has been obtained starting from (**242**; $R^1 = CO_2H$, $R^2 = CH_2COMe$) ⟨72JCS(P1)705⟩.

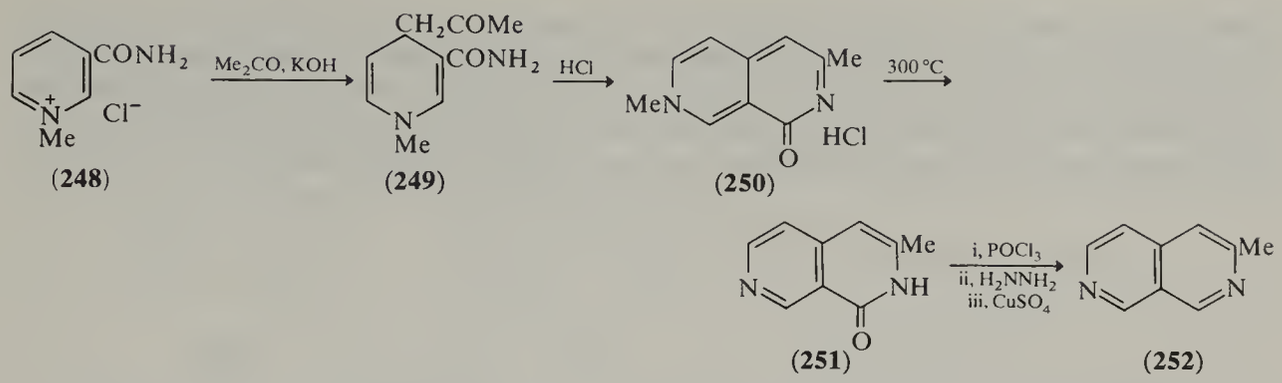


2.11.4.7 Synthesis of 2,7-Naphthyridines

The parent compound (**6**) and its 3-methyl derivative (**246**; R = Me) were both obtained by means of a series of reactions starting from 4-methylnicotinic acid (**247**) ⟨58CPB269⟩.

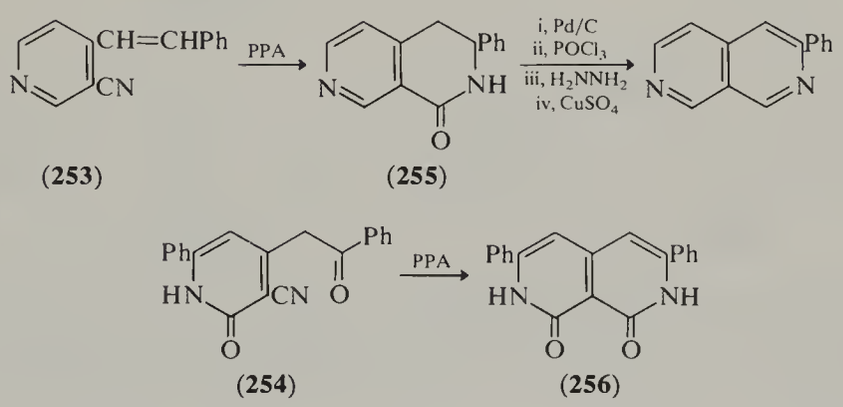


The reaction between nicotinamide methochloride (**248**) and acetone in the presence of base gives compound (**249**) which on acid treatment gives the 2,7-naphthyridine derivative (**250**) ⟨56LA(600)198, 78MI21106⟩. Compound (**250**) had been previously obtained but wrongly reported to be a 1,6-naphthyridine ⟨47JBC(167)151⟩. Conversion of (**250**) into 3-methyl-2,7-naphthyridin-1-one (**251**) took place on sublimation and this was then converted into 3-methyl-2,7-naphthyridine (**252**) by standard procedures ⟨56LA(600)198⟩. Compounds of similar structure to (**250**) have also been obtained by reaction of ketones and other active methylene compounds with *N*-alkylnicotinamides ⟨74JCS(P1)57, 73TL1447⟩.



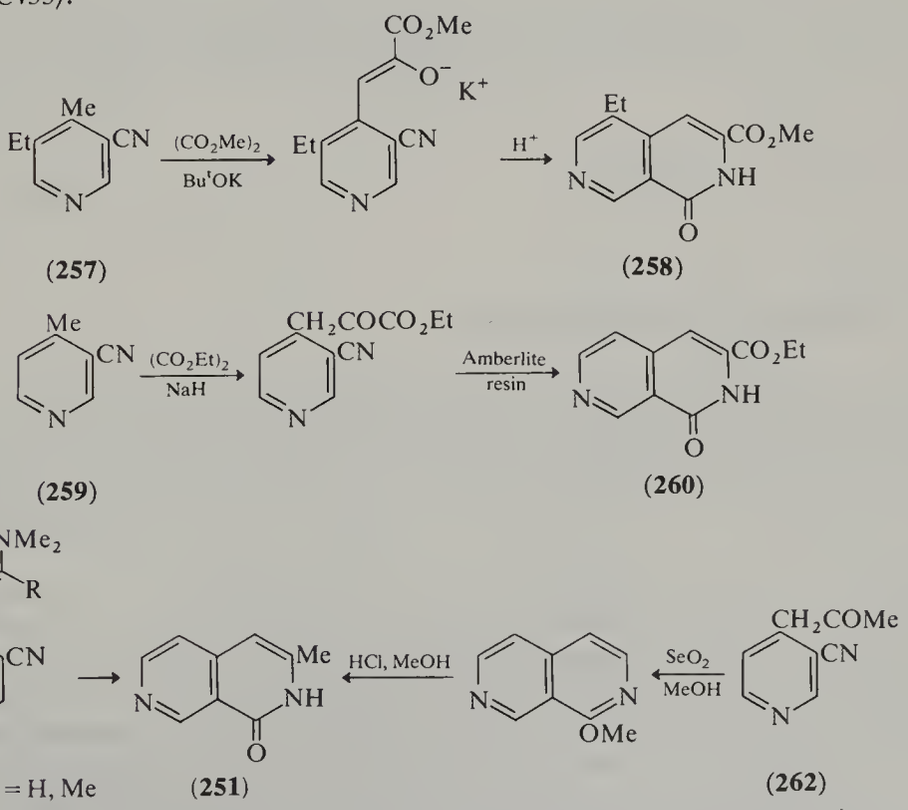
(248) (249) (250) (251) (252)

The intramolecular cyclizations of the cyanopyridines (**253**) and (**254**) using polyphosphoric acid resulted in the formation of the 2,7-naphthyridinones (**255**) and (**256**) which were subsequently converted into the phenyl-substituted 2,7-naphthyridines ⟨64JOC2298, 65JA5198⟩.



(253) (255) (254) (256)

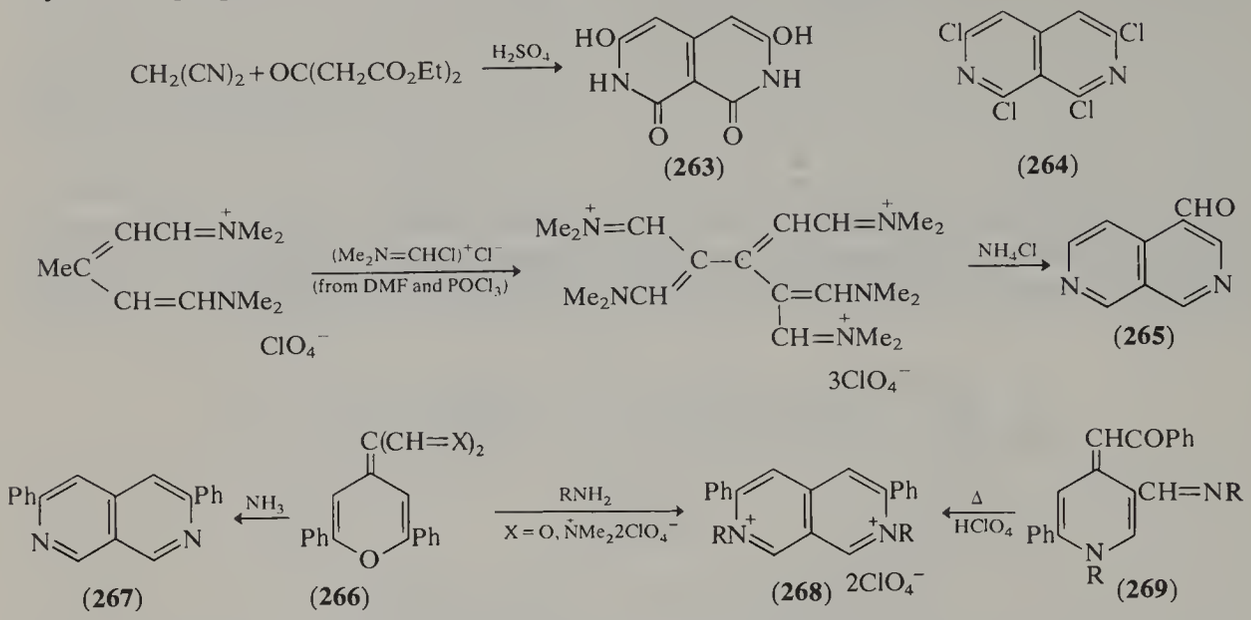
Amongst other syntheses involving 3-cyanopyridines are the following: (a) the condensation under basic conditions of the cyanopyridine (**257**) with dimethyl oxalate gave a product which cyclized on acidification to (**258**) ⟨67JA6741⟩; (b) a similar condensation of the cyanopyridine (**259**) with diethyl oxalate in the presence of sodium hydride gave an intermediate which cyclized to (**260**) on treatment with Amberlite resin ⟨72JCS(P1)2506⟩; (c) cyclization of the enamine (**261**) gave the 2,7-naphthyridinone (**251**), the 1-methoxy derivative of which was also obtained on reaction of the ketone (**262**) with selenium dioxide in methanol ⟨72AJC433⟩.



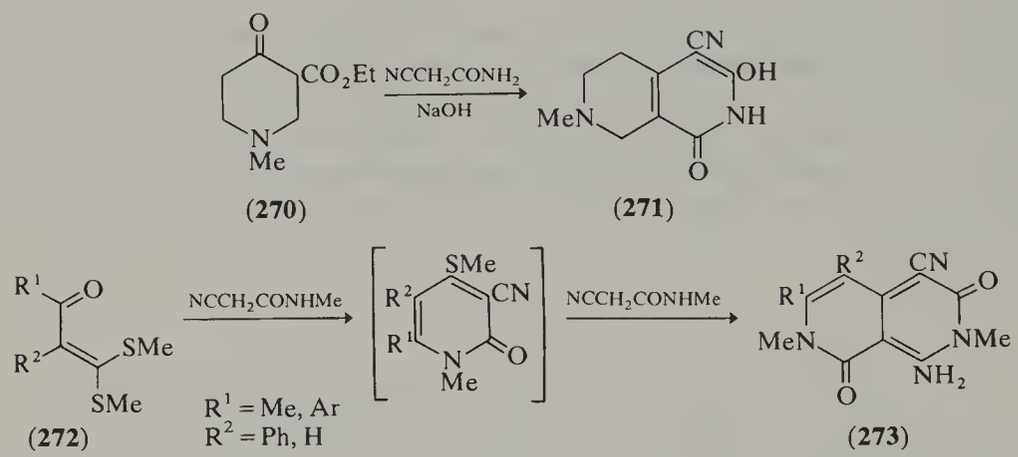
(257) (258) (259) (260) (261) R = H, Me (251) (262)

The condensation product of malononitrile and ethyl acetonedicarboxylate cyclizes in acid conditions to give the 2,7-naphthyridine (**263**), reaction of which with $POCl_3$ gave the

tetrachloro compound (**264**) ⟨60JCS3513⟩. The formation of 2,7-naphthyridine-4-carbaldehyde (**265**) has been achieved *via* the novel cyclization shown ⟨63CCC2040, 66CB2479⟩. Reactions of the pyrone derivatives (**266**) with ammonia or with amines give the 3,6-diphenyl-2,7-naphthyridine (**267**) or the corresponding diquaternary salt (**268**). The latter may also be prepared starting from the pyridine derivative (**269**) ⟨72JHC1229⟩.



The condensation of the *N*-methylpiperidine (**270**) with cyanoacetamide gives the hexahydro-2,7-naphthyridine (**271**) ⟨67AK(26)489⟩, and the reaction between α-oxoketene *S,S*-acetals (**272**) and *N*-methylcyanoacetamide gives the 2,7-naphthyridine derivatives (**273**) ⟨78JCS(P1)554⟩.

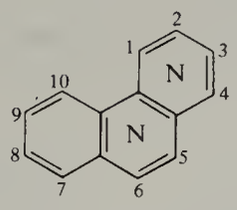


2.11.4.8 Synthesis of Benzonaphthyridines

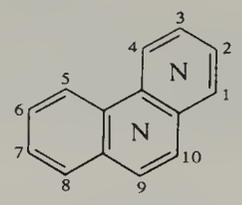
The fusion of a benzene ring to one of the naphthyridine system could result in three possible types of compound, which may be considered as diazaphenanthrenes (**274**), diazaanthracenes (**275**) and diazaphenalenes (**276**). Few of the possible isomers have so far been reported. In the past the diazaphenanthrenes have received the greatest attention, and the benzonaphthyridine review ⟨72MI21104⟩ covers the chemistry of just six members of this group.

Nomenclature in this series, and also for the triaza compounds (the pyridonaphthyridines), is unfortunately in a very confused state. Until the mid-1950s (*i.e.* up to and including the Fifth Cumulative Index), *Chemical Abstracts* used the pyrido-quinoline/-isoquinoline nomenclature; since the adoption of the name naphthyridine they have been called benzonaphthyridines. Both systems use 'regular' numbering schemes, as shown around structure (**274a**). The alternative nomenclature system, defining the compounds as aza-substituted derivatives of phenanthrene, is probably more widely used in practice, and is that adopted in this chapter, and also in the monograph of Van Allan ⟨58HC(12)⟩. The use of this system requires that the irregular numbering system appropriate to phenanthrene (*cf.* **274b**) be

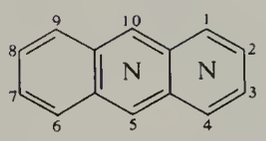
used. Unfortunately, Van Allan and also Thirtle ⟨58HC(12), pp. 165, 320⟩ apply regular numbering to azaphenanthrene names. Curiously, the chapter on the azaanthracenes by Wilson in the same monograph ⟨58HC(12), p. 14⟩ correctly applies anthracene numbering (also irregular; *cf.* **275b**) to these names. As pyridoquinolines (early *Chemical Abstracts*) and as benzonaphthyridines (later *Chemical Abstracts*) the regular numbering (*cf.* **275a**) is appropriate, as it is also when the anthyridine nomenclature is used.



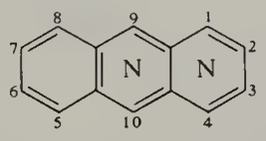
(**274a**) Pyrido(iso)quinoline
Benzonaphthyridine



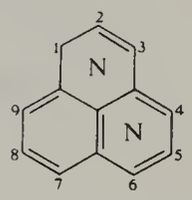
(**274b**) Diazaphenanthrene



(**275a**) Pyrido(iso)quinoline
Benzonaphthyridine



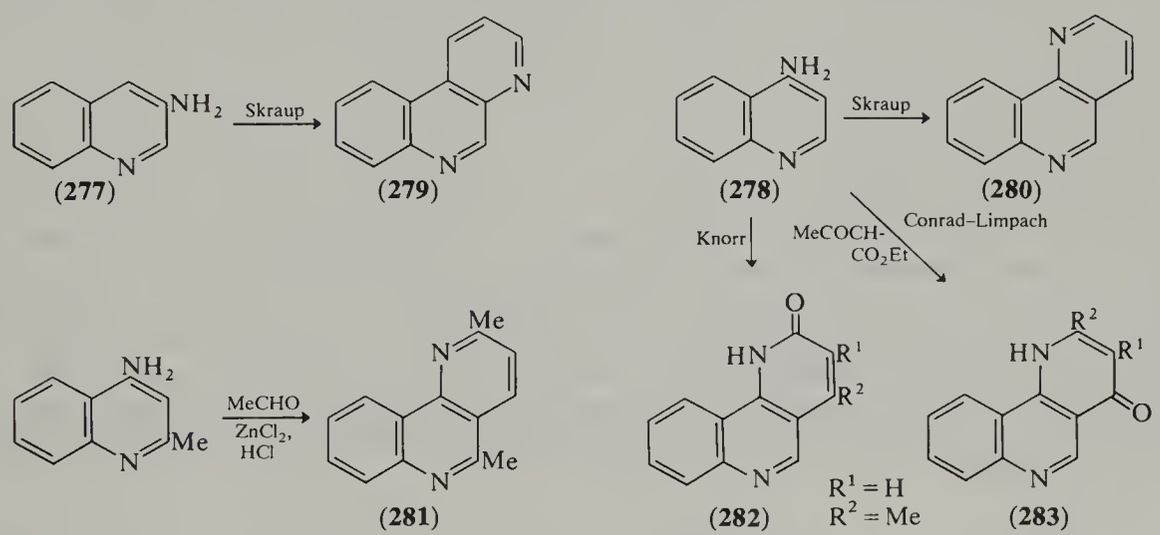
(**275b**) Diazaanthracene



(**276**) Diazaphenalene

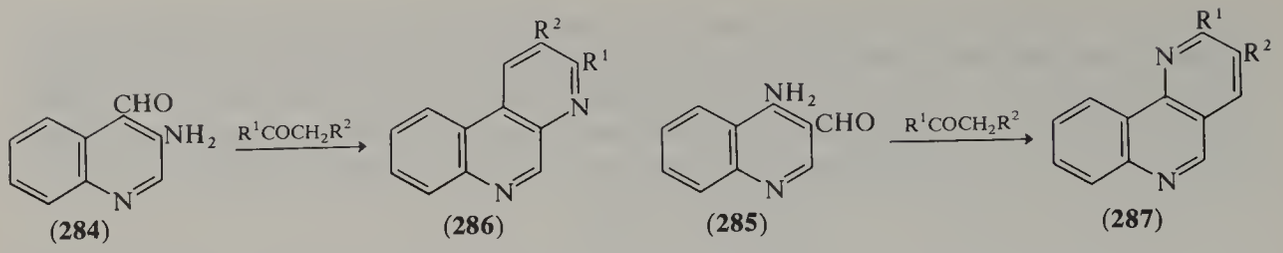
2.11.4.8.1 Synthesis of diazaphenanthrenes

The Skraup synthesis applied to 3- (**277**) and 4-aminoquinolines (**278**) results in the formation of 1,9- (**279**) and 4,9- (**280**) diazaphenanthrenes (these compounds are also described as benzo[*f*][1,7]naphthyridines and benzo[*h*][1,6]naphthyridines respectively) ⟨58JCS828, 67JOC2616, 78MI21105⟩. The corresponding 3- and 4-aminoisoquinolines yield 1,10- and 4,10-diazaphenanthrenes in this reaction ⟨78MI21103⟩. Alkylated derivatives of (**280**), *e.g.* (**281**), have been obtained *via* the Doebner–Miller reaction ⟨58JCS828⟩, whilst reaction of (**278**) with ethyl acetoacetate under Knorr conditions gives compound (**282**; $R^1 = H$, $R^2 = Me$) ⟨50JOC1224⟩. Compound (**278**) also reacts with this ester under Conrad–Limpach conditions to give the isomeric product (**283**; $R^1 = H$, $R^2 = Me$) ⟨50JOC1224⟩. 4-Aminoquinoline (**278**) will react with EMME to give (**283**; $R^1 = CO_2Et$, $R^2 = H$) ⟨50JOC1224⟩.

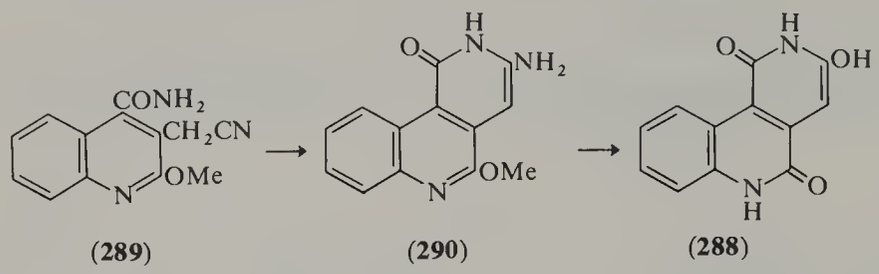


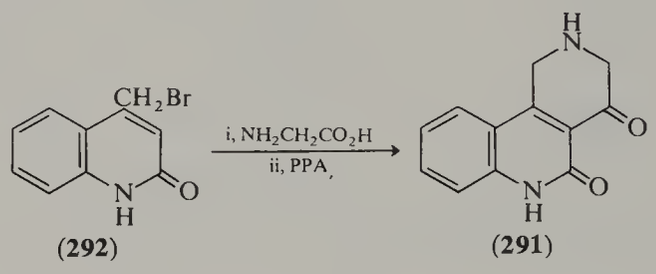
The Friedländer synthesis of quinolines has been adapted to give derivatives of compounds (**279**) and (**280**). The isomeric quinoline aldehydes (**284**) and (**285**) react with various ketones to give (**286**) and (**287**) ⟨77CR(C)(284)459, 82JHC1289⟩. Compound (**286**) has also been obtained starting from the Schiff's base derivative of (**284**) ⟨81JHC925⟩.

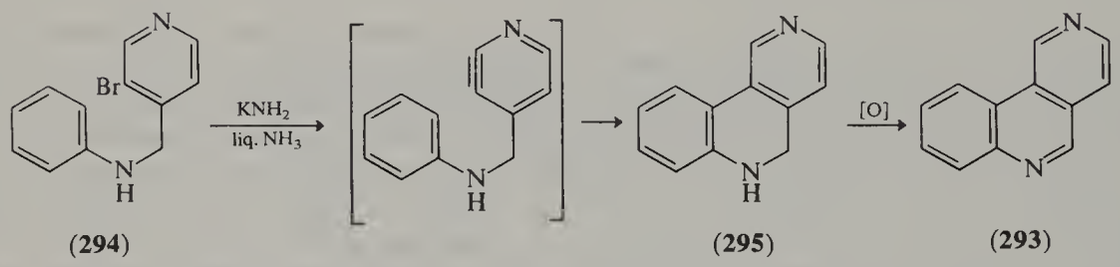
The 3,9-diazaphenanthrene derivative (**288**) has been obtained by hydrolysis of the nitrile (**289**), probably *via* the intermediate (**290**) ⟨67LA(707)242⟩, and compound (**291**) is formed by the condensation of the 2-quinolone (**292**) with glycine followed by cyclization in PPA



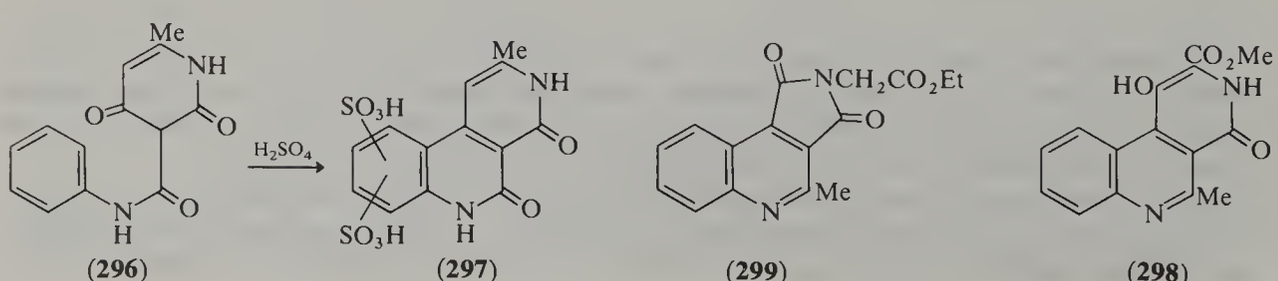
⟨79M913⟩. The parent 3,9-diazaphenanthrene (**293**) has been obtained by cyclization of the amine (**294**) on treatment with potassamide in liquid ammonia followed by oxidation of the dihydro intermediate (**295**) ⟨79PIA(A)191⟩.

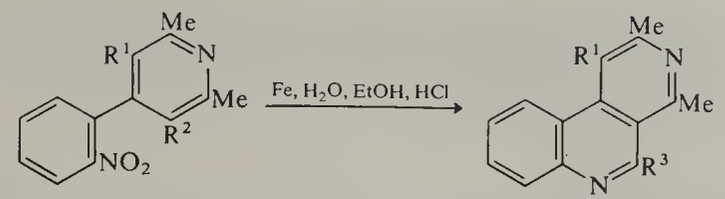






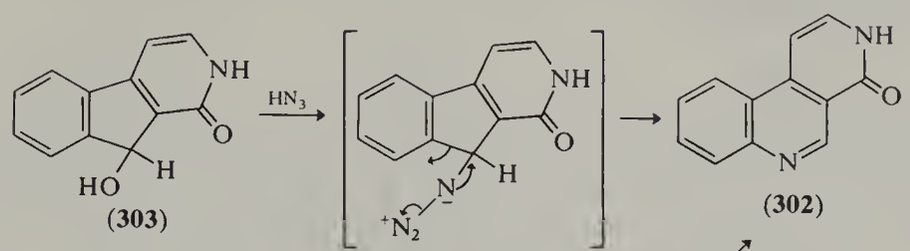
A 2,9-diazaphenanthrene derivative was first obtained by treatment of the amide (**296**) with sulfuric acid, but the position of the sulfonic acid groups in the product (**297**) was not determined ⟨41JIC120⟩. By adaptation of the ring expansion of imides to give quinolines, the 2,9-diazaphenanthrene derivative (**298**) was synthesized from compound (**299**) ⟨41MI21100⟩. A number of different 2,9-diazaphenanthrene derivatives (**300**) have been prepared by reductive cyclization of the pyridines (**301**), which were obtained *via* Hantzsch syntheses ⟨46JCS884, 46JCS888, 53JCS350, 51JCS932⟩. One of the alkaloids present in perennial rye grass is perlolidine, 2,9-diazaphenanthren-1-one, (**302**), for which a number of different syntheses have been reported. Treatment of the tricyclic secondary alcohol (**303**) with hydrazoic acid gives (**302**) *via* a ring expansion reaction ⟨68JA7102⟩. Of the other methods, all but one are multistep processes that require an intermediate of the type (**304**) which is then cyclized in one or more stages ⟨68JA7108, 67JCS(C)859⟩. A more recent method gave (**302**) by cyclization of the quinoline derivative (**305**) ⟨80JHC1761⟩. A synthesis of the parent 2,9-diazaphenanthrene (**306**) involves treatment of the secondary amine (**307**) with potassamide in liquid ammonia; this generates the intermediate pyridyne which cyclizes to (**308**), which can then be oxidized with manganese dioxide to give (**306**) ⟨76TL3207⟩ (*cf.* **294** → **293**).



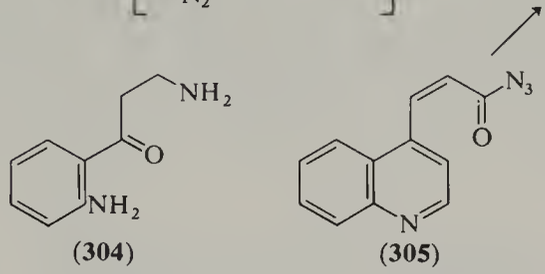


(**301**) $R^1 = CO_2Et$
$R^2 = CO_2Et$, CN, COMe

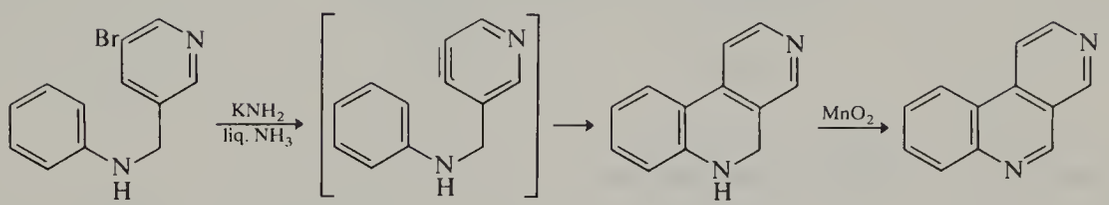
(**300**) $R^1 = CO_2Et$
$R^3 = OH, NH_2$, Me



(**303**) (**302**)

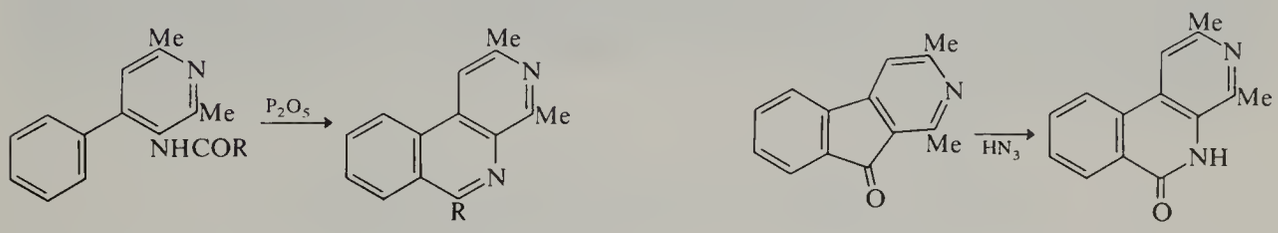


(**304**) (**305**)

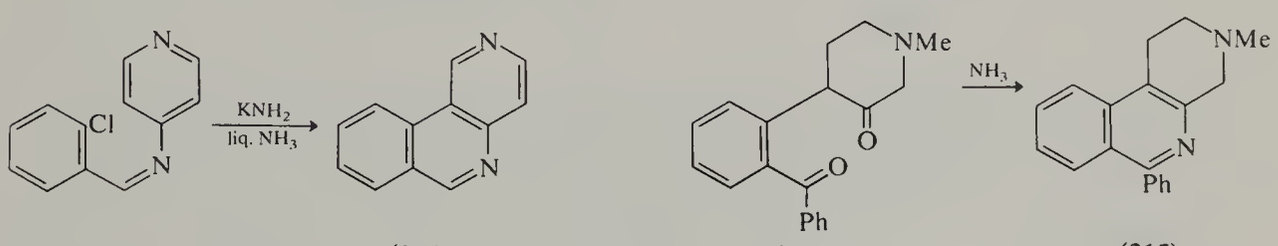


(**307**) (**308**) (**306**)

2,10-Diazaphenanthrenes (**309**; R = Me, Ph) were first obtained by cyclization of the amides (**310**) by heating with phosphorus pentoxide ⟨46JCS200⟩. Ring expansion of the tricyclic ketone (**311**) by heating with hydrazoic acid gave (**312**) ⟨46JCS200, 52JCS3713⟩, and variants of this method have yielded other 2,10-diazaphenanthrenes ⟨42JOC497, 37JA8⟩. Cyclization of the Schiff's base (**313**) to 2,10-diazaphenanthrene (**314**) by treatment with potassamide in liquid ammonia probably proceeds *via* a benzyne intermediate ⟨73T419⟩. The 1,2,3,4-tetrahydro-2,10-diazaphenanthrene (**315**) has been prepared by reaction of the diketone (**316**) with ammonia ⟨55JOC1412⟩.



(**310**) (**309**) R = Me, Ph (**311**) (**312**)

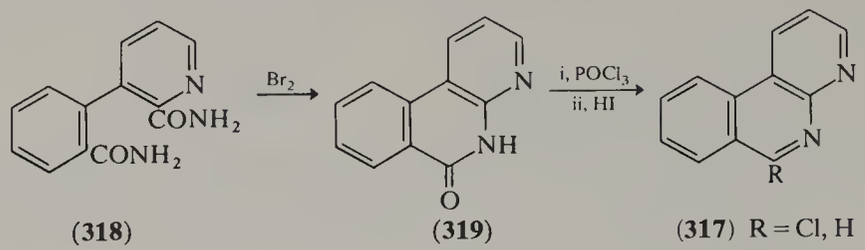


(**313**) (**314**) (**316**) (**315**)

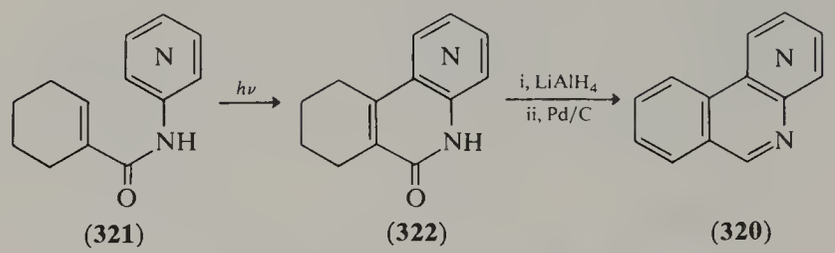
The 1,10-diazaphenanthrene system (**317**; R = H) was first obtained by oxidation of the dicarboxamide (**318**) with bromine to give (**319**) which was then converted to (**317**; R = H) by reduction of the 9-chloro compound (**317**; R = Cl) ⟨02CB296⟩.

A general method for the formation of four isomeric diazaphenanthrenes (**320**) involves the cyclization under photochemical conditions of the enamides (**321**) to give (**322**) which

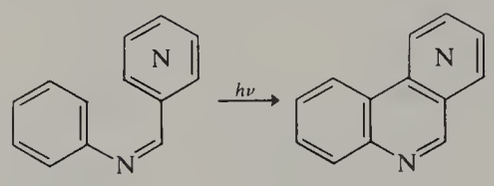
could then be converted into the parent compounds by reduction followed by dehydrogenation ⟨76JCS(P1)1861⟩. The photochemical cyclization of the Schiff's bases (**323**) also yields the diazaphenanthrenes (**324**) ⟨74JHC511⟩.



(**318**) (**319**) (**317**) R = Cl, H



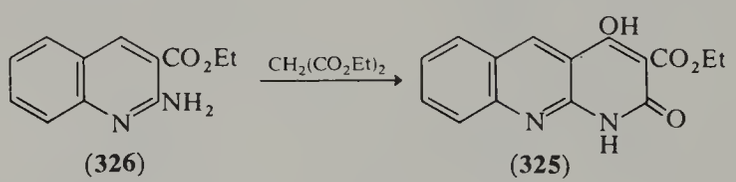
(**321**) (**322**) (**320**)



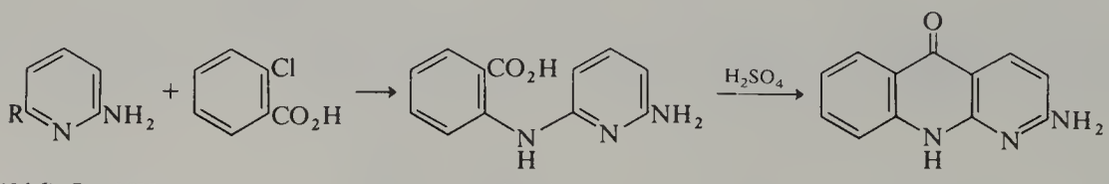
(**323**) (**324**)

2.11.4.8.2 Synthesis of diazaanthracenes

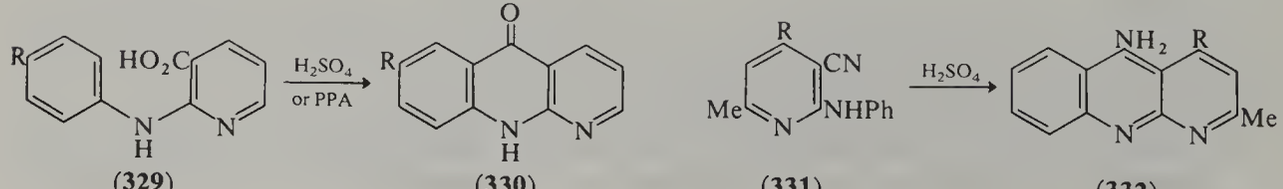
The first 1,9-diazaanthracene (benzo[*b*][1,8]naphthyridine) derivative (**325**) was obtained by reaction of ethyl 2-aminoquinoline-3-carboxylate (**326**) with diethyl malonate ⟨28M(50)144⟩. A second example was prepared from 2,6-diaminopyridine (**216**; R = NH_2) and 2-chlorobenzoic acid which gave compound (**327**), cyclizing to (**328**) in sulfuric acid ⟨39JGU1734⟩. A modification of this method involves cyclization of the 2-aminonicotinic acid derivative (**329**) to (**330**) with either sulfuric acid or polyphosphoric acid ⟨77KGS1241⟩, and similar treatment of the 3-cyanopyridine (**331**) furnished the 10-amino-1,9-diazaanthracene (**332**) ⟨82KGS674⟩. Disubstituted derivatives of 1,9-diazaanthracene (**333**) have been prepared by applying the Friedländer synthesis with 2-aminoquinoline-3-carbaldehyde (**334**) ⟨82JHC1289⟩, and 5,6,7,8-tetrahydro derivatives of (**333**) have also been obtained by this method ⟨77JHC685⟩. The reaction between acetanilide (**335**) and DMF/$POCl_3$ (Vilsmeier conditions) results in a yield of 59% of the 1,9-diazaanthracen-2-one (**336**), probably *via* the intermediate (**337**) ⟨80TL3721⟩.



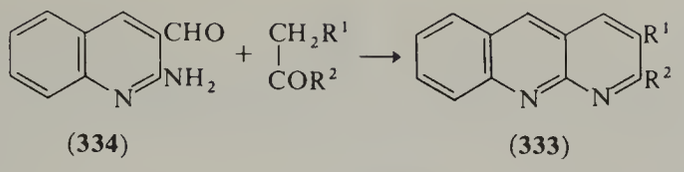
(**326**) (**325**)



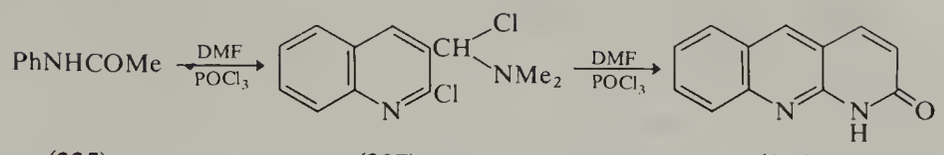
(**216**) R = NH_2 (**327**) (**328**)



(**329**) (**330**) (**331**) (**332**)

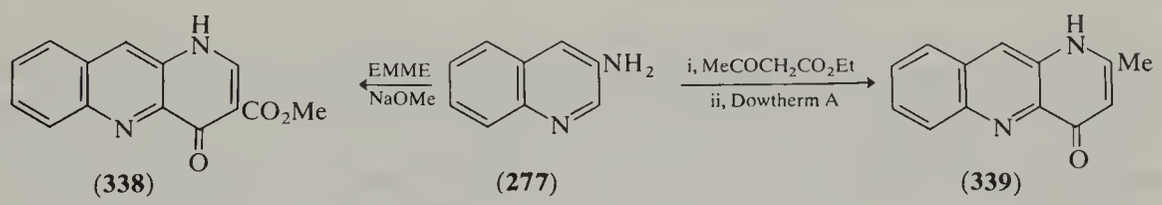


(334) (333)

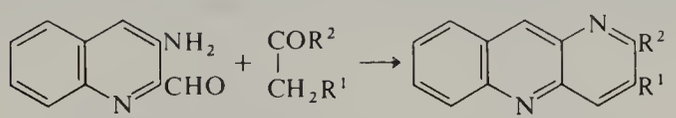


(335) (337) (336)

Whilst the Skraup reaction on 3-aminoquinoline (**277**) gives the diazaphenanthrene (**279**), treatment of (**277**) with diethyl ethoxymethylenemalonate (EMME) gives rise to the 1,10-diazaanthracene derivative (**338**), albeit in lower yield and at a slower rate than in the corresponding reaction with 4-aminoquinoline ⟨50JOC1224⟩. The reaction of (**277**) with ethyl acetoacetate to give the amide (Conrad–Limpach conditions) followed by cyclization in Dowtherm also gives a substituted 1,10-diazaanthracene (**339**) ⟨50JOC1224⟩. The Friedländer synthesis applied to 3-aminoquinoline-2-carbaldehyde (**340**) also provides 1,10-diazaanthracene derivatives (**341**) ⟨82JHC1289⟩. For further details of the chemistry of 1,9- and 1,10-diazaanthracenes see ⟨79MI21102⟩.

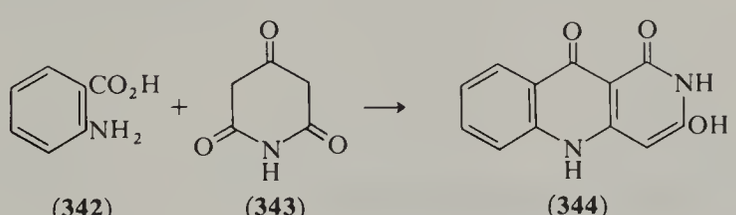


(338) (277) (339)

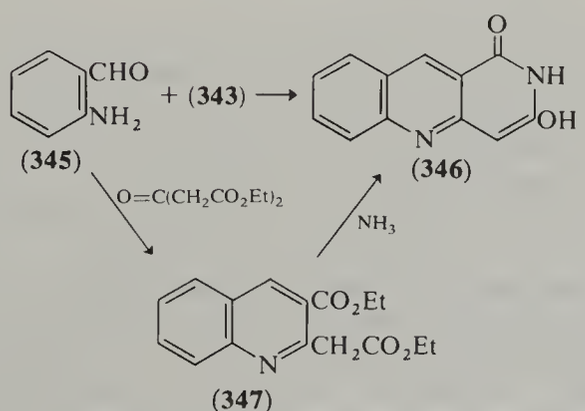


(340) (341)

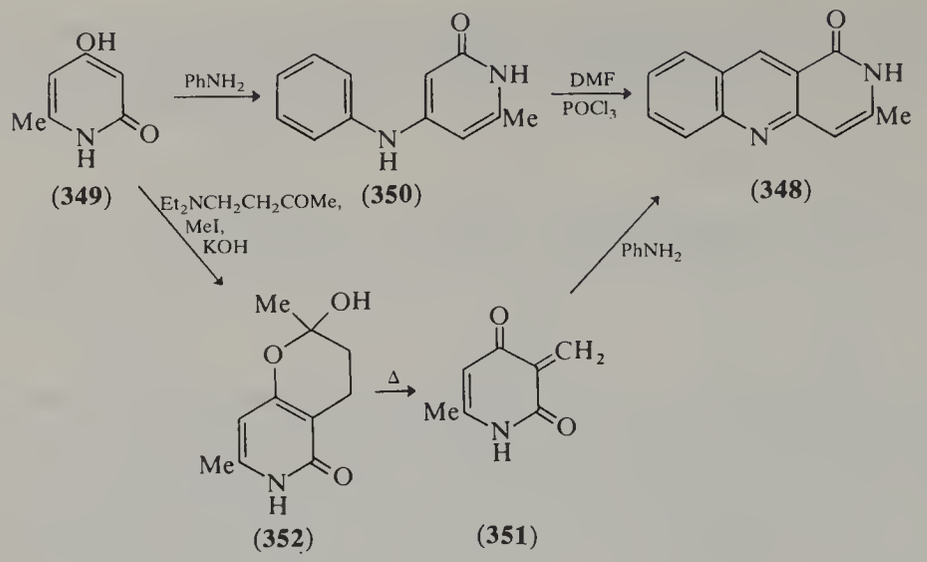
2,10-Diazaanthracene derivatives were first obtained by condensation of anthranilic acid (**342**) with 2,4,6-trioxopiperidine (**343**) to give the 3-hydroxy-2,10-diazaanthracene-1,9-dione (**344**) ⟨16JPR(94)193⟩ and a similar condensation between anthranaldehyde (**345**) and (**343**) gave the analogue (**346**) ⟨19CB484⟩. Compound (**346**) was also obtained by reaction of (**345**) with ethyl acetonedicarboxylate to give the quinoline (**347**) followed by treatment with ammonia ⟨27MI21100⟩. 3-Methyl-2,10-diazaanthracen-1-one (**348**) has been obtained in two different series of reactions which require the same starting material. In one, the pyridine derivative (**349**) reacts with aniline to give (**350**) which cyclizes to (**348**) on treatment with $DMF/POCl_3$ ⟨80JHC245⟩, whilst in the other the quinone methide (**351**), which is generated by heating the pyridone hemiacetal (**352**) derived from (**349**), reacts with aniline to give (**348**) directly ⟨80JCS(P1)522⟩.



(342) (343) (344)

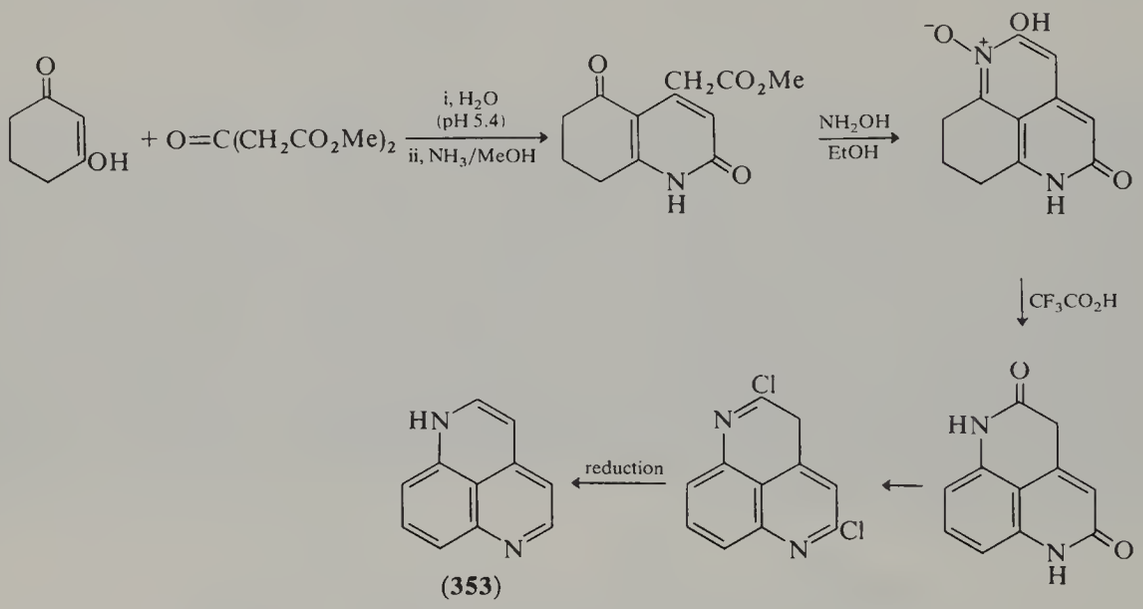


(345) (346) (347)



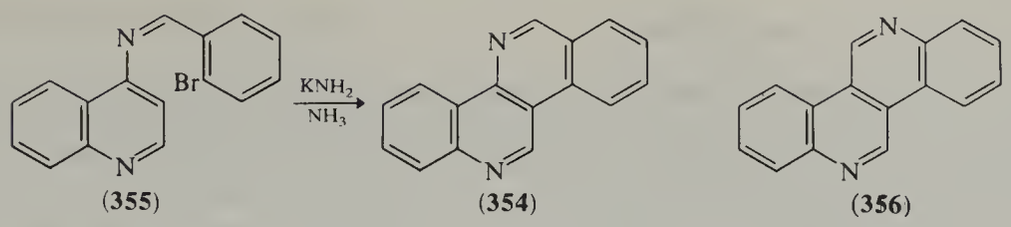
2.11.4.8.3 Synthesis of diazaphenalenes

The first member of the diazaphenalene system (which could be considered to be a benzonaphthyridine) to be synthesized was the 1,6-diazaphenalene (**353**). This was obtained in six steps starting from the reaction of dimethyl acetonedicarboxylate with cyclohexane-1,3-dione. The intermediate steps are shown ⟨78H(9)1561, 79H(12)903⟩. Compound (**353**) has similar chemical and physical properties to those of imidazole. For a full account of the syntheses and reactions of this ring system the review ⟨83H(20)87⟩ should be consulted.

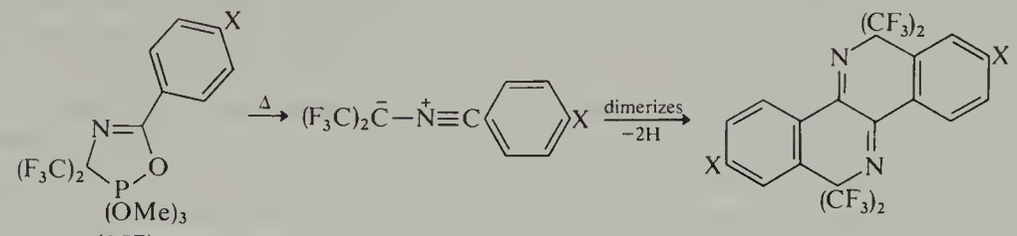


2.11.4.9 Synthesis of Dibenzonaphthyridines

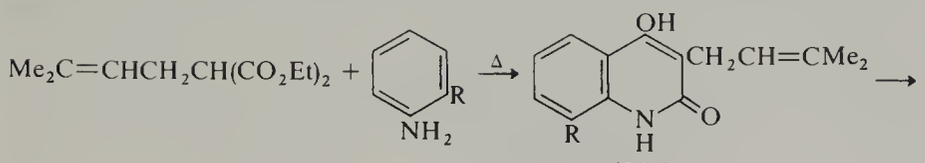
The dibenzo[*c*,*h*][1,6]naphthyridine (**354**) has been synthesized in a reaction similar to those used to obtain benzo-2,6- and benzo-3,6-naphthyridines (*cf.* Section 2.11.4.8.1), by generation of a benzyne intermediate from the Schiff's base (**355**) followed by cyclization. The dibenzo[*c*,*h*][2,6]naphthyridine (**356**) was obtained similarly ⟨78IJC(B)92⟩. Thermolysis of the dihydro-1,4,2-oxazaphosphol-4-enes (**357**) gives the nitrile ylides (**358**) which dimerize to the dibenzo[*c*,*h*][1,5]naphthyridine derivatives (**359**) ⟨81ZN(B)345⟩. The reaction of diethyl 2-(3-methylbut-2-enyl)malonate with anilines gave, in addition to the expected 3-dimethylallyl-4-hydroxyquinolin-2-ones (*e.g.* **360**) a product which oxidized readily to the dibenzo[*b*,*h*][1,6]naphthyridine (**361**) ⟨77JCS(P1)2546⟩. That a necessary intermediate in this reaction is compound (**362**; R = OMe) was shown by reaction of (**362**; R = H) with aniline to give (**361**; R = H) in 36% yield ⟨80JCS(P1)512⟩. The dibenzo[*c*,*h*]-[1,6]naphthyridines (**364**) have been synthesized by heating the Schiff's bases (**365**) ⟨82M751⟩.



(355) (354) (356)



(357) (358) (359)



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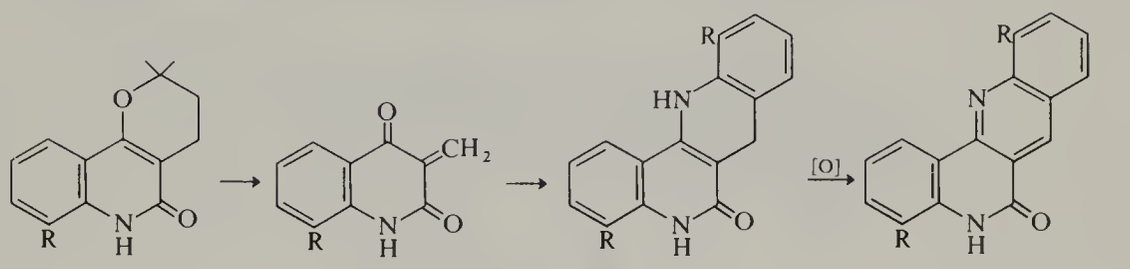
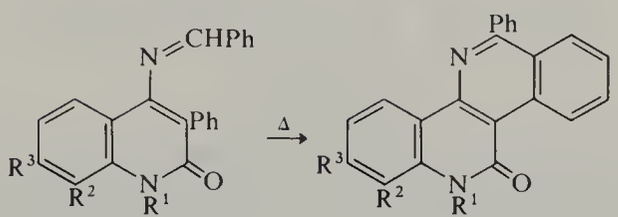


(362) (363) (361) R = OMe

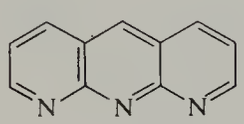


(365) (364)

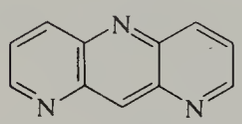
2.11.5 ANTHYRIDINES AND TRIAZAPHENANTHRENES

Of the many possible structures for these compounds few have been synthesized.

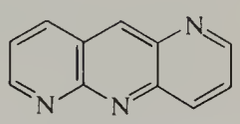
Anthyridines



(366) 1,9,10-Anthyridine
1,8,9-Triazaanthracene

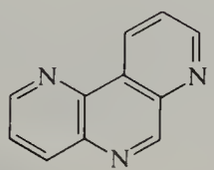


(367) 1,5,9-Anthyridine
1,8,10-Triazaanthracene

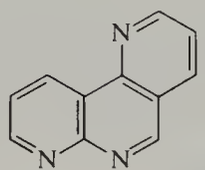


(368) 1,6,10-Anthyridine
1,5,9-Triazaanthracene

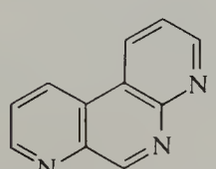
Triazaphenanthrenes



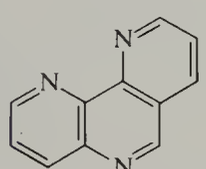
(129) 1,5,9-Triazaphenanthrene



(369) 1,5,10-Triazaphenanthrene



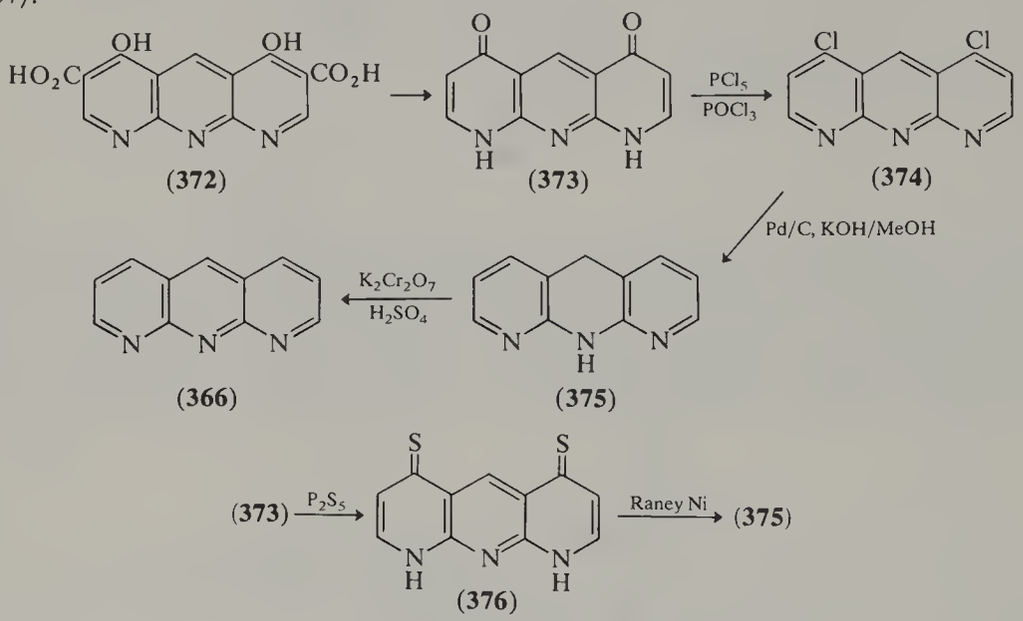
(370) 1,8,9-Triazaphenanthrene



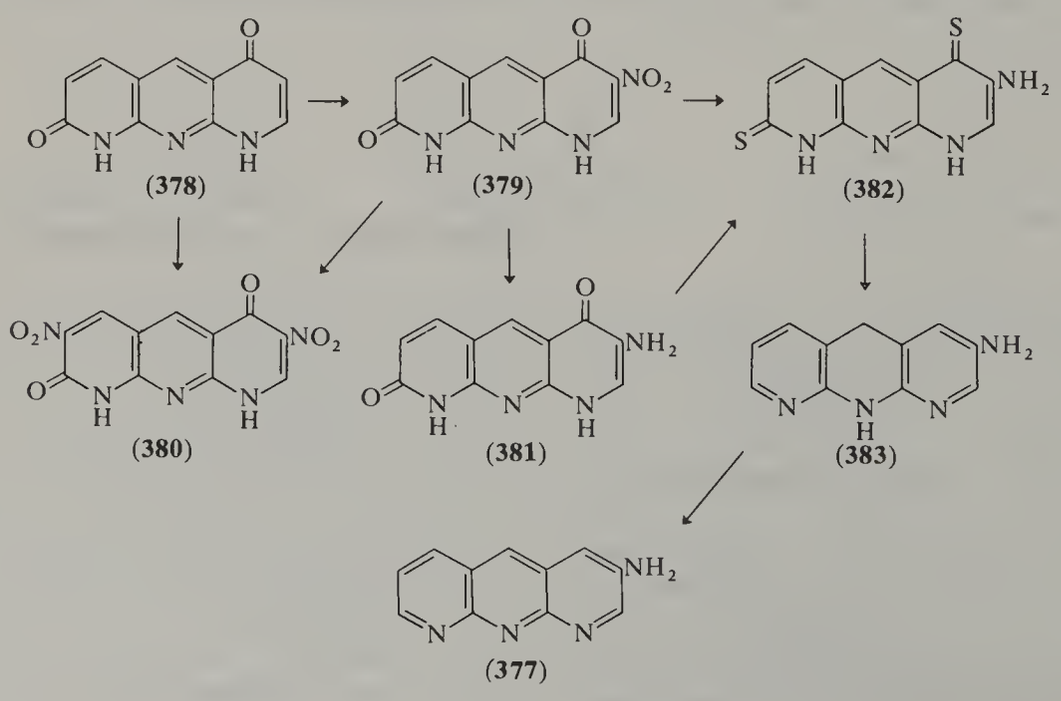
(371) 4,5,9-Triazaphenanthrene

2.11.5.1 Reactivity of Anthyridines

Most of the reactions carried out on anthyridine derivatives have been attempts to synthesize the parent compounds. Thus, treatment of 4,6-dihydroxy-1,9,10-anthyridine-3,7-dicarboxylic acid (**372**) with copper chromite in hot quinoline produces the 4,6-dioxo compound (**373**) ⟨70JHC875⟩. This, with phosphorus pentachloride and phosphorus oxychloride, yields 4,6-dichloro-1,9,10-anthyridine (**374**), which can be converted into the 5,10-dihydroanthyridine (**375**) by Pd/C in potassium hydroxide/methanol or by heating with zinc dust and zinc chloride. The parent 1,9,10-anthyridine (**366**) is formed by treatment of the 5,10-dihydro compound (**375**) with potassium dichromate in sulfuric acid ⟨70JHC875⟩. An alternative route from the 4,6-dioxo compound (**373**) provides higher yields of the anthyridine (**366**) and entails heating (**373**) with phosphorus pentasulfide to give the 4,6-dithioxo analogue (**376**) followed by reaction of this with Raney nickel to produce the dihydroanthyridine (**375**); this could then be oxidized as before to (**366**) ⟨71JHC637⟩.



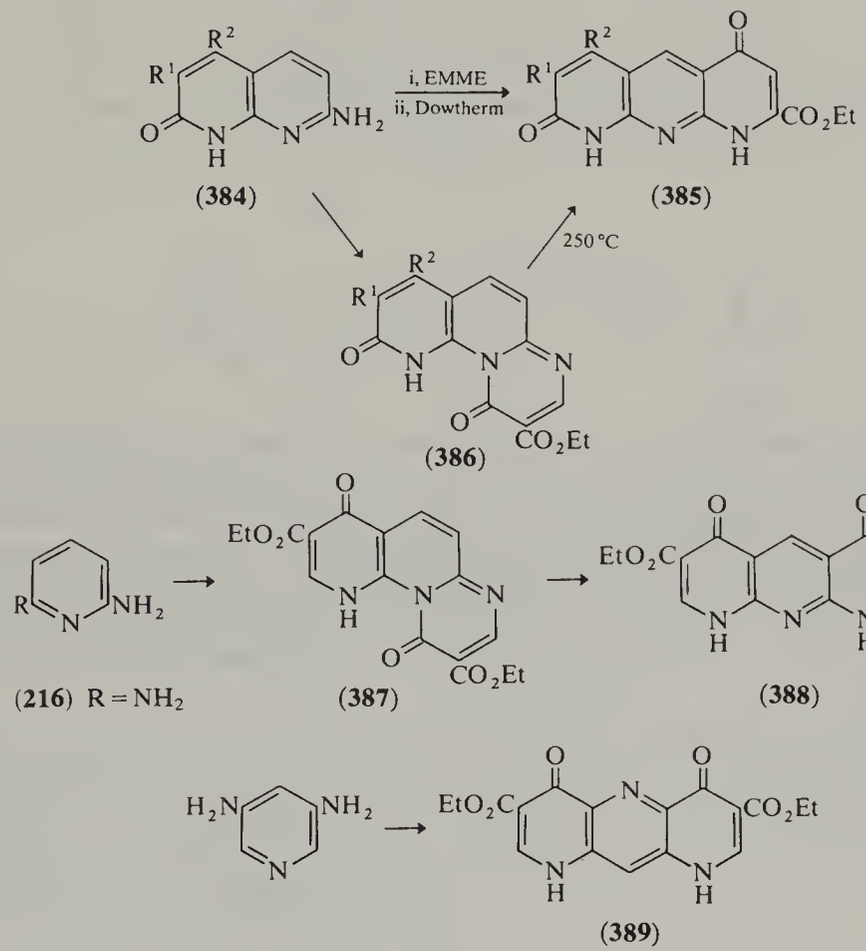
The preparation of 3-amino-1,9,10-anthyridine (**377**) has been carried out by means of the following series of reactions ⟨72JHC801⟩. Nitration of 1,9,10-anthyridine-2,6-dione (**378**) gives a mixture of the 7-nitro (**379**) and the 3,7-dinitro (**380**) compounds. Reduction of the 7-nitro compound (**379**) to the 7-amino-1,9,10-anthyridine-2,6-dione (**381**) can be accomplished using sodium dithionite, but a better method uses phosphorus pentasulfide in pyridine, which gives the sulfur analogue (**382**) of (**381**). Reduction of (**382**) with Raney nickel gives the 3-aminodihydroanthyridine (**383**) which, on heating in nitrobenzene, affords the amino anthyridine (**377**) ⟨72JHC801⟩.



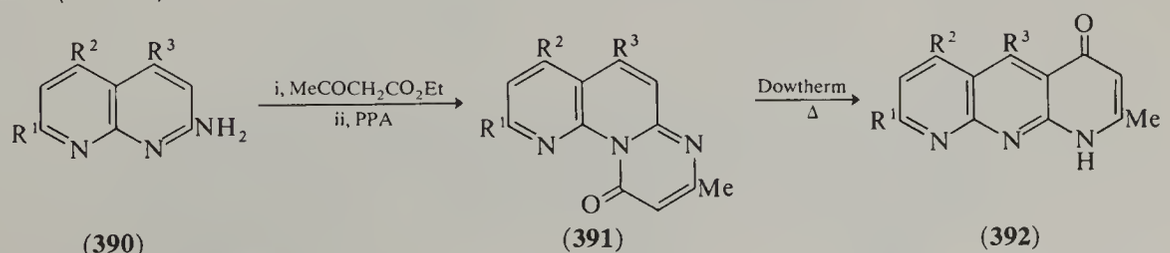
2.11.5.2 Synthesis of Anthyridines

The Skraup reaction, in all of its modifications, has proved to be unsuccessful as a method of obtaining anthyridines. Thus when 2-amino-1,8-naphthyridine (**112**; R = H) and 3-amino-1,5-naphthyridine (**127**) are subjected to the modified Skraup reaction using 'sulfomix' the products are either triazaphenanthrenes or naphthyridine by-products ⟨75MI21103⟩. Similarly 3,5-diaminopyridine (**126**) gives 1,5,9-triazaphenanthrene (**129**) as the only tricyclic product (see Section 2.11.5.3) ⟨67MI21102⟩.

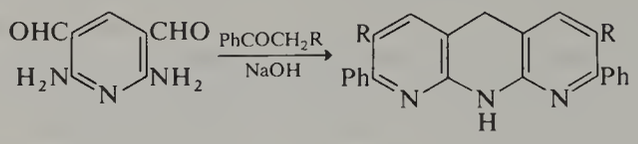
However, more success has been obtained by the use of diethyl ethoxymethylenemalonate (EMME) followed by cyclization in Dowtherm. Substituted 7-amino-1,8-naphthyridin-2-ones (**384**) produce 7-ethoxycarbonyl-1,9,10-anthyridine-2,6-diones (**385**) using this method ⟨67G1274, 69G677⟩. The major reaction product, however, is the pyrimido[1,2-*a*]-[1,8]naphthyridinedione (**386**); it has been shown that (**386**) is converted into (**385**) on heating at 250 °C and is apparently the initial reaction product, the anthyridine only being formed after rearrangement. Similarly, when 2,6-diaminopyridine (**216**; R = NH_2) is treated with EMME followed by heating in Dowtherm, the initially obtained pyrimido[1,8]naphthyridine (**387**) rearranges to give the anthyridine derivative (**388**) ⟨70JHC875, 77JCS(P1)789⟩. The isomeric 3,5-diaminopyridine (**126**) also undergoes reaction with EMME/Dowtherm to give 3,7-diethoxycarbonyl-1,5,9-anthyridine-4,6-dione (**389**) ⟨78BAP509⟩.



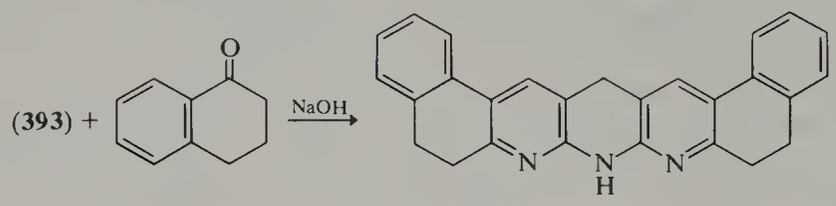
Carboni and co-workers have used 1,3-dicarbonyl compounds to cyclize a large variety of aminonaphthyridines ⟨66G1443, 67G1262, 69G677⟩. The use of ethyl acetoacetate on 2-aminonaphthyridines (**390**) followed by polyphosphoric acid or Dowtherm treatment produces oxopyrimidonaphthyridines (**391**) which can be rearranged to the isomeric 1,8,9-anthyridines (**392**). The products obtained from diethyl acetonedicarboxylate are very similar ⟨69G677⟩.



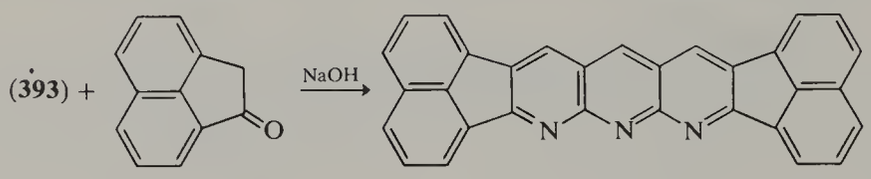
The Friedländer condensation of 2,6-diaminopyridine-3,5-dicarbaldehyde (**393**) with various ketones has been reported ⟨77JOC3410⟩. Reaction of the aldehyde with acetophenone, with deoxybenzoin and with α-tetralone generates the 5,10-dihydro-1,9,10-anthyridine derivatives (**394**; R = H), (**394**; R = Ph) and (**395**) respectively, whilst with acenaphthenone the nonacyclic anthyridine (**396**) is obtained. The condensation between 2-amino-3-ethoxycarbonyl-1,8-naphthyridine (**225**) and alkyl carboxylates under basic conditions produces 4-hydroxy-1,9,10-anthyridin-2-ones (**397**) ⟨79BAP571⟩.



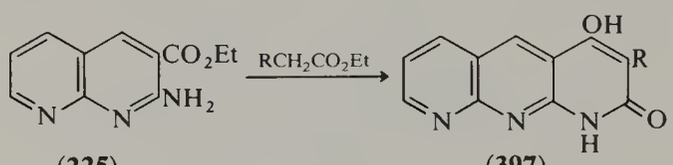
(**393**) (**394**) R = H, Ph



(**395**)

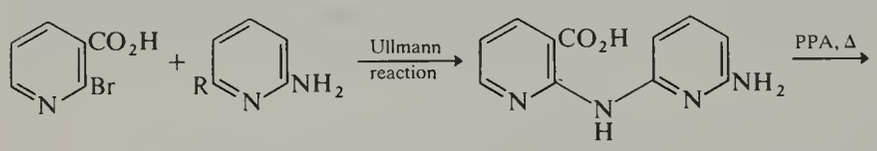


(**396**)

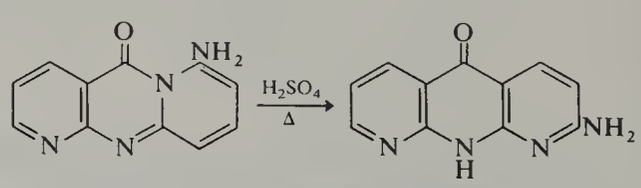


(**225**) (**397**)

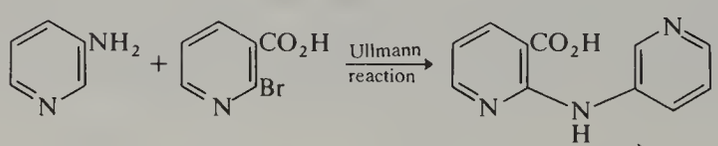
The Ullmann reaction between 2-bromonicotinic acid (**398**) and 2,6-diaminopyridine (**216**; R = NH_2) gives 6′-amino-2,2′-dipyridylamine-3-carboxylic acid (**399**); this on heating in PPA cyclizes to give the dipyridopyrimidine (**400**) which in hot concentrated sulfuric acid rearranges to 2-amino-1,8,9-anthyridin-2-one (**401**) ⟨69JHC369⟩. A similar Ullmann reaction between 3-aminopyridine and (**398**) gives the dipyridylamine (**402**) which on heating in an $AlCl_3$/NaCl melt at 260 °C gives the 1,6,9-anthyridin-5-one (**403**). Successive treatment of (**403**) with zinc and then with Pd/C gave the parent anthyridine (**368**) ⟨78MI21103⟩.



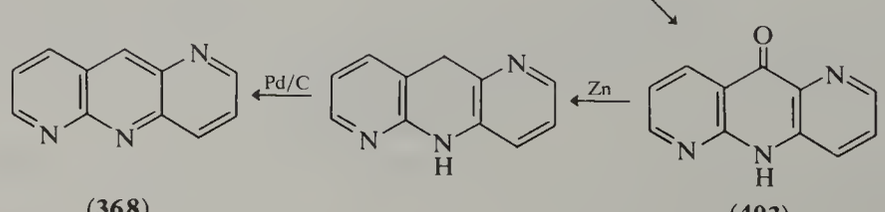
(**398**) (**216**) R = NH_2 (**399**)



(**400**) (**401**)



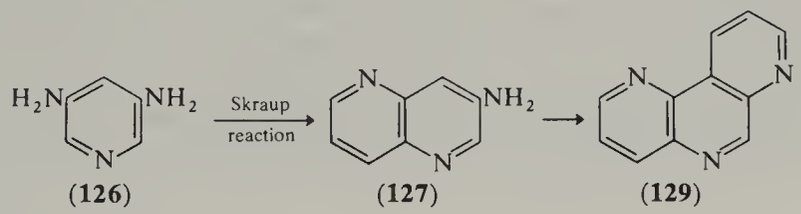
(**125**) (**398**) (**402**)



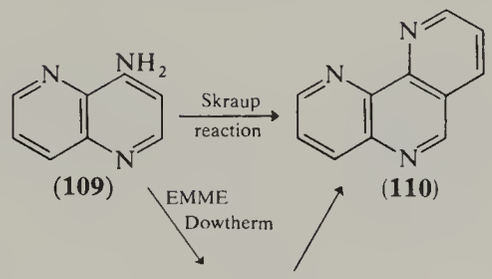
(**368**) (**403**)

2.11.5.3 Synthesis of Triazaphenanthrenes

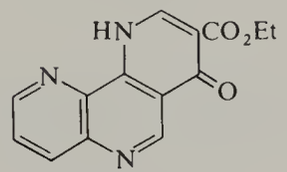
As mentioned in Section 2.11.5.2, the Skraup reaction in its modified 'sulfo-mix' form has proved successful for the synthesis of triazaphenanthrenes; 3-amino-1,5-naphthyridine (**127**) gives 1,5,9-triazaphenanthrene (**129**) and the isomer 4-amino-1,5-naphthyridine (**109**) produces 4,5,9-triazaphenanthrene (**110**). Compound (**129**) has also been obtained starting from 3,5-diaminopyridine (**126**) ⟨67MI21102, 72JHC801, 75YZ1492⟩. The reaction between 4-amino-1,5-naphthyridine (**109**) and EMME/Dowtherm gives the 4,5,9-triazaphenanthrenone (**404**) which was converted into the parent compound (**110**) by standard procedures ⟨59JA6297⟩. A similar reaction on 3-amino-1,8-naphthyridine (**405**) gave the 1,8,9-triazaphenanthren-4-one derivative (**406**) ⟨78YZ1279⟩.



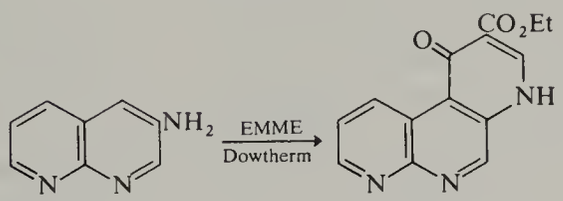
(126) (127) (129)



(109) (110)

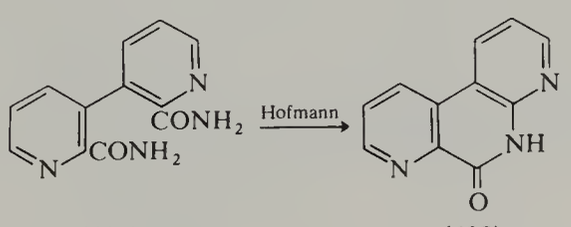


(404)

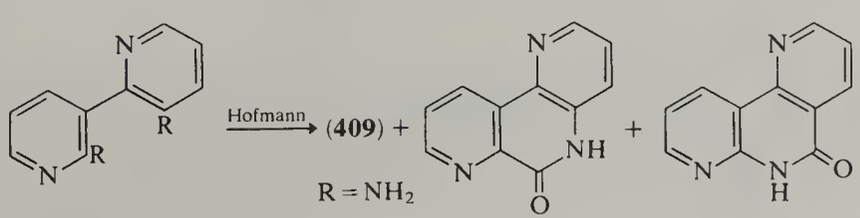


(405) (406)

A number of triazaphenanthrenes have been obtained as by-products in the preparation of aminobipyridyls. The Hofmann degradation of the bipyridyl (**407**) resulted in the formation of 1,8,9-triazaphenanthren-10-one (**408**) as a minor product ⟨35MI21100⟩ and a similar reaction on the substituted bipyridyl (**409**; R = $CONH_2$) gave the main product (**409**; R = NH_2) together with 1,5,9-triazaphenanthren-10-one (**410**) and 1,5,10-triazaphenanthren-9-one (**411**) ⟨34MI21100⟩.



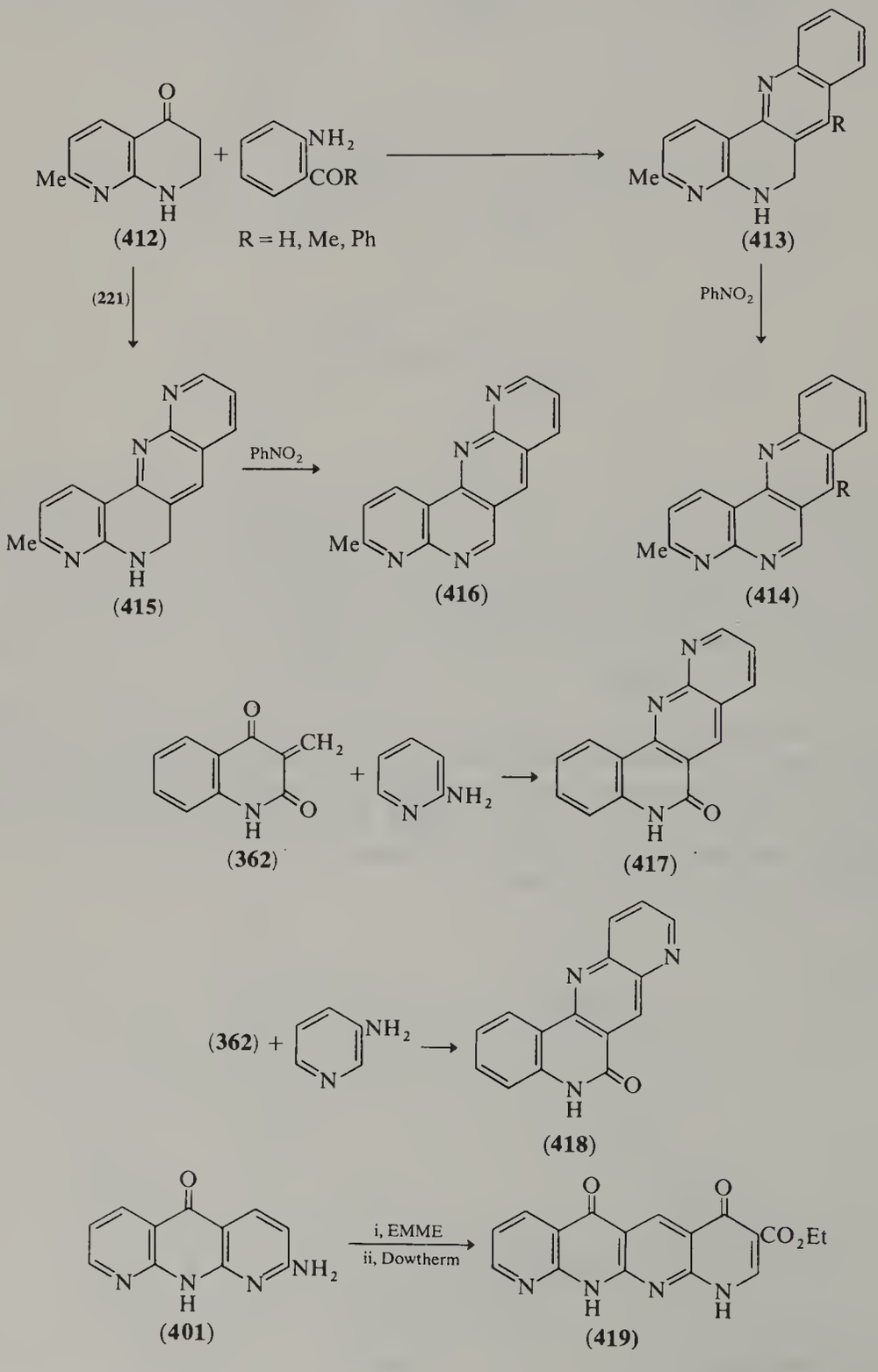
(407) (408)



(409) R = $CONH_2$ (410) (411)

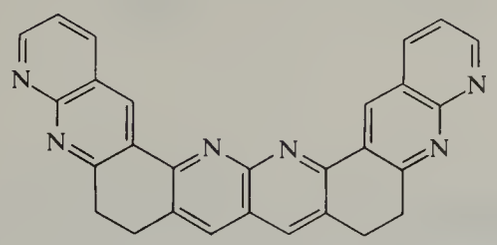
2.11.5.4 Miscellaneous Syntheses

The Friedländer synthesis of quinolines has been adapted for the preparation of tetracyclic triaza and tetraaza compounds. The reaction between 4-oxo-7-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine (**412**) and 2-aminobenzaldehyde gave the 4,5,12-triazabenz[*a*]anthracene (**413**) (named as a quino[3,2-*c*][1,8]naphthyridine by the authors). The compound could be converted into the fully aromatic compound (**414**) by dehydrogenation with nitrobenzene ⟨79JHC169⟩. Further examples of the formation of this ring system were obtained when the aminobenzaldehyde was replaced with 2-aminoacetophenone and with 2-aminobenzophenone ⟨80JHC1225⟩. A further modification was obtained by using 2-aminonicotinaldehyde (**221**), when the product was the [1,8]naphthyrido[3,2-*c*]-[1,8]naphthyridine (**415**) which was aromatized to (**416**) ⟨81JHC1007⟩. The reaction between the quinolone (**362**; R = H) and aniline to give the dibenzo-1,6-naphthyridine (**363**; R = H) has been modified to obtain benzanthyridines. Replacement of the aniline in the above reaction with 2-aminopyridine gave rise to a low yield of compound (**417**), and replacement with 3-aminopyridine gave the isomeric product (**418**), again in low yield ⟨80JCS(P1)512⟩.

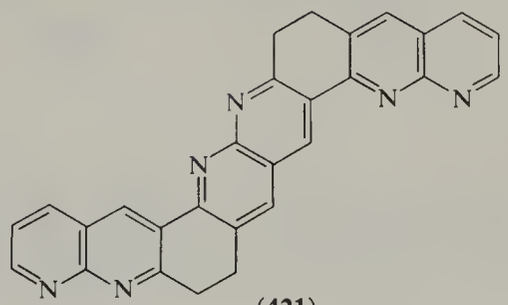


The formation of a linear tetraaza tetracyclic compound was accomplished when the amino-1,8,9-anthyridinone (**401**) was reacted with EMME and the product heated in Dowtherm to give the tetraazanaphthacene (**419**) ⟨74FES366⟩.

The possibility of regioselective angular fusion has been demonstrated in the annelation of two benzo[*b*][1,8]naphthyridine units on to a 1,8-naphthyridine nucleus, leading to three isomeric octacyclic compounds ⟨79JOC531⟩. The condensation between two molecules of 2-aminonicotinaldehyde, two of cyclohexane-1,3-dione and one of 4-aminopyrimidine-5-carbaldehyde gave a mixture of the three isomeric products (**420**), (**421**) and (**422**).



(420)



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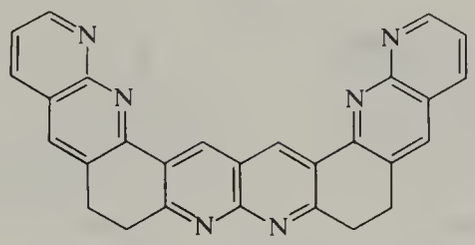
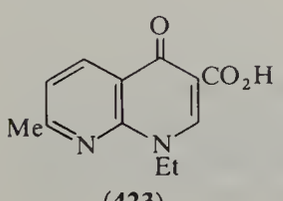


(422)

2.11.6 USEFUL AND NATURALLY OCCURRING NAPHTHYRIDINES

Since the discovery in 1962 that 1-ethyl-3-carboxy-4-oxo-7-methyl-1,4-dihydro-1,8-naphthyridine (nalidixic acid; **423**) is a powerful antibacterial agent, numerous publications have appeared describing its derivatives, detection and physiological and chemical properties (for a list of references the review ⟨70AHC(11)123⟩ should be consulted). A detailed review of the development of antibacterial agents of the nalidixic acid type ⟨77MI21100⟩ and a discussion of its mechanism of action ⟨80MI21101⟩ are particularly valuable. Several 1,5-, 1,6-, 1,7- and 1,8-naphthyridines have been screened for antimalarial activity, some activity being shown in 1,7-naphthyridine analogues of chloroquine ⟨68JMC164⟩. The benzo-1,5-naphthyridine (**424**), which has shown significant activity against chloroquine-resistant strains of *Plasmodium falciparum* ⟨79MI21105⟩, has been given the name pyronaridine.

Other 1,5-naphthyridine derivatives (**425**) and (**426**) have some antitubercular and antidysenteric activity ⟨75MI21103⟩, and 2-methyl-1,5-naphthyridine has some insecticidal activity against *Musca domestica* ⟨76CPB1813⟩. Of the 1,6-naphthyridines, the *N*-oxides (**427**), (**428**) and (**429**) have some general antibacterial activity ⟨69YZ1260⟩, the 5-oxo compound (**430**) shows some insecticidal action against *Nepotettix cincticeps* ⟨76CPB1813⟩, and the tetrahydro derivatives (**431**) show some muscle relaxant activity ⟨82FRP2492825⟩. Variously substituted 1,7-naphthyridines have been shown to possess activity as antifungal and antiviral agents, as antiobesity agents, in the treatment of thrombosis, as hypotensives, and as insecticides ⟨82H(19)363⟩, whilst 1,8-naphthyridines have demonstrated antithrombic activity, *e.g.* (**432**) ⟨76FES175⟩, and anticonvulsant behavior, *e.g.* (**433**) ⟨75FES237⟩. Certain



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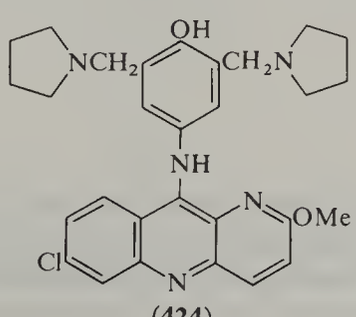

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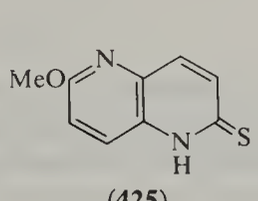

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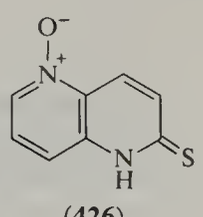
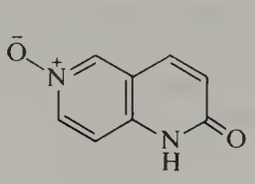


(426)

1,8-naphthyridin-4-one hydrazones (**434**) exhibit a marked hypotensive activity ⟨82MI21101⟩, whilst the 1,8-naphthyridin-2-ones (**435**) have the property of inhibiting gastric acid secretion ⟨79JMC301⟩. Other uses of naphthyridines are as analytical reagents, as antioxidants, as dyestuffs, and as polymer constituents ⟨70AHC(11)123⟩.



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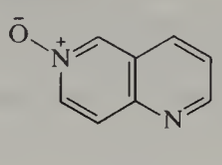

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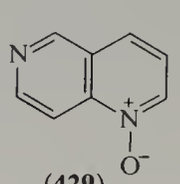

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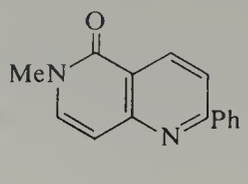

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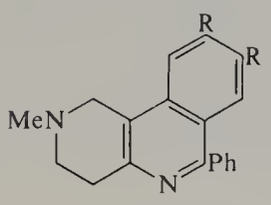

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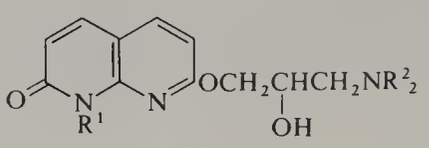

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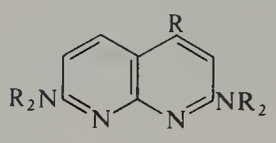

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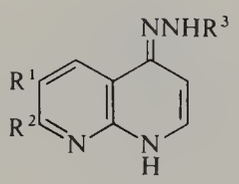

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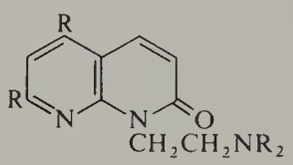
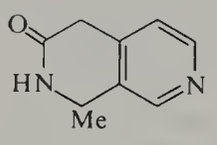


(**435**)

Whilst many alkaloids contain the pyridine ring system, the combination of two pyridine rings as exemplified in the naphthyridines is rather uncommon in nature. The alkaloid jasminine (**436**), a 2,7-naphthyridine derivative, has been isolated from *Jasminium* species ⟨68AJC1321⟩ whilst 4-methyl-2,6-naphthyridine (**437**) occurs in the aerial parts of *Antirrhinum majus* and *aronticus* ⟨71P2849⟩.



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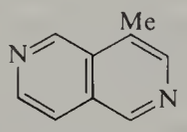

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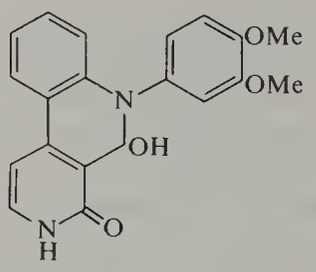
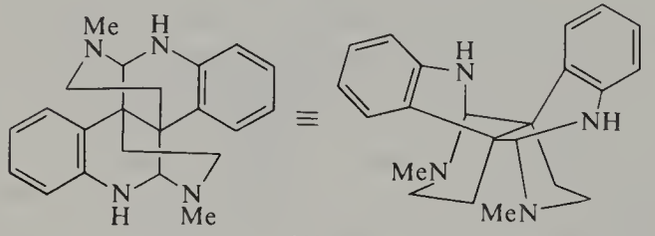


(**438**)



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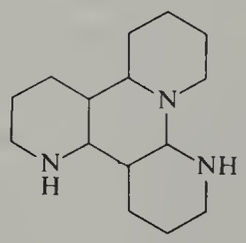
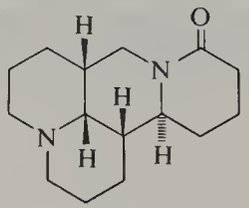
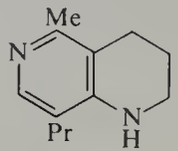


(**440**)



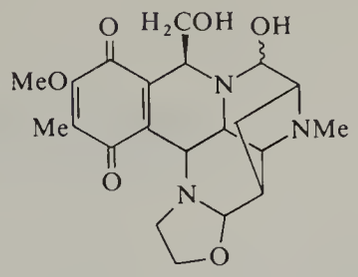
(**441**)



(**442**)

The alkaloids of perennial rye grass, perloline (**438**) and perlolidine (**302**), have been shown to be benzo[*f*][2,7]naphthyridine derivatives ⟨66JCS(B)454⟩, whilst degradation of calycanthine (**439**) affords calycanine or dibenzo[*c*,*h*][2,6]naphthyridine (**356**), the structure of which was proven by an unequivocal synthesis from leucoisoindigo ⟨60MI21100⟩. A number

of alkaloids isolated from *Haloxylon salicornicum* have the basic skeleton (**440**) which can be considered to be derived from either 1,6- or 1,8-naphthyridine ⟨67MI21100⟩, and the lupin alkaloid matrine (**441**) is also a 1,6-naphthyridine derivative; indeed, one of its degradation products is 5-methyl-8-propyl-1,2,3,4-tetrahydro-1,6-naphthyridine (**442**) ⟨56CPB257⟩.



(**443**)

(**444**)

The broad spectrum antibiotic naphthyridomycin (**443**), isolated from *Streptomyces lusitanus*, can be considered to be a derivative of 1,5-naphthyridine ⟨75MI21101⟩, as is the β-lactam antibiotic apalcillin (**444**) ⟨80YZ49⟩.

References

EXPLANATION OF THE REFERENCE SYSTEM

Throughout this work, 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 the Introduction (Chapter 1.01). 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 journals which have been assigned codes is given (in alphabetical order) together with their codes immediately following these notes. Journal names are abbreviated throughout by the CASSI (Chemical Abstracts Service Source Index) system.
2. A list of journal codes in alphabetical order, together with the journals to which they refer, is given on the end papers of each volume.
3. Each volume contains all the references cited *in that volume*; no separate lists are given for individual chapters.
4. 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.
5. 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.*
6. For non-twentieth century references the year is given in full in the code.
7. 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.
8. 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.
9. Patents are assigned appropriate three letter codes.
10. Frequently cited books are assigned codes, but the whole code is now prefixed by the letter 'B-'.
11. Less common journals and books are given the code 'MI' for miscellaneous.
12. 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.*

Journals

Acc. Chem. Res.	ACR
Acta Chem. Scand., Ser. B	ACS(B)
Acta Chim. Acad. Sci. Hung.	ACH
Acta Crystallogr., Part B	AX(B)
Adv. Phys. Org. Chem.	APO
Agric. Biol. Chem.	ABC

Angew. Chem.	AG
Angew. Chem., Int. Ed. Engl.	AG(E)
Ann. Chim. (Rome)	AC(R)
Ann. N.Y. Acad. Sci.	ANY
Arch. Pharm. (Weinheim, Ger.)	AP
Ark. Kemi	AK
Arzneim.-Forsch.	AF
Aust. J. Chem.	AJC
Biochem. Biophys. Res. Commun.	BBR
Biochemistry	B
Biochem. J.	BJ
Biochim. Biophys. Acta	BBA
Br. J. Pharmacol.	BJP
Bull. Acad. Pol. Sci., Ser. Sci. Chim.	BAP
Bull. Acad. Sci. USSR, Div. Chem. Sci.	BAU
Bull. Chem. Soc. Jpn.	BCJ
Bull. Soc. Chim. Belg.	BSB
Bull. Soc. Chim. Fr., Part 2	BSF(2)
Can. J. Chem.	CJC
Chem. Abstr.	CA
Chem. Ber.	CB
Chem. Heterocycl. Compd. (Engl. Transl.)	CHE
Chem. Ind. (London)	CI(L)
Chem. Lett.	CL
Chem. Pharm. Bull.	CPB
Chem. Rev.	CRV
Chem. Scr.	CS
Chem. Soc. Rev.	CSR
Chem.-Ztg.	CZ
Chimia	C
Collect. Czech. Chem. Commun.	CCC
Coord. Chem. Rev.	CCR
C.R. Hebd. Seances Acad. Sci., Ser. C	CR(C)
Cryst. Struct. Commun.	CSC
Diss. Abstr. Int. B	DIS(B)
Dokl. Akad. Nauk SSSR	DOK
Experientia	E
Farmaco Ed. Sci.	FES
Fortschr. Chem. Org. Naturst.	FOR
Gazz. Chim. Ital.	G
Helv. Chim. Acta	HCA
Heterocycles	H
Hoppe-Seyler's Z. Physiol. Chem.	ZPC
Indian J. Chem., Sect. B	IJC(B)
Inorg. Chem.	IC
Int. J. Sulfur Chem., Part B	IJS(B)
Izv. Akad. Nauk SSSR, Ser. Khim.	IZV
J. Am. Chem. Soc.	JA
J. Biol. Chem.	JBC
J. Chem. Phys.	JCP
J. Chem. Res. (S)	JCR(S)
J. Chem. Soc. (C)	JCS(C)
J. Chem. Soc., Chem. Commun.	CC
J. Chem. Soc., Dalton Trans.	JCS(D)
J. Chem. Soc., Faraday Trans. 1	JCS(F1)
J. Chem. Soc., Perkin Trans. 1	JCS(P1)
J. Gen. Chem. USSR (Engl. Transl.)	JGU
J. Heterocycl. Chem.	JHC
J. Indian Chem. Soc.	JIC
J. Magn. Reson.	JMR

J. Med. Chem.	JMC
J. Mol. Spectrosc.	JSP
J. Mol. Struct.	JST
J. Organomet. Chem.	JOM
J. Org. Chem.	JOC
J. Org. Chem. USSR (Engl. Transl.)	JOU
J. Pharm. Sci.	JPS
J. Phys. Chem.	JPC
J. Prakt. Chem.	JPR
Khim. Geterotsikl. Soedin.	KGS
Kristallografiya	K
Liebigs Ann. Chem.	LA
Monatsh. Chem.	M
Naturwissenschaften	N
Nippon Kagaku Kaishi	NKK
Nouv. J. Chim.	NJC
Org. Magn. Reson.	OMR
Org. Mass Spectrom.	OMS
Org. Prep. Proced. Int.	OPP
Org. React.	OR
Org. Synth.	OS
Org. Synth., Coll. Vol.	OSC
Phosphorus Sulfur	PS
Phytochemistry	P
Proc. Indian Acad. Sci., Sect. A	PIA(A)
Proc. Natl. Acad. Sci. USA	PNA
Pure Appl. Chem.	PAC
Q. Rev., Chem. Soc	QR
Recl. Trav. Chim. Pays-Bas	RTC
Rev. Roum. Chim.	RRC
Russ. Chem. Rev. (Engl. Transl.)	RCR
Spectrochim. Acta, Part A	SA(A)
Synth. Commun.	SC
Synthesis	S
Tetrahedron	T
Tetrahedron Lett.	TL
Ukr. Khim. Zh. (Russ. Ed.)	UKZ
Yakugaku Zasshi	YZ
Z. Chem.	ZC
Zh. Obshch. Khim.	ZOB
Zh. Org. Khim.	ZOR
Z. Naturforsch., Teil B	ZN(B)

Book Series

'Advances in Heterocyclic Chemistry'	AHC
'Chemistry of Heterocyclic Compounds' [Weissberger–Taylor series]	HC
'Methoden der Organischen Chemie (Houben-Weyl)'	HOU
'Organic Compounds of Sulphur, Selenium, and Tellurium' [R. Soc. Chem. series]	SST
'Physical Methods in Heterocyclic Chemistry'	PMH

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Ger. Pat.	GEP
Neth. Pat.	NEP
Jpn. Pat.	JAP
Jpn. Kokai	JAP(K)
S. Afr. Pat.	SAP
U.S. Pat.	USP

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All Other Books and Journals ('Miscellaneous')	MI
All Other Patents	MIP
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For explanation of the reference system, see p. 629

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.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)

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.