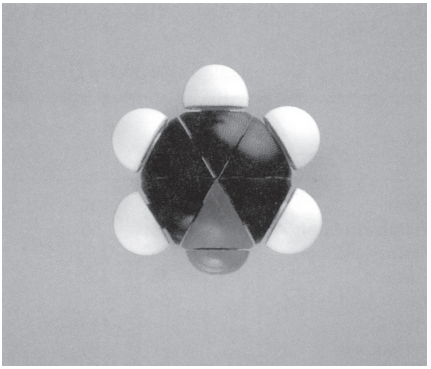
16



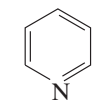
Heterocyclic Compounds

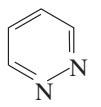
16.1 Heterocyclic systems

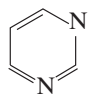
Heterocyclic compounds are those where one or more atom(s) of the ring are heteroatoms, for example, N, O, S, P, As, Se, B, and so on (Greek word "heteros" means different). More than half of the known organic compounds are heterocyclic compounds. These are widely distributed in nature, and many of them are of fundamental importance for life processes. For example, nucleic acid bases containing purines and pyrimidines; hemoglobin and chlorophyll containing porphyrin rings; essential dietary ingredients containing vitamins B_1, B_2, B_3, B_6, and ascorbic acid; the three essential amino acids, namely, histidine, proline, and tryptophan; almost all the drugs and pharmaceuticals; and many natural products like alkaloids, carbohydrates, and plant pigments. All these compounds contain hetero ring(s) in their molecules. These are the reasons why a great deal of recent research work is concerned with the methods of synthesis of hetero rings and studying their properties.

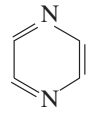
16.2 Common structural types of heterocycles

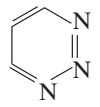
The heterocycles with the structures analogous to that of benzene but with a heteroatom replacing at least one carbon atom of the benzene ring are called aromatic heterocycles, for example, pyridine. There are other analogous heterocycles where more than one carbon atom of the benzene ring are replaced by heteroatoms, for example, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine.

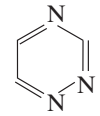

Pyridine

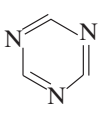

Pyridazine

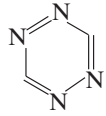

Pyrimidine


Pyrazine


1,2,3-Triazine


1,2,4-Triazine


1,3,5-Triazine


1,2,4,5-Tetrazine

All of the above heterocycles are six-atom, six-π-electron aromatic heterocycles.

There are five-atom, six-π-electron aromatic heterocycles, for example, pyrrole, furan, and thiophene contain only one heteroatom in the ring system, and oxazole, thiazole, isothiazole, 1H-pyrazole, 1H-imidazole, and 1H-tetrazole contain two heteroatoms in the ring.


Pyrrole

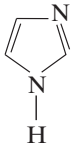

Furan


Thiophene


Oxazole

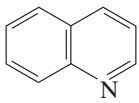

Thiazole

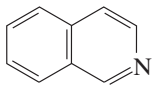

1H-pyrazole

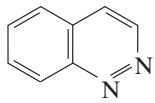

1H-imidazole

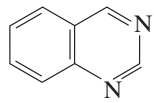

1H-tetrazole

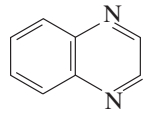
There are fused-ring system aromatic heterocycles. For example, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, indole, isoindole, and benzimidazole.

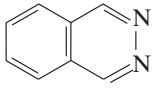

Quinoline

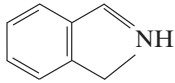

Isoquinoline

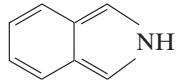

Cinnoline

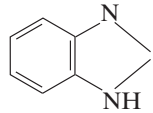

Quinazoline


Quinoxaline

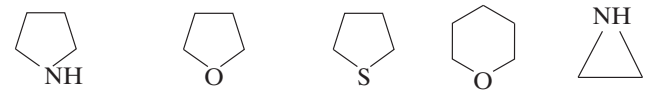

Phthalazine


Indole


Isoindole


Benzimidazole

Besides the above fully unsaturated aromatic heterocycles, there are other nonaromatic small-ring heterocyclic compounds that may be either partially or fully saturated. In these heterocyclic compounds, there is no possibility of cyclic delocalization of *p*-electrons for which they lack any aromatic character and these small-ring heterocycles suffer from considerable angle strain. For example, pyrrolidine, tetrahydrofuran, thiolan, pyran, aziridine, oxiran, azetidine, oxetan, and so on, are fully saturated heterocycles and dihydropyrrole, azirine, oxetene, and so on, are partially saturated heterocycles.



Pyrrolidine Tetrahydrofuran Thiolan Pyran Aziridine

Oxiran Oxetan

Fully saturated nonaromatic heterocycles

Dihydropyrrole Azirine Oxetene

Partially saturated nonaromatic heterocycles

16.3 Nomenclature of heterocyclic compounds

Monocyclic compounds are named by prefixing the name that indicates the nature of the heteroatom. For example, nitrogen → aza, sulfur → thia, oxygen → oxa, silicon → sila, phosphorus → phospha, and boron → bora.

The size of the ring of monocyclic compounds is indicated by appropriate suffixing for each ring size.

The suffixing depends on the nature of the heteroatom—nitrogen-containing heterocycles and heterocycles without nitrogen are suffixed in different but distinct ways. The suffixing of aromatic (fully unsaturated) and nonaromatic (fully or partially saturated) heterocycles have different but related suffixes.

An example will help to understand the method of naming a heterocyclic compound.

(fully unsaturated
nitrogen-containing
three-membered heterocycle)

Azirine
Prefix: az-
Suffix: -irine

(fully unsaturated three-membered heterocycle without a nitrogen atom)

Oxiren
Prefix: ox-
Suffix: -iren

(fully saturated nitrogen containing three-membered heterocycle)

Aziridine
Prefix: az-
Suffix: -iridine

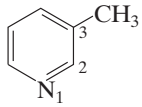
(fully saturated three-membered heterocycle without a nitrogen atom)

Oxiran
Prefix: ox-
Suffix: -iran

Naming of fully unsaturated and fully saturated monocyclic heterocycles is shown below:

	Nitrogen present		Nitrogen absent	
Number of ring members	Fully unsaturated (suffix)	Fully saturated (suffix)	Fully unsaturated (suffix)	Fully saturated (suffix)
3	-irine	-iridine	-iren	-iran
	 Azirine	 Aziridine	 Oxiren	 Oxiran
4	-ete	-etidine	-et	-etan
	 Azete	 Azetidine	 Oxet	 Oxetan
5	-ole	-olidine	-ole	-olan
	 Azole	 Azolidine	 Thiole	 Thiolan
6	-ine	-perhydro.....ine	-in	-ane
	 Azine	 Perhydroazine	 Oxin	 Oxane

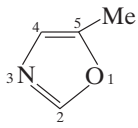
In a monocyclic compound, numbering starts from the heteroatom and moves in the direction where the substituent gets lower location. For example,



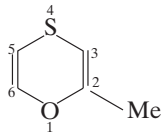
3-Methylazine

For monocyclic compounds having more than one heteroatom, the priority of the heteroatoms is decided as follows:

1. If the group number of the heteroatoms are different, the atom of the higher group number gets higher preference, for example, O (Gr. vi) > N (Gr. v)
2. If the group number of the heteroatoms are same, then the lighter atom is preferred, for example, O (atomic mass 16) > S (atomic mass 32)



5-Methyl-1,3-oxazole

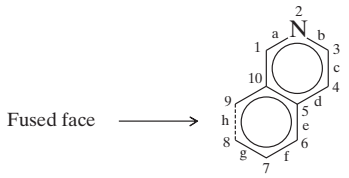


2-Methyl-1,4-thiaoxin

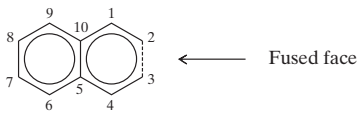
For fused-ring heterocycles, the heterocyclic ring having maximum number of rings with a simple name is chosen. If more than one heterorings are present, then the nitrogen containing ring is given preference. For heterorings having no nitrogen, the order of preference is decided by the above mentioned two rules (1) and (2). When the parent heteroring is chosen, its name is prefixed by the name of the ring fused with it, for example, benzo-, naphtho-.

The structure is now written with the greatest number of rings in horizontal position, and the other nonhorizontal rings are written at the right of the horizontal row and above it.

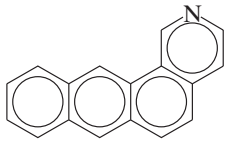
To distinguish isomers, the peripheral sides of the parent compound are lettered as a, b, c . . . , and so on, beginning with "a" for the side C_1—C_2, "b" for C_2—C_3 . . . , and so on. The numbering of the parent ring is done in such a way that the side undergoing fusion gets the *lowest alphabet*. For example heterocycle isoquinoline ring should be numbered as follows:



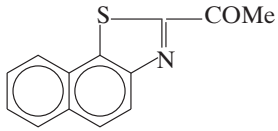
The naphthalene ring is numbered as follows:



Therefore, the name of the isomer



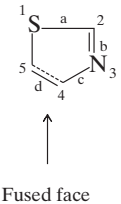
is naphtho[3,2-h]isoquinoline. Another example is given below.



In the above compound, the heteroring is

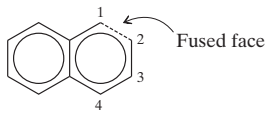
which is called 1,3-Thiazole.

The compound is, therefore, naphthothiazole. To identify the fused side, the lettering is done as follows:

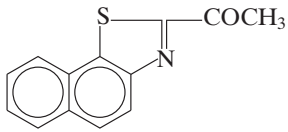


The fused face is d.

The naphthalene ring is numbered as follows:



So, the name of the compound

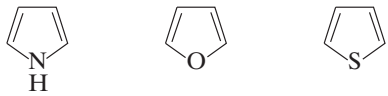


is 2-ethanoyl naphtho[2,1-d]-1,3-thiazole.

AROMATIC HETEROCYCLIC COMPOUNDS
(5-atom, six-π-electron aromatic heterocycles)

16.4 Structure of pyrrole, furan, and thiophene

The simplest of the five-membered heterocyclic compounds are **pyrrole, furan**, and **thiophene**, each of which contains a single heteroatom.



I Pyrrole II Furan III Thiophene

Judging from the commonly used structures I, II, and III, we might expect each of these compounds to have the properties of a conjugated diene and of an amine, an ether, or a sulfide (thioether). Except for a certain tendency to undergo addition reactions, however, these heterocycles do not have the expected properties: thiophene does not undergo the oxidation typical of a sulfide, for example; pyrrole does not possess the basic properties typical of amines.

Instead, these heterocycles and their derivatives most commonly undergo electrophilic substitution: nitration, sulfonation, halogenation, Friedel–Crafts acylation, even the Reimer–Tiemann reaction and coupling with diazonium salts. Heats of combustion indicate resonance stabilization to the extent of 22–28 kcal/mol; somewhat less than the resonance energy of benzene (36 kcal/mol), but much greater than that of most conjugated dienes (about 3 kcal/mol). On the basis of these properties, pyrrole, furan, and thiophene must be considered *aromatic*. Clearly, formulas I, II, and III do not adequately represent the structures of these compounds.

Let us look at the orbital picture of one of these molecules, pyrrole. Each atom of the ring, whether carbon or nitrogen, is held by a σ bond to three other atoms. In forming these bonds, the atom uses three sp^2 orbitals, which lie in a plane and are 120° apart. After contributing one electron to each σ bond, each carbon atom of the ring has left *one* electron and the nitrogen atom has left *two* electrons; these electrons occupy p orbitals. Overlap of the p orbitals gives rise to π clouds, one above and one below the plane of the ring; the π clouds contain a total of six electrons, the *aromatic sextet* (Fig. 16.1).

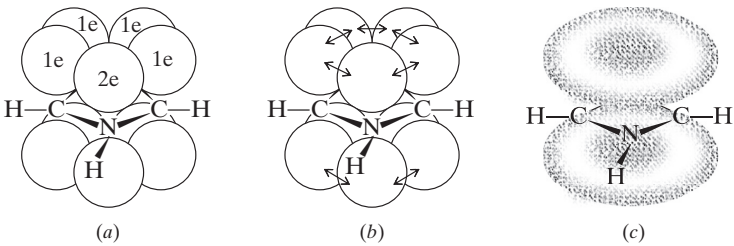
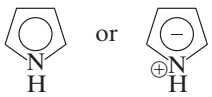


Figure 16.1 Pyrrole molecule. (*a*) Two electrons in the p orbital of nitrogen; one electron in the p orbital of each carbon. (*b*) Overlap of the p orbitals to form π bonds. (*c*) Clouds above and below the plane of the ring; a total of six π electrons, the aromatic sextet.

Delocalization of the π electrons stabilizes the ring. As a result, pyrrole has an abnormally low heat of combustion; it tends to undergo reactions in which the stabilized ring is retained, that is, to undergo substitution.

Nitrogen's extra pair of electrons, which is responsible for the usual basicity of nitrogen compounds, is involved in the π cloud, and is not available for sharing with acids. In contrast to most amines, therefore, pyrrole is an extremely weak base ($K_b \sim 2.5 \times 10^{-14}$). By the same token, there is a high electron density in the ring, which causes pyrrole to be extremely reactive toward electrophilic substitution: it undergoes reactions like nitrosation and coupling with diazonium salts which are characteristic of only the most reactive benzene derivatives, phenols and amines.

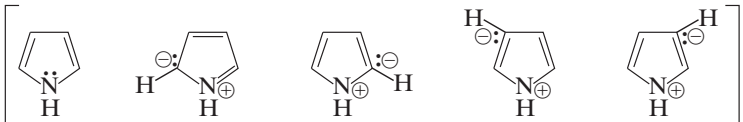
It thus appears that pyrrole is better represented by IV,



IV
Pyrrole

in which the circle represents the aromatic sextet.

What does IV mean in terms of conventional valence-bond structures? Pyrrole can be considered a hybrid of structures V-IX. Donation of electrons to the ring by



V VI VII VIII IX
Pyrrole

nitrogen is indicated by the ionic structures in which nitrogen bears a positive charge and the carbon atoms of the ring bear a negative charge.

Furan and thiophene have structures that are analogous to the structure of pyrrole. Where nitrogen in pyrrole carries a hydrogen atom, the oxygen or sulfur carries an unshared pair of electrons in an sp^2 orbital. Like nitrogen, the oxygen or

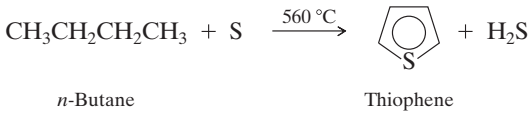
Furan Thiophene

sulfur atom provides two electrons for the π cloud; as a result these compounds, too, behave like extremely reactive benzene derivatives.

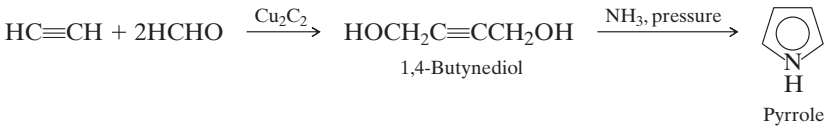
16.5 Source of pyrrole, furan, and thiophene

Pyrrole and thiophene are found in small amounts in coal tar. During the fractional distillation of coal tar, thiophene (b.p. 84°C) is collected along with the benzene (b.p. 80°C); as a result ordinary benzene contains about 0.5% of thiophene, and must be specially treated if *thiophene-free benzene* is desired.

Thiophene can be synthesized on an industrial scale by the high-temperature reaction between *n*-butane and sulfur.

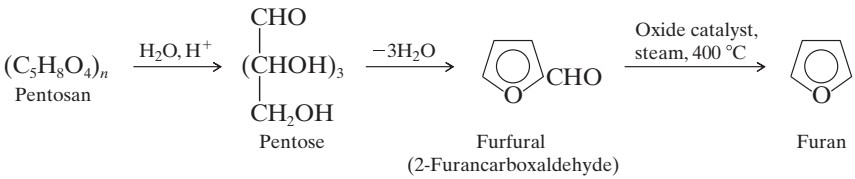


Pyrrole can be synthesized in a number of ways. For example:

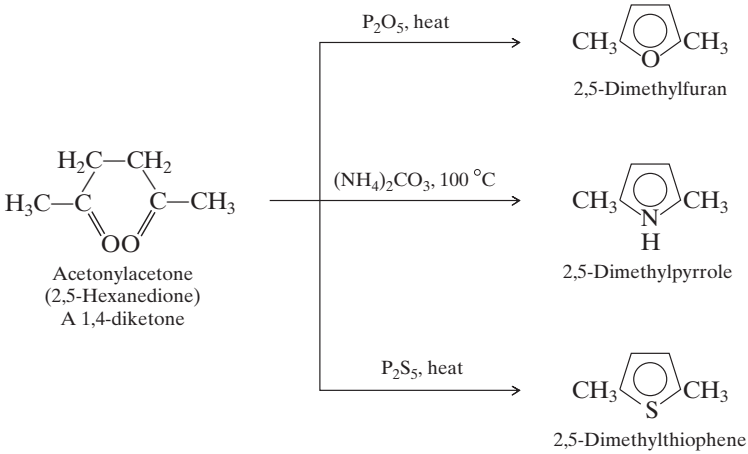


The pyrrole ring is the basic unit of the *porphyrin* system, which occurs, for example, in chlorophyll and in hemoglobin.

Furan is most readily prepared by decarbonylation (elimination of carbon monoxide) of **furfural** (furfuraldehyde), which in turn is made by the treatment of oat hulls, corncobs, or rice hulls with hot hydrochloric acid. In the latter reaction pentosans (polypentosides) are hydrolysed to pentoses, which then undergo dehydration and cyclization to form furfural.



Certain substituted pyrroles, furans, and thiophenes can be prepared from the parent heterocycles by substitution; most, however, are prepared from open-chain compounds by ring closure. For example:



Problem 16.1 Give structural formulas for all intermediates in the following synthesis of 2,5-hexanedione:

ethyl acetoacetate + $NaOC_2H_5$ ⟶ A($C_6H_9O_3Na$)

A + I_2 ⟶ B ($C_{12}H_{18}O_6$) + NaI

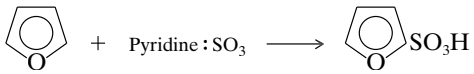
B + dilute acid + heat ⟶ 2,5-hexanedione + carbon dioxide + ethanol

Problem 16.2 Outline a synthesis of 2,5-diphenylfuran, starting from ethyl benzoate and ethyl acetate.

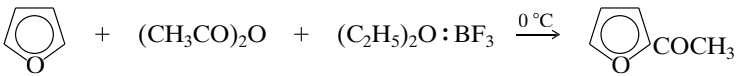
16.6 Electrophilic substitution in pyrrole, furan, and thiophene. Reactivity and orientation

Like other aromatic compounds, these five-membered heterocycles undergo nitration, halogenation, sulfonation, and Friedel–Crafts acylation. They are much more reactive than benzene, and resemble the most reactive benzene derivatives (amines and phenols) in undergoing such reactions as the Reimer–Tiemann reaction, nitrosation, and coupling with diazonium salts.

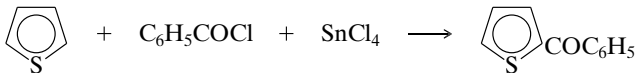
Reaction takes place predominantly at the 2-position. For example:



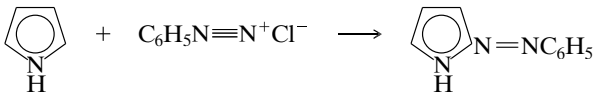
Furan — 2-Furansulfonic acid



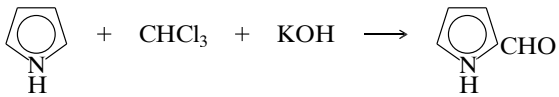
Furan — Boron trifluoride etherate — 2-Acetylfuran



Thiophene — 2-Benzoylthiophene



Pyrrole — 2-(Phenylazo)pyrrole



Pyrrole — 2-Pyrrolecarboxaldehyde (*Low yield*)

In some of the examples we notice modifications in the usual electrophilic reagents. The high reactivity of these rings makes it possible to use milder reagents in many

cases, as, for example, the weak Lewis acid stannic chloride in the Friedel-Crafts acylation of thiophene. The sensitivity to protic acids of furan (which undergoes ring opening) and pyrrole (which undergoes polymerization) makes it necessary to modify the usual sulfonating agent.

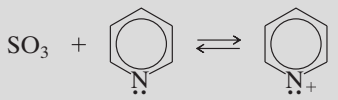
Problem 16.3 Furan undergoes ring opening upon treatment with sulfuric acid; it reacts almost explosively with halogens. Account for the fact that 2-furoic acid, however, can be sulfonated (in the 5-position) by treatment with fuming sulfuric acid, and brominated (in the 5-position) by treatment with bromine at 100°C.

2-Furoic acid

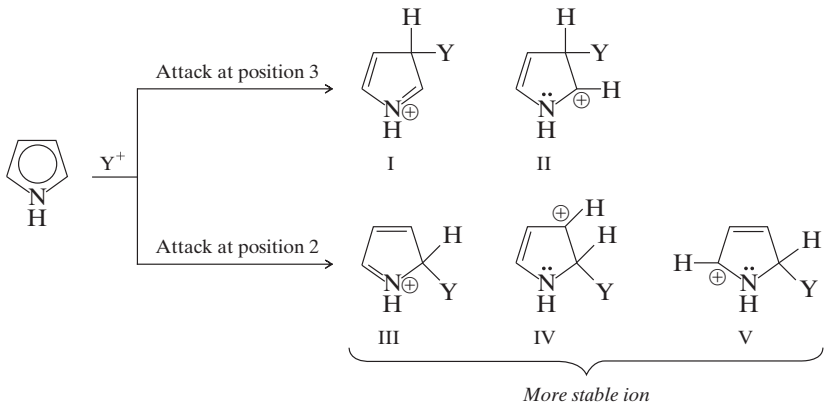
Problem 16.4 Upon treatment with formaldehyde and acid, ethyl 2,4-dimethyl-3-pyrrolecarboxylate is converted into a compound of formula $C_{19}H_{26}O_4N_2$. What is the most likely structure for this product? How is it formed?

Problem 16.5 Predict the products from the treatment of furfural (2-furancarboxaldehyde) with concentrated aqueous NaOH.

Problem 16.6 Sulfur trioxide dissolves in the tertiary amine pyridine to form a salt. Show all steps in the most likely mechanism for the sulfonation of an aromatic compound by this reagent.



In our study of electrophilic aromatic substitution, we found that we could account for orientation on the following basis: the controlling step is the attachment of the electrophilic reagent to the aromatic ring, which takes place in such a way as to yield the most stable intermediate carbocation. Let us apply this approach to the reactions of pyrrole.



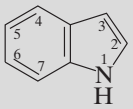
Attack at position 3 yields a carbocation that is a hybrid of structures I and II. Attack at position 2 yields a carbocation that is a hybrid not only of structures III and IV (analogous to I and II) but also of structure V; the extra stabilization conferred by V makes this ion the more stable one.

Viewed differently, attack at position 2 is faster because the developing positive charge is accommodated by *three* atoms of the ring instead of by only two.

Pyrrole is highly reactive, compared with benzene, because of contribution from the relatively stable structure III. In III *every atom has an octet of electrons*; nitrogen accommodates the positive charge simply by *sharing* four pairs of electrons. It is no accident that pyrrole resembles aniline in reactivity: both owe their high reactivity to the ability of nitrogen to share four pairs of electrons.

Orientation of substitution in furan and thiophene, as well as their high reactivity, can be accounted for in a similar way.

Problem 16.7 The heterocycle *indole*, commonly represented as formula VI, is found in coal tar and in orange blossoms.



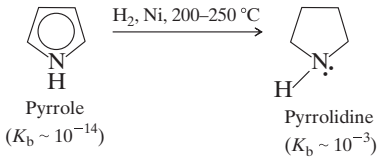
VI
Indole

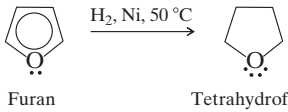
It undergoes electrophilic substitution, chiefly at position 3. Account (a) for the aromatic properties of indole, and (b) for the orientation in electrophilic substitution.

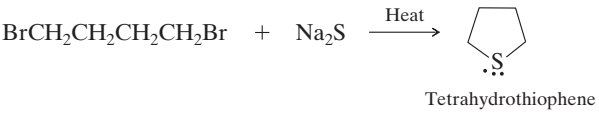
NONAROMATIC HETEROCYCLES

16.7 Saturated five-membered heterocycles

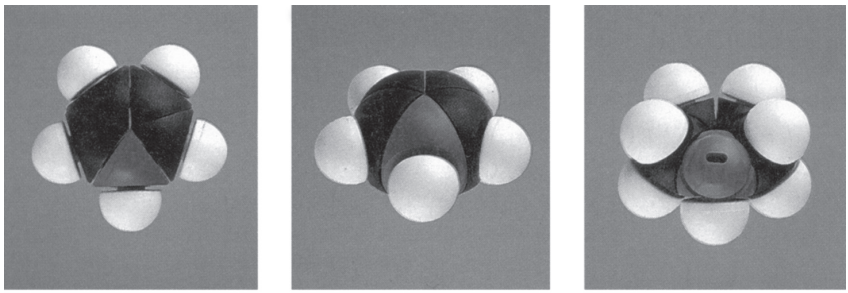
Catalytic hydrogenation converts pyrrole and furan into the corresponding saturated heterocycles, *pyrrolidine* and *tetrahydrofuran*. Since thiophene poisons most catalysts, *tetrahydrothiophene* is made instead from open-chain compounds.







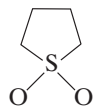
Saturation of these rings destroys the aromatic structure and, with it, the aromatic properties. Each of the saturated heterocycles has the properties we would expect of it: the properties of a secondary aliphatic amine, an aliphatic ether, or an aliphatic sulfide. With nitrogen's extra pair of electrons now available for sharing with acids, pyrrolidine ($K_b \sim 10^{-3}$) has the normal basicity of an aliphatic amine. Hydrogenation of pyrrole increases the base strength by a factor of 10^{11} (100 billion); clearly a fundamental change in structure has taken place. (See Fig. 16.2.)



(*a*) (*b*) (*c*)

Figure 16.2 Electronic configuration and molecular shape: (*a*) and (*b*) pyrrole, aromatic; (*c*) pyrrolidine, aliphatic.
The fundamental difference in structure is reflected by the striking difference in shape between the two molecules. As we see, pyrrole has the characteristic aromatic shape: flat, like benzene—or, closer yet, like the cyclopentadienyl anion, with which it is isoelectronic. Pyrrolidine, on the other hand, is clearly aliphatic, and closely resembles cyclopentane, with an unshared pair of electrons taking the place of one hydrogen atom.

Tetrahydrofuran is an important solvent, used, for example, in reductions with lithium aluminum hydride, in the preparation of arylmagnesium chlorides, and in hydroborations. Oxidation of tetrahydrothiophene yields *tetramethylene sulfone* (or *sulfolane*), also used as an aprotic solvent.



Tetramethylene sulfone
(Sulfolane)

We have encountered pyrrolidine as a secondary amine commonly used in making enamines. The pyrrolidine ring occurs naturally in a number of alkaloids, providing the basicity that gives these compounds their name (*alkali-like*).

Problem 16.8 An older process for the synthesis of both the adipic acid and the hexamethylenediamine needed in the manufacture of nylon-6,6 started with tetrahydrofuran. Using only familiar chemical reactions, suggest possible steps in their synthesis.

Problem 16.9 Predict the products of the treatment of pyrrolidine with:

(a) aqueous HCl
(b) aqueous NaOH
(c) acetic anhydride
(d) benzenesulfonyl chloride + aqueous NaOH
(e) methyl iodide, followed by aqueous NaOH
(f) repeated treatment with methyl iodide, followed by Ag_2O and then strong heating

Problem 16.10 The alkaloid *hygrine* is found in the coca plant. Suggest a structure for it on the basis of the following evidence:

Hygrine ($C_8H_{15}ON$) is insoluble in aqueous NaOH but soluble in aqueous HCl. It does not react with benzenesulfonyl chloride. It reacts with phenylhydrazine to yield a phenylhydrazone. It reacts with NaOI to yield a yellow precipitate and a carboxylic acid ($C_7H_{13}O_2N$). Vigorous oxidation by CrO_3 converts hygrine into *hygrinic acid* ($C_6H_{11}O_2N$).

Hygrinic acid can be synthesized as follows:

$$BrCH_2CH_2CH_2Br + CH(COOC_2H_5)_2^-Na^+ \longrightarrow A(C_{10}H_{17}O_4Br)$$

$$A + Br_2 \longrightarrow B(C_{10}H_{16}O_4Br_2)$$

$$B + CH_3NH_2 \longrightarrow C\ (C_{11}H_{19}O_4N)$$

$$C + \text{aq. } Ba(OH)_2 + \text{heat} \longrightarrow D \xrightarrow{HCl} E \xrightarrow{\text{heat}} \text{hygrinic acid} + CO_2$$

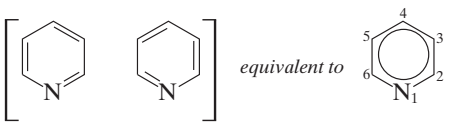
SIX-MEMBERED HETEROAROMATIC RINGS
(six-atom, six-π-electron aromatic heterocycles)

16.8 Structure of pyridine

Of the six-membered aromatic heterocycles, we shall take up only one, **pyridine**.

Pyridine is classified as aromatic on the basis of its properties. It is flat, with bond angles of 120°; the four carbon-carbon bonds are of the same length, and so are the two carbon-nitrogen bonds. It resists addition and undergoes electrophilic substitution. Its heat of combustion indicates a resonance energy of 23 kcal/mol.

Pyridine can be considered a hybrid of the Kekulé structures I and II. We shall represent it as structure III in which the circle represents the aromatic sextet.



I II III

In electronic configuration, the nitrogen of pyridine is considerably different from the nitrogen of pyrrole. In pyridine the nitrogen atom, like each of the carbon atoms, is bonded to other members of the ring by the use of sp^2 orbitals, and provides one electron for the π cloud. The third sp^2 orbital of each carbon atom is used to form a bond to hydrogen; the third sp^2 orbital of nitrogen simply contains a pair of electrons, which are available for sharing with acids (Fig. 16.3).

Because of this electronic configuration, the nitrogen atom makes pyridine a much stronger base than pyrrole, and affects the reactivity of the ring in a quite different way, as we shall see.

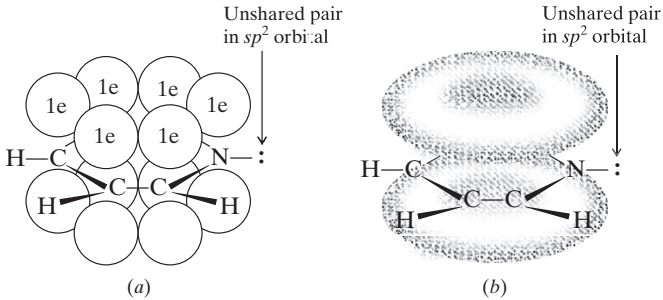
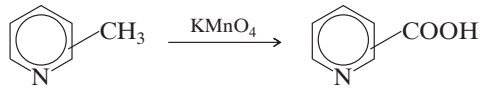


Figure 16.3 Pyridine molecule. (*a*) One electron in each *p* orbital; two electrons in an sp^2 orbital of nitrogen. (*b*) The *p* orbital overlap to form π clouds above and below the plane of the ring; two unshared electrons are still in an sp^2 orbital of nitrogen.

16.9 Source of pyridine compounds

Pyridine is found in coal tar. Along with it are found a number of methylpyridines, the most important of which are the monomethyl compounds, known as *picolines*.

Oxidation of the picolines yields the pyridinecarboxylic acids.



Picoline
(2-, 3-, or 4-)

Pyridinecarboxylic acid
(2-, 3-, or 4-)

The 3-isomer (*nicotinic acid* or *niacin*) is a vitamin. The 4-isomer (*isonicotinic acid*) has been used, in the form of its hydrazide, in the treatment of tuberculosis.

Nicotinic acid
Niacin
3-Pyridinecarboxylic acid
Anti-pellagra factor

Isonicotinic acid hydrazide
(Isoniazid)

16.10 Reactions of pyridine

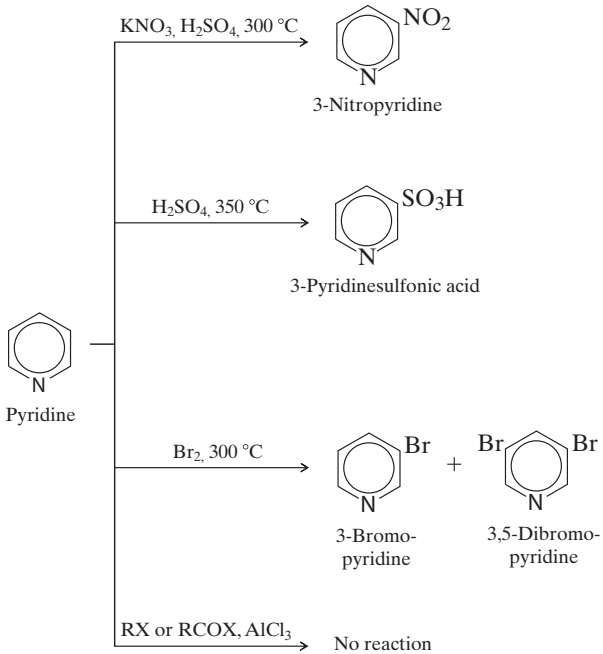
The chemical properties of pyridine are those we would expect on the basis of its structure. The ring undergoes the substitution, both electrophilic and nucleophilic, typical of aromatic rings; our interest will lie chiefly in the way the nitrogen atom affects these reactions.

There is another set of reactions in which pyridine acts as a base or nucleophile; these reactions involve nitrogen directly and are due to its unshared pair of electrons.

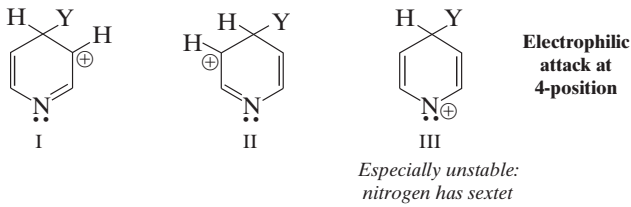
16.11 Electrophilic substitution in pyridine

Toward electrophilic substitution pyridine resembles a highly deactivated benzene derivative. It undergoes nitration, sulfonation, and halogenation only under very vigorous conditions, and does not undergo the Friedel–Crafts reaction at all.

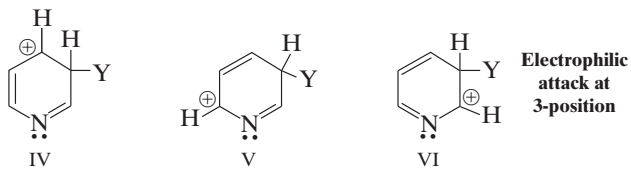
Substitution occurs chiefly at the 3-(or β-) position.



Let us see if we can account for the reactivity and orientation on our usual basis of stability of the intermediate carbocation. Attack at the 4-position yields a carbocation that is a hybrid of structures I, II, and III.



Attack at the 3-position yields an ion that is a hybrid of structures IV, V, and VI.



(Attack at the 2-position resembles attack at the 4-position just as *ortho* attack resembles *para* attack in the benzene series.)

All these structures are less stable than the corresponding ones for attack on benzene, because of electron withdrawal by the nitrogen atom. As a result, pyridine undergoes substitution more slowly than benzene.

Of these structures, III is *especially* unstable, since in it the electronegative nitrogen atom has only a sextet of electrons. As a result, attack at the 4-position (or 2-position) is especially slow, and substitution occurs predominantly at the 3-position.

It is important to see the difference between substitution in pyridine and substitution in pyrrole. In the case of pyrrole, a structure in which nitrogen bears a positive charge is especially stable since every atom has an octet of electrons; nitrogen accommodates the positive charge simply by sharing four pairs of electrons. In the case of pyridine, a structure in which nitrogen bears a positive charge (III) is especially unstable since nitrogen has only a sextet of electrons; nitrogen *shares* electrons readily, but as an electronegative atom it resists the *removal* of electrons.

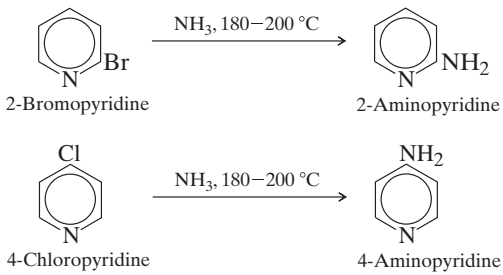
Problem 16.11 2-Aminopyridine can be nitrated or sulfonated under much milder conditions than pyridine itself; substitution occurs chiefly at the 5-position. Account for these facts.

Problem 16.12 Because of the difficulty of nitrating pyridine, 3-aminopyridine is most conveniently made via nicotinic acid. Outline the synthesis of 3-aminopyridine from β-picoline.

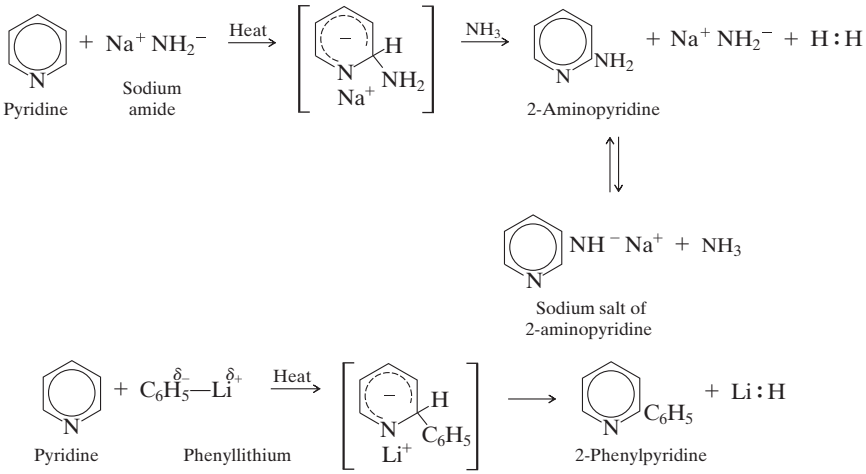
Problem 16.13 Account for the following: (a) treatment of quinolin with HNO_3 and H_2SO_4 gives 5- and 8-nitroquinolines; (b) oxidation with $KMnO_4$ gives 2,3-pyridinedi-carboxylic acid.

16.12 Nucleophilic substitution in pyridine

Here, as in electrophilic substitution, the pyridine ring resembles a benzene ring that contains strongly electron-withdrawing groups. Nucleophilic substitution takes place readily, particularly at the 2- and 4-positions. For example:

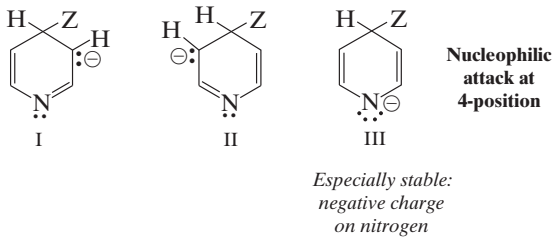


The reactivity of pyridine toward nucleophilic substitution is so great that even the powerfully basic hydride ion, :$\mathbf{H}^-$, can be displaced. Two important examples of this reaction are amination by sodium amide (**Chichibabin reaction**), and alkylation or arylation by organolithium compounds.

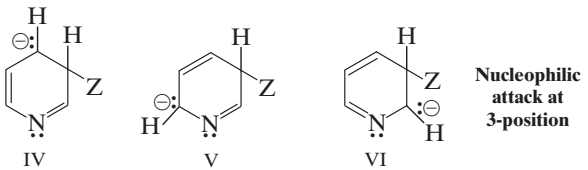


As we have seen, nucleophilic aromatic substitution can take place by a mechanism that is quite analogous to the mechanism for electrophilic substitution. Reaction proceeds by two steps; the rate of the first step, formation of a charged particle, determines the rate of the overall reaction. In electrophilic substitution, the intermediate is positively charged; in nucleophilic substitution, the intermediate is negatively charged. The ability of the ring to accommodate the charge determines the stability of the intermediate and of the transition state leading to it, and hence determines the rate of the reaction.

Nucleophilic attack at the 4-position yields a carbanion that is a hybrid of structures I, II, and III:



Attack at the 3-position yields a carbanion that is a hybrid of structures IV, V, and VI:



(As before, attack at the 2-position resembles attack at the 4-position.)

All these structures are more stable than the corresponding ones for attack on a benzene derivative, because of electron withdrawal by the nitrogen atom. Structure III is *especially* stable, since the negative charge is located on the atom that can best accommodate it, the electronegative nitrogen atom. It is reasonable, therefore, that nucleophilic substitution occurs more rapidly on the pyridine ring than on the benzene ring, and more rapidly at the 2- and 4-positions than at the 3-position.

The same electronegativity of nitrogen that makes pyridine unreactive toward electrophilic substitution makes pyridine highly reactive toward nucleophilic substitution.

16.13 Basicity of pyridine

Pyridine is a base with $K_b = 2.3 \times 10^{-9}$. It is thus much stronger than pyrrole ($K_b \sim 2.5 \times 10^{-14}$) but much weaker than aliphatic amines ($K_b \sim 10^{-4}$).

Pyridine has a pair of electrons (in an sp^2 orbital) that is available for sharing with acids; pyrrole has not, and can accept an acid only at the expense of the aromatic character of the ring.

The fact that pyridine is a weaker base than aliphatic amines is more difficult to account for, but at least it fits into a pattern. Let us turn for a moment to the basicity of the carbon analogs of amines, the carbanions.

Benzene is a stronger acid than an alkane, as shown by its ability to displace an alkane from its salts; this, of course, means that the phenyl anion, $C_6H_5^-$, is a weaker base than an alkyl anion, R^-.

$$\underset{\text{Stronger base}}{R:{}^-Na^+} + \underset{\text{Stronger acid}}{C_6H_5:H} \rightleftharpoons \underset{\text{Weaker acid}}{R:H} + \underset{\text{Weaker base}}{C_6H_5:{}^-NA^+}$$

In the same way, acetylene is a stronger acid than benzene, and the acetylide ion is a weaker base than the phenyl anion.

$$\underset{\text{Stronger base}}{C_6H_5:{}^-Na^+} + \underset{\text{Stronger acid}}{HC{\equiv}C:H} \rightleftharpoons \underset{\text{Weaker acid}}{C_6H_5:H} + \underset{\text{Weaker base}}{HC{\equiv}C:{}^-NA^+}$$

Thus we have the following sequences of acidity of hydrocarbons and basicity of their anions:

Acidity	$HC{\equiv}C{:}H > C_6H_5{:}H > R{:}H$
Basicity	$HC{\equiv}C{:}^- < C_6H_5{:}^- < R{:}^-$

A possible explanation for these sequences can be found in the electronic configuration of the carbanions. In the alkyl, phenyl, and acetylide anions, the unshared pair of electrons occupies respectively an sp^3, an sp^2, and an sp orbital. The availability of this pair for sharing with acids determines the basicity of the particular anion. As we proceed along the series sp^3, sp^2, sp, the p character of the orbital decreases and the s character increases. Now, an electron in a p orbital is at some distance from the nucleus and is held relatively loosely; an electron in an s orbital, on the other hand, is close to the nucleus and is held more tightly. Of the

three anions, the alkyl ion is the strongest base since its pair of electrons is held most loosely, in an sp^3 orbital. The acetylide ion is the weakest base since its pair of electrons is held most tightly, in an *sp* orbital.

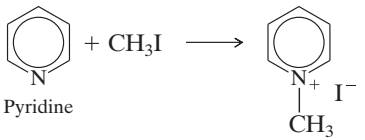
Pyridine bears the same relationship to an aliphatic amine as the phenyl anion bears to an alkyl anion. The pair of electrons that gives pyridine its basicity occupies an sp^2 orbital; it is held more tightly and is less available for sharing with acids than the pair of electrons of an aliphatic amine, which occupies an sp^3 orbital.

Problem 16.14 Predict the relative basicities of amines (RCH_2NH_2), imines (RCH═NH), and nitriles (RC≡N).

Pyridine is widely used in organic chemistry as a water-soluble base, as, for example, in the Schotten–Baumann acylation procedure.

Problem 16.15 Ethyl bromosuccinate is converted into the unsaturated ester ethyl fumarate by the action of pyridine. What is the function of the pyridine? What advantage does it have here over the usual alcoholic KOH?

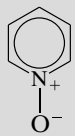
Like other amines, pyridine has nucleophilic properties, and reacts with alkyl halides to form quaternary ammonium salts.



Pyridine

N-Methylpyridinium iodide
(Pyridine methiodide)

Problem 16.16 Like any other tertiary amine, pyridine can be converted (by peroxy-benzoic acid) into its *N*-oxide. In contrast to pyridine itself, pyridine *N*-oxide readily undergoes nitration, chiefly in the 4-position. How do you account for this reactivity and orientation?

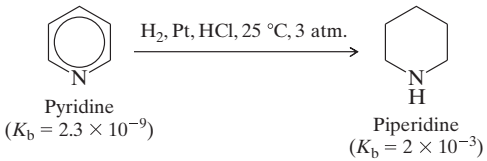


Pyridine *N*-oxide

Problem 16.17 Pyridine *N*-oxides not only are reactive toward electrophilic substitution, but also seem to be reactive toward nucleophilic substitution, particularly at the 2- and 4-positions. For example, treatment of 4-nitropyridine. *N*-oxide with hydrobromic acid gives 4-bromopyridine *N*-oxide. How do you account for this reactivity and orientation?

16.14 Reduction of pyridine

Catalytic hydrogenation of pyridine yields the aliphatic heterocyclic compound **piperidine**, $C_5H_{11}N$.



Piperidine ($K_b = 2 \times 10^{-3}$) has the usual basicity of a secondary aliphatic amine, a million times greater than that of pyridine; again, clearly, a fundamental change in structure has taken place (see Fig. 16.4). Like pyridine, piperidine is often used as a basic catalyst in such reactions as the Michael addition.

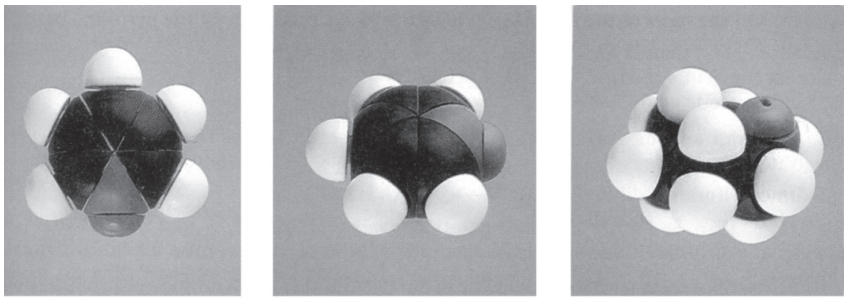


Figure 16.4 Electronic configuration and molecular shape: (*a*) and (*b*) pyridine, aromatic; (*c*) piperidine, aliphatic.

Here again we see the contrast between aromatic and aliphatic structures reflected in a contrast in molecular shape. Pyridine has the shape of benzene with an unshared pair of electrons taking the place of one hydrogen. Piperidine has the familiar shape of chair cyclohexane with an unshared pair occupying an equatorial—or, in another conformation, an axial—position.

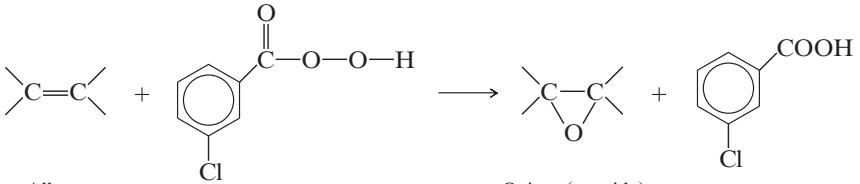
Like the pyrrolidine ring, the piperidine and pyridine rings are found in a number of alkaloids, including *nicotine*, *strychnine*, *cocaine*, and *reserpine*.

Problem 16.18 Why can piperidine not be used in place of pyridine in the Schotten–Baumann procedure?

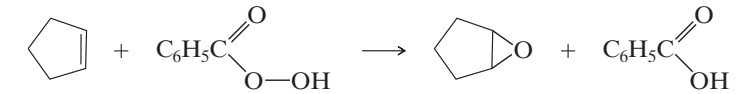
16.15 Small heterocyclic rings (epoxides)

Epoxides are compounds containing a three-membered ring with oxygen as a heteroatom. The IUPAC name of such rings is oxiran. They are cyclic ethers, but the three-membered ring gives them unusual properties that make them exceedingly important class of compounds having numerous synthetic applications.

Such a ring is generally synthesized by the oxidation of a C═C bond of alkenes with peracids like *m*-chloroperbenzoic acid (MCPBA).



When allowed to stand in ether or chloroform solution, the peroxy acid and the unsaturated compound—which need not be a simple alkene—react to yield benzoic acid and the epoxide. For example:



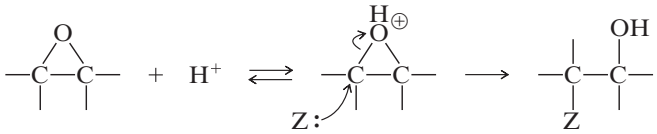
Problem 16.19 Treatment of ethyl chlorohydrin with concentrated aqueous sodium hydroxide gives ethylene oxide. (a) Show all steps in a likely mechanism or mechanisms for this conversion. This is an adaptation of what synthesis? (b) Using this approach, show all steps in the synthesis of propylene oxide from isopropyl alcohol.

16.16 Reactions of epoxides

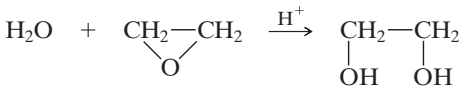
Epoxides owe their importance to the ease of opening of the highly strained three-membered ring. They undergo acid-catalyzed reactions with extreme ease and—unlike ordinary ethers—can even be cleaved by bases. Some of their important reactions are outlined below.

REACTIONS OF EPOXIDES

1. Acid-catalysed cleavage.



Examples:



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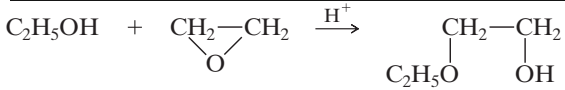
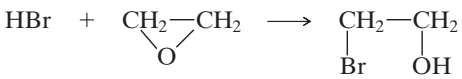
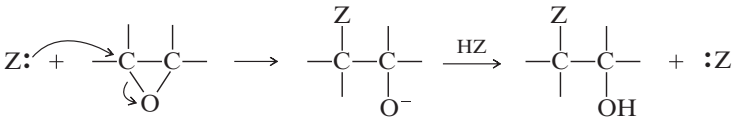


2-Ethoxyethanol

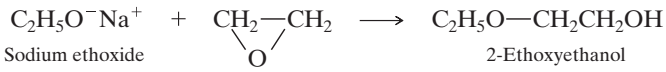


Ethylene bromohydrin
(2-Bromoethanol)

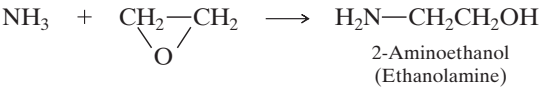
2. Base-catalysed cleavage.



Examples:

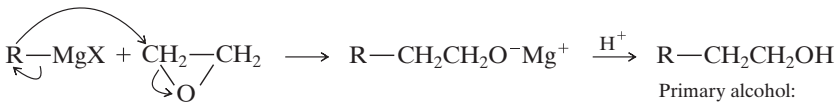


Sodium ethoxide — 2-Ethoxyethanol



2-Aminoethanol
(Ethanolamine)

3. Reaction with Grignard reagents.



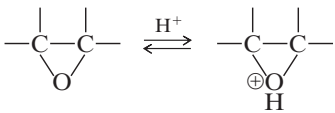
Primary alcohol:
chain has been lengthened by two carbons

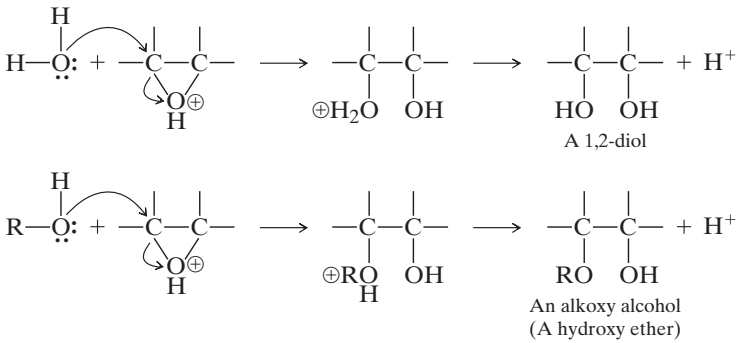
■

16.17 Acid-catalysed cleavage of epoxides. *anti*-Hydroxylation

Like other ethers, an epoxide is protonated by acid; the protonated epoxide can then undergo attack by any of a number of nucleophilic reagents.

An important feature of the reactions of epoxides is the formation of compounds that contain *two* functional groups. Thus, reaction with water yields a 1,2-diol; reaction with an alcohol yields a compound that is both ether and alcohol.





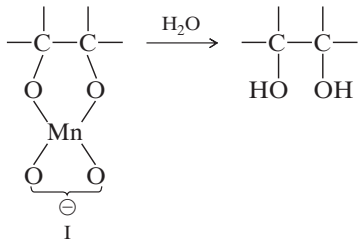
Problem 16.20 The following compounds are commercially available for use as water-soluble solvents. How could each be made?

(a) $CH_3CH_2—O—CH_2CH_2—O—CH_2CH_2—OH$	Carbitol
(b) $C_6H_5—O—CH_2CH_2—O—CH_2CH_2—OH$	Phenyl carbitol
(c) $HO—CH_2CH_2—O—CH_2CH_2—OH$	Diethylene glycol
(d) $HO—CH_2CH_2—O—CH_2CH_2—O—CH_2CH_2—OH$	Triethylene glycol

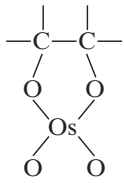
Problem 16.21 Show in detail (including structures and transition states) the steps in the acid-catalysed hydrolysis of ethylene oxide by an S_N1 mechanism; by an S_N2 mechanism.

The two-stage process of epoxidation followed by hydrolysis is stereoselective, and gives 1,2-diols corresponding to *anti*-addition to the carbon-carbon double bond. Exactly the same stereochemistry was observed for hydroxylation of alkenes by peroxyformic acid—and for good reason: an epoxide is formed there, too, but is rapidly cleaved in the acidic medium, formic acid. The interpretation is exactly the same as that given to account for *anti*-addition of halogens; indeed, epoxides and their hydrolysis served as a model on which the halonium ion mechanism was patterned.

Hydroxylation with permanganate gives *syn*-addition. To account for this stereochemistry it has been suggested that an intermediate like I is involved:



Hydrolysis of such an intermediate would yield the *cis* diol. This mechanism is supported by the fact that osmium tetroxide, OsO_4, which also yields the *cis* diol, actually forms stable intermediates of structure II.



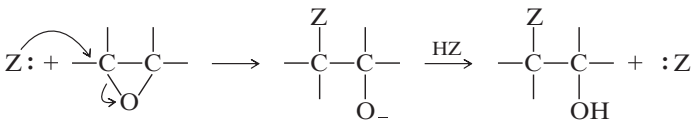
II

Thus, the two methods of hydroxylation—by peroxy acids and by permanganate-differ in stereochemistry because they differ in mechanism.

Problem 16.22 Using both models and drawings of the kind in section on 'Mechanism of addition of halogens to alkenes', show all steps in the formation and hydrolysis of the epoxide of: (a) cyclopentene; (b) *cis*-2-butene; (c) *trans-2-butene*; (d) *cis*-2-pentene; (e) *trans*-2-pentene. (f) Which (if any) of the above products, as obtained, would be optically active?

16.18 Base-catalysed cleavage of epoxides

Unlike ordinary ethers, epoxides can be cleaved under alkaline conditions. Here it is the epoxide itself, not the protonated epoxide, that undergoes nucleophilic attack:

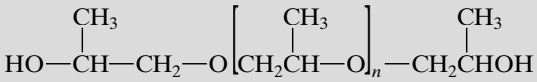


The lower reactivity of the non-protonated epoxide is compensated for by the more basic, more strongly nucleophilic reagents that are compatible with the alkaline solution: alkoxides, phenoxides, ammonia, etc.

Like alkyl halides and sulfonates, and like carbonyl compounds, epoxides are an important source of *electrophilic* carbon: of carbon that is highly susceptible to attack by a wide variety of nucleophiles. (Epoxides generated from carcinogenic hydrocarbons are even attacked by the nucleophilic portion of the genetic material DNA and thereby induce mutation and tumors.)

Problem 16.23 Write equations for the reaction of ethylene oxide with: (a) methanol in the presence of a little H_2SO_4; (b) methanol in the presence of a little $CH_3O^-\ Na^+$; (c) methylamine, CH_3NH_2.

Problem 16.24 Poly(oxypropylene)glycols,

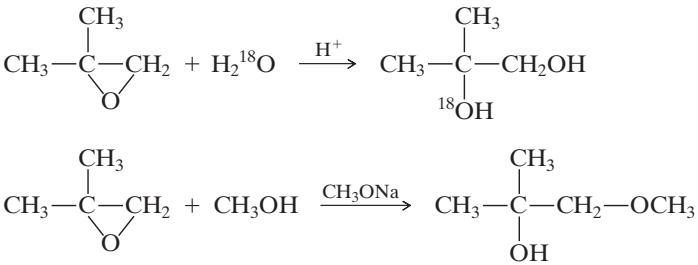


which are used in the manufacture of polyurethane foam rubber, are formed by the action of base (e.g. hydroxide ion) on propylene oxide in the presence of 1,2-propanediol as an initiator. Write all steps in a likely mechanism for their formation.

16.19 Orientation of cleavage of epoxides

There are two carbon atoms in an epoxide ring and, in principle, either one can suffer nucleophilic attack. In a symmetrical epoxide like ethylene oxide, the two carbons are equivalent, and attack occurs randomly at either. But in an unsymmetrical epoxide, the carbons are *not* equivalent, and the product we obtain depends upon which one is preferentially attacked. Just what is the orientation of cleavage of epoxides, and how does one account for it?

The preferred point of attack, it turns out, depends chiefly on whether the reaction is acid-catalysed or base-catalysed. Consider, for example, two reactions of isobutylene oxide:



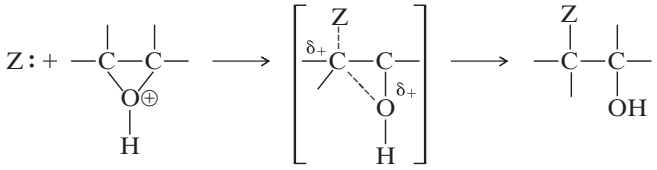
Here, as in general, the nucleophile attacks the more substituted carbon in acid-catalysed cleavage, and the less substituted carbon in base-catalysed cleavage.

Our first thought is that two different mechanisms are involved here, S_N1 and S_N2. But the evidence indicates pretty clearly that both are of the S_N2 type: cleavage of the carbon-oxygen bond and attack by the nucleophile occur in a single step. (There is not only stereochemical evidence—complete inversion—but also evidence of several kinds that we cannot go into here.) How, then, are we to account for the difference in orientation—in particular, for S_N2 attack at the *more hindered* position in acid-catalysed cleavage?

In the transition state of most S_N2 reactions, bond-breaking and bond-making have proceeded to about the same extent, and carbon has not become appreciably positive or negative; as a result steric factors, not electronic factors, chiefly determine reactivity. But in acid-catalysed cleavage of an epoxide, the carbon-oxygen bond, already weak because of the angle strain of the three-membered ring, is further weakened by protonation: the leaving group is a very good one, the weakly basic

alcohol hydroxyl. The nucleophile, on the other hand, is a poor one (water, alcohol). In the transition state bond-breaking has proceeded further than bond-making, and carbon has acquired a considerable positive charge.

Acid-catalysed S_N2 cleavage

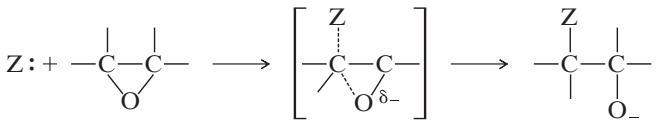


Bond-breaking exceeds bond-making: Positive charge on carbon

Since both leaving group and nucleophile are far away, crowding is relatively unimportant. The stability of the transition state is determined chiefly by electronic factors and not steric factors, and the reaction has considerable S_N1 character. *Attack occurs at the carbon that can best accommodate the positive charge.*

In base-catalysed cleavage, the leaving group is a poorer one—a strongly basic alkoxide oxygen—and the nucleophile is a good one (hydroxide, alkoxide). Bond-breaking and bond-making are more nearly balanced, and reactivity is controlled in the more usual way, by steric factors. *Attack occurs at the less hindered carbon.*

Base-catalysed S_N2 cleavage

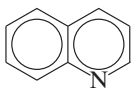


Bond-making balances bond-breaking: no particular charge on carbon

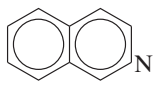
16.20 Fused ring heterocycles

(A) Quinoline and isoquinoline (benzopyridines)

Two isomeric benzopyridines are quinoline and isoquinoline. Quinoline is the benzo[b]pyridine and isoquinoline is the benzo[c]pyridine isomer. These two are very important heterocyclic units because their derivatives widely occur in nature as alkaloids. For example, the antimalarial quinine and the pain reliever morphine.



Quinoline

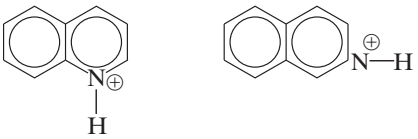


Isoquinoline

General properties

Both of these compounds are basic in nature since the lone pair of electrons on the nitrogen atom is not utilized in the internal resonance for the aromaticity of the compounds. But unlike benzene, the bond lengths of both the compounds are irregular, and both of them possess considerable dipole moment directed toward the nitrogen atom.

Both of these compounds react with acids and Lewis acids at the basic nitrogen atom, forming quinolium and isoquinolium salts, respectively.

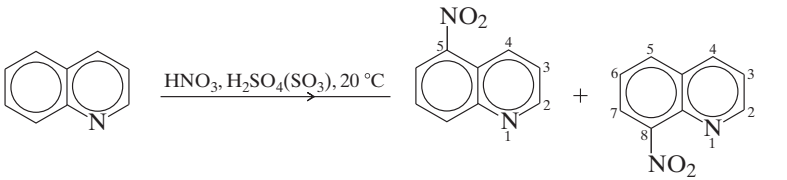


Quinolium ion Isoquinolium ion

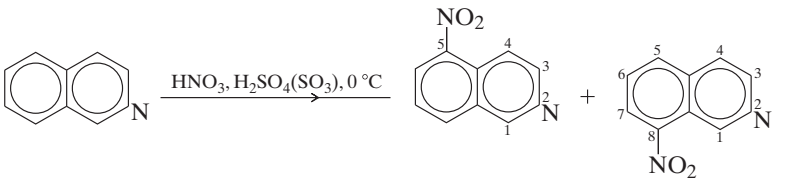
Therefore, the products of electrophilic substitution of the compounds depend on the nature of the reagent used for the reaction.

Since the electron density of the pyridine ring is lower than that of the benzene ring, the electrophilic substitutions of both quinoline and isoquinoline take place in the benzene ring. For example,

1. The nitration of quinoline with fuming nitric acid in concentrated (conc.) sulfuric acid containing SO_3 at room temperature gives a mixture of 5-nitro-and 8-nitroquinolines, whereas isoquinoline reacts with same reagent at 0°C to give a mixture of 5- and 8-nitroisoquinolines.

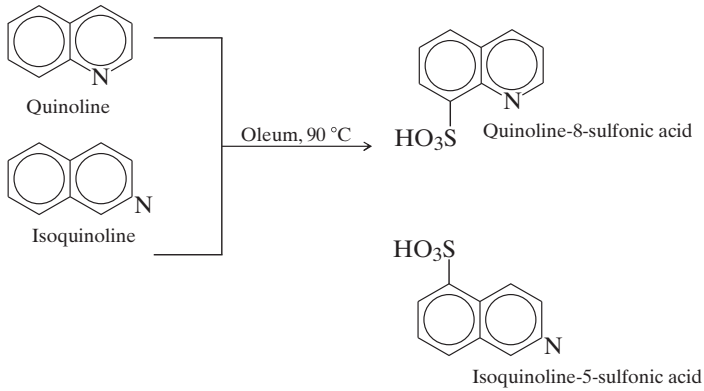


Quinoline 5-Nitroquinoline 8-Nitroquinoline

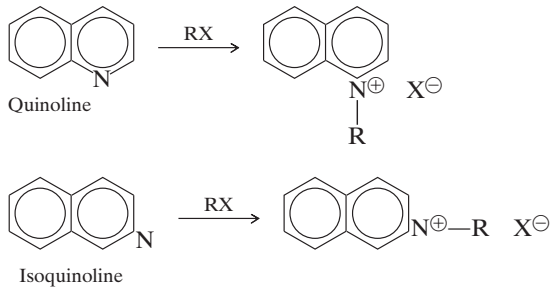


Isoquinoline 5-Nitroquinoline 8-Nitroquinoline

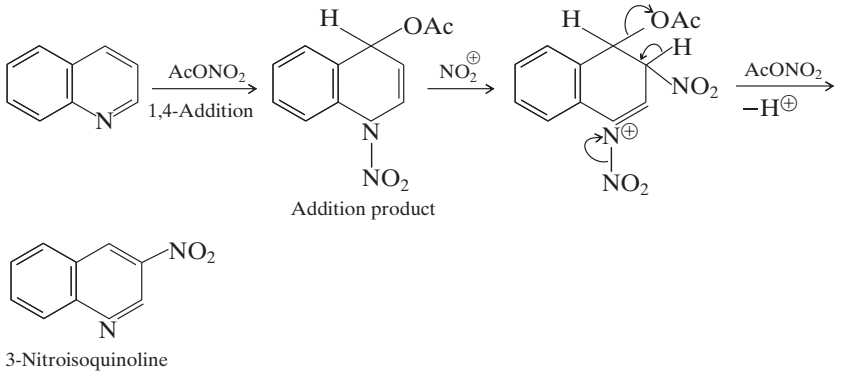
2. Sulfonation of quinoline with oleum at 92°C gives mainly quinoline-8-sulfonic acid. But, isoquinoline under similar condition gives isoquinoline-5-sulfonic acid.



3. Alkyl and acyl halides react directly with the basic nitrogen atom of both the compounds to give quaternary salts.

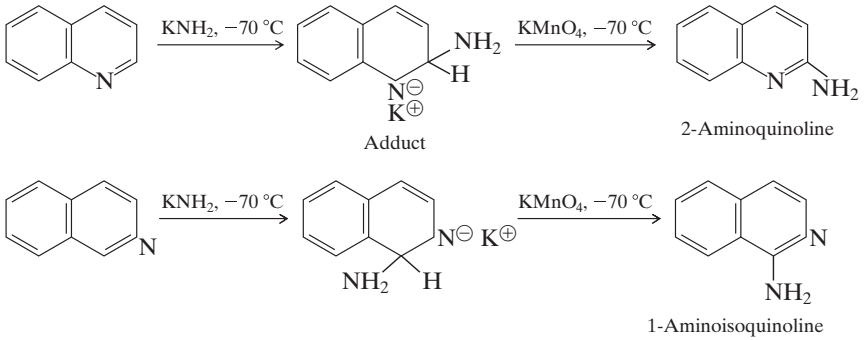


However, with acetyl nitrate at 20°C, quinoline undergoes an addition-substitution reaction to give 3-nitroquinoline. Isoquinoline undergoes no such reaction in the pyridine ring.



The C═N bond of the pyridine ring in both of these compounds undergoes nucleophilic addition at low temperature with KNH_2, and the adduct on

oxidation with $KMnO_4$ at low temperature gives 2-aminoquinoline and 1-aminoisoquinoline in a Chichibabin-type reaction.

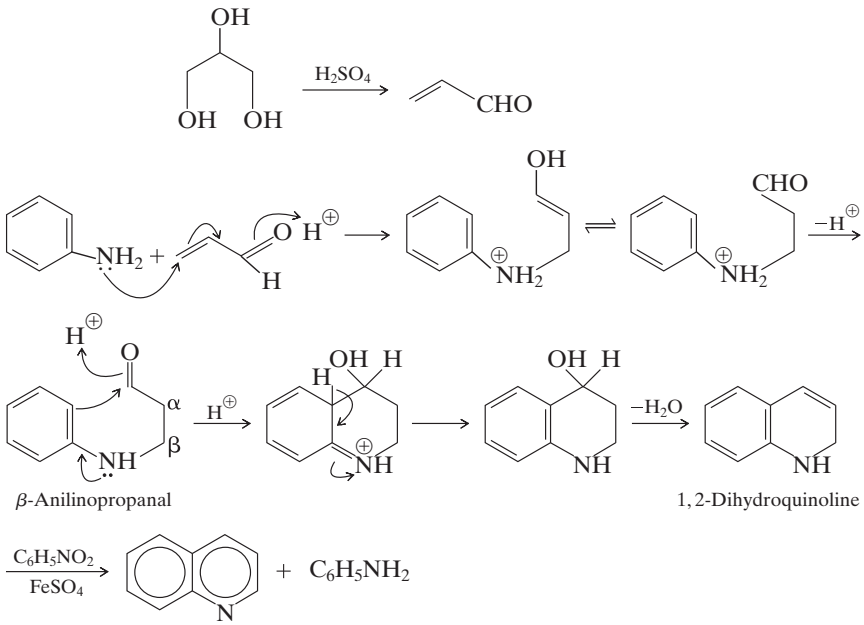


Synthesis of benzopyridines

1. *Synthesis of quinoline*: Skraup synthesis

A mixture of glycerol, amiline, sulfuric acid, nitrobenzene, and ferrous sulfate and heating gives quinoline.

Glycerol is dehydrated by sulfuric acid to acrolein. Aniline undergoes a Michael-type addition with acrolein in an acid-promoted reaction to form β-anilinopropanal that, in turn, undergoes an acid-catalysed cyclization to give 1,2-dihydroquinoline. Nitrobenzene aromatizes this dihydro compound to quinoline and itself is reduced to aniline. Ferrous sulfate moderates this last exothermic step.

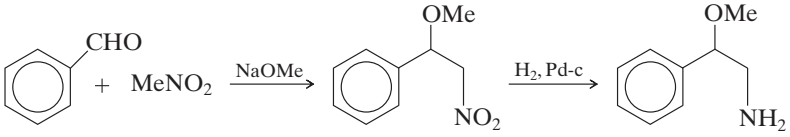


This method can be applied to synthesize benzene ring-substituted quinoline provided the substituents are not strongly deactivating in nature.

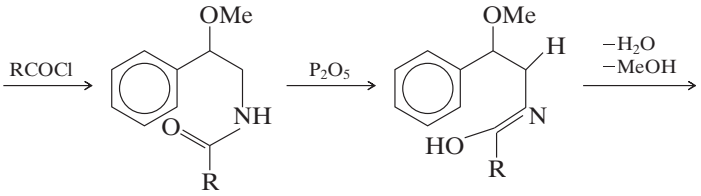
2. *Synthesis of isoquinoline*

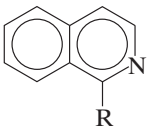
(a) Bischler–Napieralski synthesis.

1-Alkyl isoquinolines can be synthesized by this method, which involves the following steps:



Benzaldehyde Nitromethane

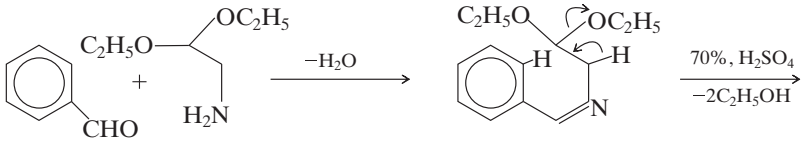




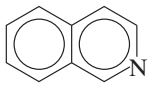
1-Alkyl isoquinoline

(b) Pomeranz–Fritsch reaction.

The parent compound, that is, isoquinoline can be synthesized by this reaction, which is as follows:



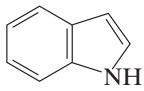
Benzaldehyde Acetal of aminoethanal



Isoquinoline

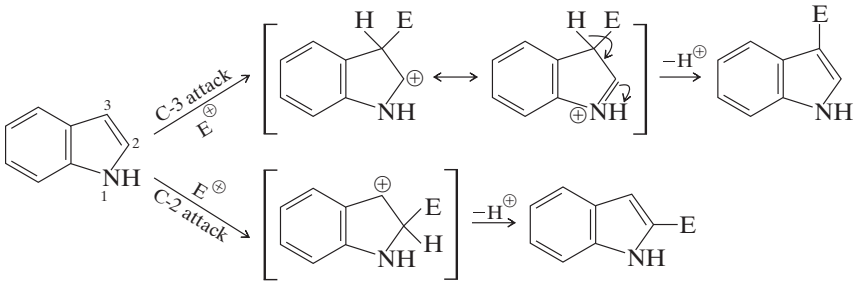
(B) Indole (benzo[b]pyrrole)

Indole ring occurs widely in nature as alkaloids. The alkaloids have medicinal values. In these compounds, a benzene ring is fused with a pyrrole ring and hence behaves as an aromatic heterocyclic compound. Because of the aromatic stability of the benzene ring, the most important contributing structure of indole to its resonance hybrid is its enamine form.

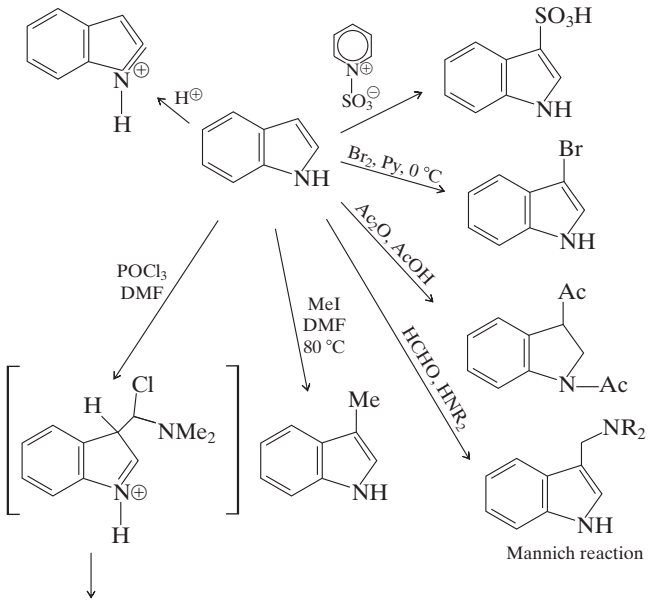


Indole in the enamine form

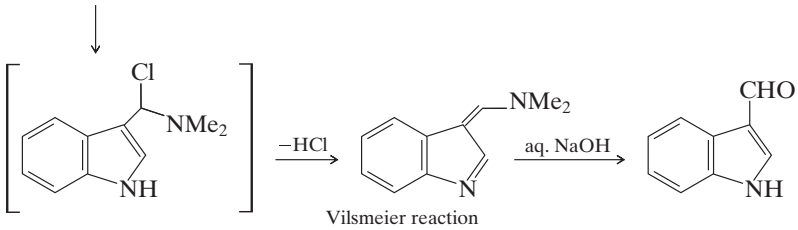
Because of the higher electron density in the heteroring, indole undergoes electrophilic substitution at C-2 in the pyrrole ring and regioselectively at C-3 due to higher resonance stabilization of the intermediate formed by C-3 attack.



However, indole easily undergoes protonation to give indolenium cation for which the electrophilic substitutions of indole cannot be carried out under the similar conditions as are used in benzene series. For example, indole is sulfonated at C-3 with pyridinium–*N*-sulfonate, brominated at C-3 with bromine in pyridine at 0°C, acetylated at C-1 and C-3 to give diacetyl derivative with acetic anhydride in acetic acid, methylated at C-3 with methyl iodide in DMF at 80°C, formylated at C-3 with $POCl_3$ and DMF at 5°C followed by alkaline hydrolysis (Vilsmeier reaction), and amino methylated at C-3 with HCHO and amines (Mannich reaction).



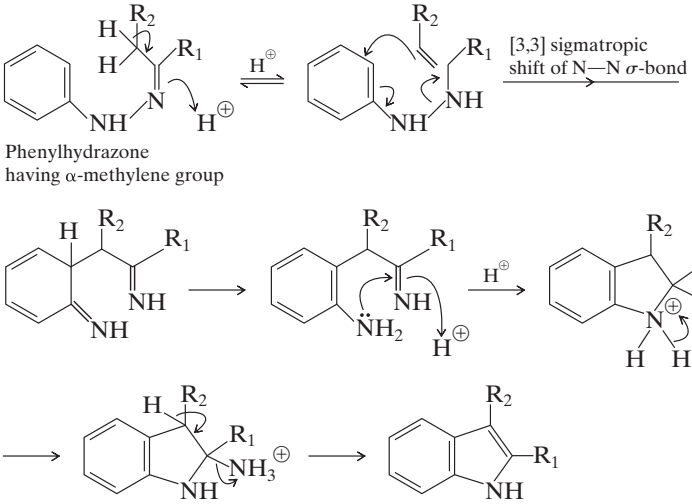
Mannich reaction



Vilsmeier reaction

Synthesis of indole (Fischer's indole synthesis)

Phenylhydrazones having an α-methylene group on treatment with a mineral acid undergoes ring closure through a [3,3] sigmatropic shift with the loss of ammonia. The reaction is known as Fisher's indole synthesis.



Phenylhydrazone
having α-methylene group

EXERCISE

1. Give structures and names of the principal products from the reaction (if any) of pyridine with:

(a) Br_2, 300°C
(b) H_2SO_4, 350°C
(c) acetyl chloride, $AlCl_3$
(d) KNO_3, H_2SO_4, 300°C
(e) $NaNH_2$, heat
(f) C_6H_5Li
(g) dilute HCl
(h) dilute NaOH
(i) acetic anhydride
(j) benzenesulfonyl chloride
(k) ethyl bromide
(l) benzyl chloride
(m) peroxybenzoic acid, then HNO_3, H_2SO_4
(n) H_2,Pt

2. Give structures and names of the principal products from each of the following reactions:

(a) thiophene + conc. H_2SO_4
(b) thiophene + acetic anhydride, $ZnCl_2$
(c) thiophene + acetyl chloride, $TiCl_4$

(d) thiophene + fuming nitric acid in acetic anhydride
(e) product of (d) + Sn, HCl
(f) thiophene + 1 mol Br_2
(g) product of (f) + Mg; then CO_2; then H^+
(h) pyrrole + pyridine: SO_3
(i) pyrrole + diazotized sulfanilic acid
(j) pyrrole + H_2,Ni $\longrightarrow$ C_4H_9N
(k) furfural + acetone + base

3. Pyrrole can be reduced by zinc and acetic acid to a *pyrroline*, C_4H_7N. (a) What structures are possible for this pyrroline?

(b) On the basis of the following evidence which structure must the pyrroline have?

pyrroline + O_3; then H_2O; then H_2O_2 $\longrightarrow$ A ($C_4H_7O_4N$)
chloroacetic acid + NH_3 $\longrightarrow$ B ($C_2H_5O_2N$)
B + chloroacetic acid $\longrightarrow$ A

4. Furan and its derivatives are sensitive to protic acids. The following reactions illustrate what happens.

2,5-dimethylfuran + dilute H_2SO_4 $\longrightarrow$ C ($C_6H_{10}O_2$)
C + NaOI $\longrightarrow$ succinic acid

(a) What is C? (b) Outline a likely series of steps for its formation from 2,5-dimethylfuran.

5. Pyrrole reacts with formaldehyde in hot pyridine to yield a mixture of products from which there can be isolated a small amount of a compound of formula $(C_5H_5N)_4$. Suggest a possible structure for this compound.

6. There are three isomeric pyridinecarboxylic acids, $(C_5H_4N)COOH$: D, m.p. 137°C; E, m.p. 234–237°C; and F, m.p. 317°C. Their structures were proved as follows:

quinoline + $KMnO_4$, OH^- $\longrightarrow$ a diacid ($C_7H_5O_4N$) $\xrightarrow{\text{heat}}$ E, m.p. 234–237 °C

isoquinoline + $KMnO_4$, OH^- $\longrightarrow$ a diacid ($C_7H_5O_4N$) $\xrightarrow{\text{heat}}$ E, m.p. 234–237 °C and F, m.p. 317 °C

What structures should be assigned to D, E, and F?

7. Outline all steps in each of the following syntheses, using any other needed reagents:

(a) β-cyanopyridine from β-picoline
(b) 2-methylpiperidine from pyridine
(c) ethyl 5-nitro-2-furoate from furfural
(d) furylacrylic acid,  from furfural
(e) 1,2,5-trichloropentane from furfural
(f) 3-indolecarboxaldehyde from indole

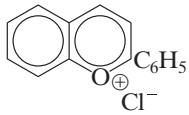
8. (–)-*Nicotine*, the alkaloid in tobacco, can be synthesized in the following way:

nicotinic acid + $SOCl_2$, heat $\longrightarrow$ nicotinoyl chloride (C_6H_4ONCl)
nicotinoyl chloride + $C_2H_5OCH_2CH_2CH_2CdCl$ $\longrightarrow$ G ($C_{11}H_{15}O_2N$), a ketone
G + NH_3, H_2, catalyst $\longrightarrow$ H ($C_{11}H_{18}ON_2$)
H + HBr + strong heat $\longrightarrow$ I ($C_9H_{12}N_2$) + ethyl bromide
I + CH_3I, NaOH $\longrightarrow$ (±)-nicotine ($C_{10}H_{14}N_2$)
(±)-nicotine + (+)-tartaric acid $\longrightarrow$ J and K (both $C_{14}H_{20}O_6N_2$)
J + NaOH $\longrightarrow$ (–)- nicotine + sodium tartrate

What is the structure of (±)-nicotine? Write equations for all the above reactions.

9. The red and blue colors of many flowers and fruits are due to the *anthocyanins*, glycosides of pyrylium salts. The parents structure of the pyrylium salts is *flavylium chloride*, which can be synthesized as follows:

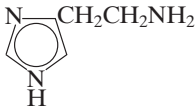
Salicylaldehyde + acetophenone $\xrightarrow{\text{adol}}$ L ($C_{15}H_{12}O_2$)
L + HCl $\longrightarrow$ flavylium chloride, a salt containing three aromatic rings



Flavylium chloride

(a) What is the structure of L? (b) Outline a likely series of steps leading from L to flavylium chloride. (c) Account for the aromatic character of the fused-ring system.

10. (a) Account for the aromatic properties of the imidazole ring.
(b) Arrange the nitrogen atoms of *histamine* (the substance responsible for many allergenic reactions) in order of their expected basicity, and account for your answer.



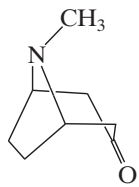
Histamine

(c) Account for the particular dipolar structure given for the amino acid *histidine*.

11. *Tropinic acid*, $C_8H_{13}O_4N$, is a degradation product of atropine, an alkaloid of the deadly nightshade, *Atropa belladonna*. It has a neutralization equivalent of 94 ± 1. It does not react with benzenesulfonyl chloride, cold dilute $KMnO_4$, or Br_2/CCl_4. Exhaustive methylation gives the following results:

tropinic acid + CH_3I $\longrightarrow$ M ($C_9H_{16}O_4NI$)
M + Ag_2O, then strong heat $\longrightarrow$ N ($C_9H_{15}O_4N$)
N + CH_3I $\longrightarrow$ O ($C_{10}H_{18}O_4NI$)
O + Ag_2O, then strong heat $\longrightarrow$ P ($C_7H_8O_4$) + $(CH_3)_3N$ + H_2O
P + H_2, Ni $\longrightarrow$ heptanedioic acid (pimelic acid)

(a) What structures are likely for tropinic acid?
(b) Tropinic acid is formed by oxidation with CrO_3 of *tropinone*, whose structure has been determined by synthesis. Now what is the most likely structure for tropinic acid?



Tropinone

12. *Tropilidine*, 1,3,5-cycloheptatrine, has been made from tropinone (Problem 11). Show how this might have been done.

13. Reduction of tropinone (Problem 11) gives *tropine* and *pseudotropine*, both $C_8H_{15}ON$. When heated with base, tropine is converted into pseudotropine. Give likely structures for tropine and pseudotropine, and explain your answer.

14. *Arecaidine*, $C_7H_{11}O_2N$, an alkaloid of betel nut, has been synthesized in the following way:

ethyl acrylate + NH_3 $\xrightarrow{\text{Michael}}$ Q ($C_5H_{11}O_2N$)

Q + ethyl acrylate $\xrightarrow{\text{Michael}}$ R ($C_{10}H_{19}O_4N$)

R + sodium ethoxide $\xrightarrow{\text{Dieckmnan}}$ S ($C_8H_{13}O_3N$)

S + benzoyl chloride $\longrightarrow$ T ($C_{15}H_{17}O_4N$)

T + H_2, Ni $\longrightarrow$ U ($C_{15}H_{19}O_4N$)

U + acid, heat $\longrightarrow$ V ($C_6H_9O_2N$), *guvacine*, another betel nut alkaloid + $C_6H_5COOH + C_2H_5OH$

V + CH_3I $\longrightarrow$ arecaidine ($C_7H_{11}O_2N$)

(a) What is the most likely structure of arecaidine? Of guvacine?
(b) What will guavacine give upon dehydrogenation?

15. Give the structures of compounds W through CC.

thiophene + 3-hexanone + H_2SO_4 $\longrightarrow$ W($C_{14}H_{18}S_2$)

W + $(CH_3CO)_2O$ + $HClO_4$ $\longrightarrow$ X ($C_{16}H_{20}OS_2$)

X + N_2H_4 + KOH + heat $\longrightarrow$ Y ($C_{16}H_{22}S_2$)

Y + $C_6H_5N(CH_3)CHO$ $\longrightarrow$ Z ($C_{17}H_{22}OS_2$), an aldehyde

Z + Ag_2O $\longrightarrow$ AA ($C_{17}H_{22}O_2S_2$)

AA *was resolved*

(+)-AA + Cu, quinoline, heat $\longrightarrow$ CO_2 + (+)-BB($C_{16}H_{22}S_2$)

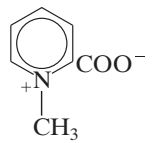
(+)-BB + H_2/Ni $\longrightarrow$ CC($C_{16}H_{34}$), *optically inactive*

What is the significance of the optical inactivity of CC?

16. When heated in solution, 2-pyridinecarboxylic acid (I) loses carbon dioxide and forms pyridine. The rate of this decarboxylation is slowed down by addition of either acid or base. When decarboxylation is carried out in the presence of the ketone, R_2CO, there is obtained not only pyridine but also the tertiary alcohol II. The *N*-methyl derivative (III) is decarboxylated much faster than I.

I

II



III

IV

(a) Show all steps in the most likely mechanism for decarboxylation of I. Show how this mechanism is consistent with each of the above facts.

(b) In the decarboxylation of the isomeric pyridinecarboxylic acids (I and its isomers), the order of reactivity is:

$$2 > 3 > 4$$

In the decarboxylation of the isomeric pyridineacetic acids (IV and its isomers), on the other hand, the order of reactivity is:

$$2 \text{ or } 4 > 3$$

How do you account for each order of reactivity? Why is there a difference between the two sets of acids? (The same mechanism seems to be involved in the both cases.)