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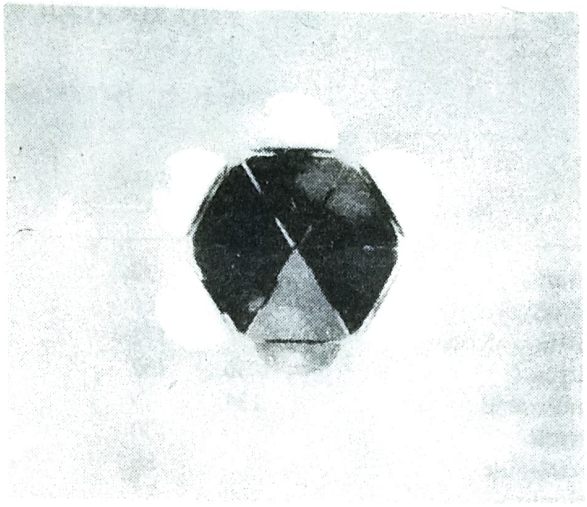
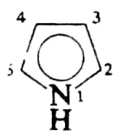


Heterocyclic Compounds

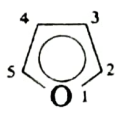
30.1 Heterocyclic systems

A heterocyclic compound is one that contains a ring made up of more than one kind of atom.

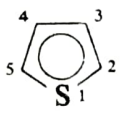
In many of the cyclic compounds that we have studied so far—benzene, naphthalene, cyclohexanol, cyclopentadiene—the rings are made up only of carbon atoms; such compounds are called *homocyclic* compounds. But there are also rings containing, in addition to carbon, other kinds of atoms, most commonly nitrogen, oxygen, or sulfur. For example:



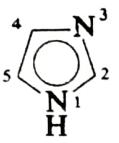
Pyrrole



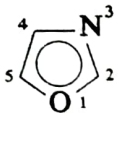
Furan



Thiophene



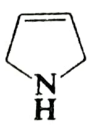
Imidazole



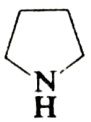
Oxazole

Thiazole

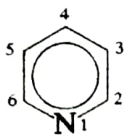
Pyrazole



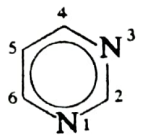
3-Pyrroline



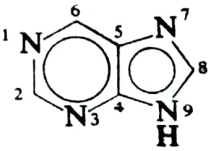
Pyrrolidine



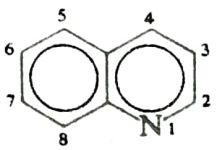
Pyridine



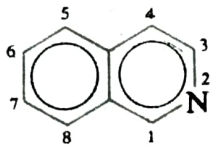
Pyrimidine



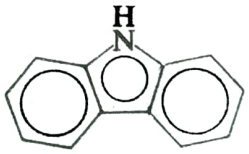
Purine



Quinoline



Isoquinoline



Carbazole

Table 30.1 HETEROCYCLIC COMPOUNDS

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Furan	−30	32	Pyridine	−42	115
Tetrahydrofuran	−108	66	α-Picoline	−64	128
Furfuryl alcohol		171	β-Picoline		143
Furfural	−36	162	γ-Picoline		144
Furoic acid	134		Piperidine	−9	106
Pyrrole		130	Picolinic acid	137	
Pyrrolidine		88	Nicotinic acid	237	
Thiophene	−40	84	Isonicotinic acid	317	
			Indole	53	254
			Quinoline	−19	238
			Isoquinoline	23	243

We notice that, in the numbering of ring positions, hetero atoms are generally given the lowest possible numbers.

Actually, of course, we have already dealt with numerous heterocyclic compounds: *cyclic anhydrides* (Sec. 20.9) and *cyclic imides* (Sec. 20.14), for example; *lactones* (Sec. 20.15) and *lactams* (Problem 22.10, p. 840); *cyclic acetals* of dihydroxy alcohols (Problem 15, p. 704); the solvents *dioxane* and *tetrahydrofuran* (Sec. 13.18). In all these, the chemistry is essentially that of their open-chain analogs.

Crown ethers (Sec. 13.19) are, of course, heterocyclic compounds, and with them we found an ordinary property of ethers—the ability to solvate cations—taking on a special importance because these molecules are rings, and rings of a particular size. In Sec. 22.14 we looked very briefly at a few nitrogen heterocycles, but only for the property they share with other amines: basicity.

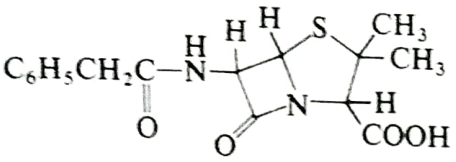
We have encountered three-membered heterocyclic rings which, because of ring strain, are highly reactive: *epoxides* (Secs. 13.20 and 24.14) and *aziridines* (Sec. 22.6); the fleeting but important intermediates, cyclic *halonium ions* (Secs. 9.13, 10.2, and 29.2) and cyclic *sulfonium ions* (Sec. 29.4).

Heterocyclic intermediates are being used more and more in synthesis as *protecting groups*, readily generated and, when their job is done, readily removed. We have seen two examples of this: the temporary incorporation of the carboxyl group into a *2-oxazoline* ring (Sec. 25.6), and the temporary formation of *tetrahydropyranyl* (*THP*) *ethers* and *esters*, resistant toward alkali but extremely easily cleaved by acid (Sec. 18.19 and Problem 15, p. 788).

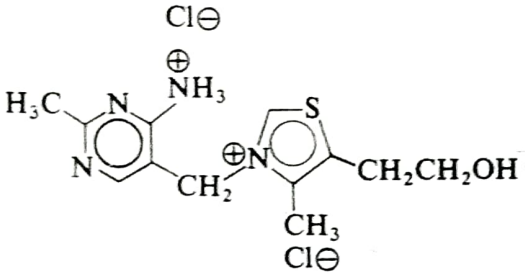
In the biological world, as we shall see in the final chapters of this book, heterocyclic compounds are everywhere. Carbohydrates are heterocyclic; so are chlorophyll and heme, which make leaves green and blood red and bring life to plants and animals. Heterocycles form the sites of reaction in many enzymes and coenzymes. Heredity comes down, ultimately, to the particular sequence of attachment of a half-dozen heterocyclic rings to the long chains of nucleic acids.

In this chapter we can take up only a very few of the many different heterocyclic systems, and look only briefly at them. Among the most important and most interesting heterocycles are the ones that possess aromatic properties; we shall focus our attention on a few of these, and in particular upon their aromatic properties.

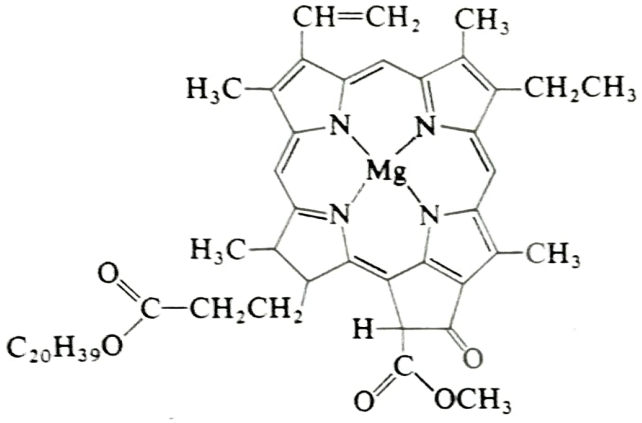
We can get some idea of the importance—as well as complexity—of heterocyclic systems from the following examples. Some others are *heme* (p. 1228), *nicotinamide adenine dinucleotide* (p. 1228), and *oxytocin* (p. 1217).



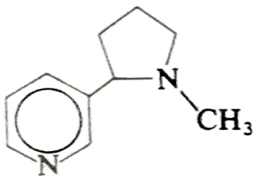
Penicillin G
Antibiotic



Thiamine
Vitamin B_1
Anti-beriberi factor



Chlorophyll a
Green plant pigment: catalyst for photosynthesis

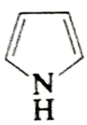


Nicotine
A tobacco alkaloid

FIVE-MEMBERED RINGS

30.2 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 hetero atom.



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. 30.1).

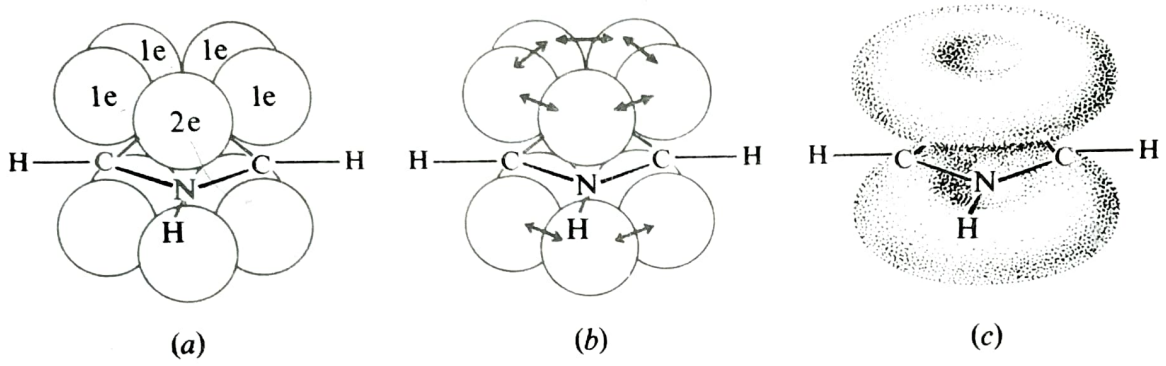
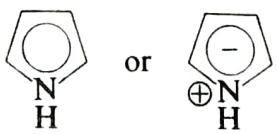


Figure 30.1 Pyrrole molecule. (*a*) Two electrons in the *p* orbital of nitrogen; one electron in the *p* orbital of each carbon. (*b*) Overlap of the *p* orbitals to form π bonds. (*c*) Clouds above and below the plane of the ring; a total of six π electrons, the aromatic sextet.

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,

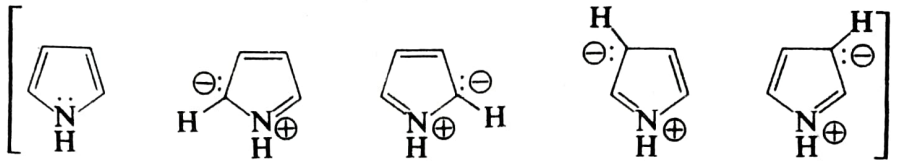


IV

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 nitrogen is



V VI VII VIII IX

Pyrrole

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

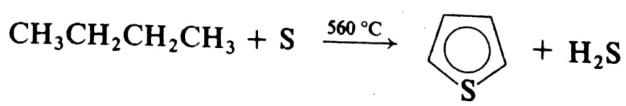
Furan Thiophene

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

30.3 Source of pyrrole, furan, and thiophene

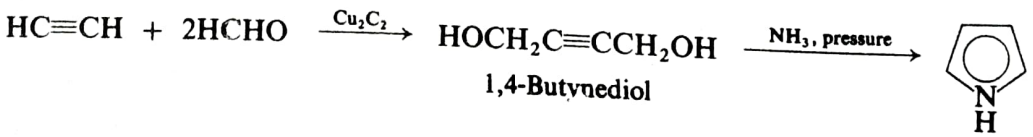
Pyrrole and thiophene are found in small amounts in coal tar. During the fractional distillation of coal tar, thiophene (b.p. 84 °C) is collected along with the benzene (b.p. 80 °C); as a result ordinary benzene contains about 0.5% of thiophene, and must be specially treated if *thiophene-free benzene*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

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



n-Butane Thiophene

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



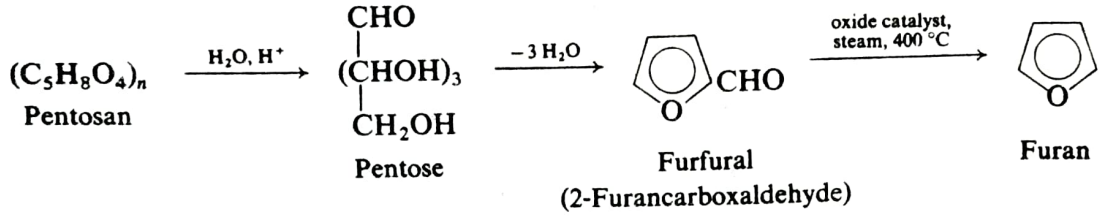
1,4-Butynediol

Pyrrole

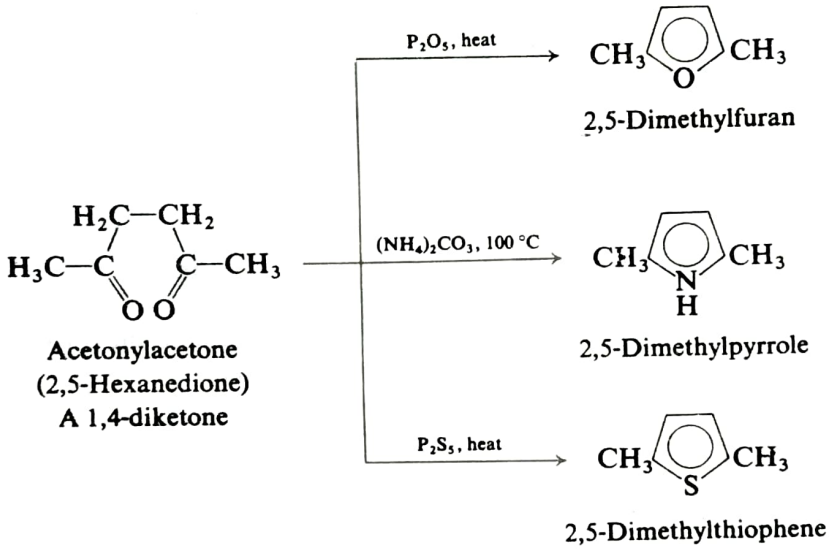
The pyrrole ring is the basic unit of the *porphyrin* system, which occurs, for example, in chlorophyll (p. 1059) and in hemoglobin (p. 1228).

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 hydrolyzed 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 (see Sec. 30.4); most, however, are prepared from open-chain compounds by ring closure. For example:



Problem 30.1 Give structural formulas for all intermediates in the following synthesis of 2,5-hexanedione:

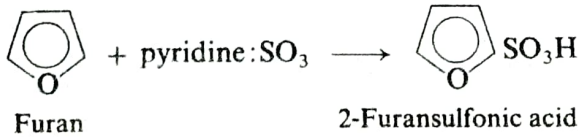
ethyl acetoacetate + $NaOC_2H_5$ ⟶ A ($C_6H_9O_3Na$)
A + I_2 ⟶ B ($C_{12}H_{18}O_6$) + NaI
B + dilute acid + heat ⟶ 2,5-hexanedione + carbon dioxide + ethanol

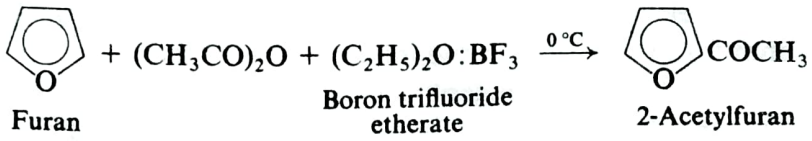
Problem 30.2 Outline a synthesis of 2,5-diphenylfuran, starting from ethyl benzoate and ethyl acetate.

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

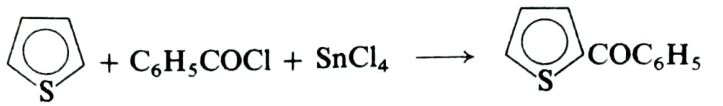
Like other aromatic compounds, these five-membered heterocycles undergo nitration, halogenation, sulfonation, and Friedel–Crafts acylation. They are much more reactive than benzene, and resemble the most reactive benzene derivatives (amines and phenols) in undergoing such reactions as the Reimer–Tiemann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

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

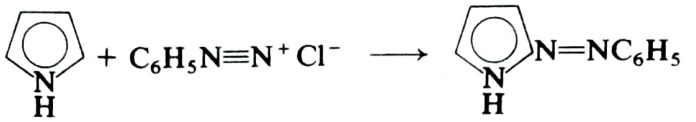




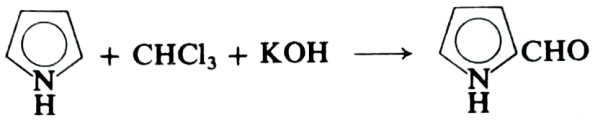
Furan — Boron trifluoride etherate — 2-Acetylfuran



Thiophene — 2-Benzoylthiophene



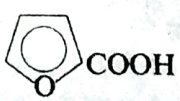
Pyrrole — 2-(Phenylazo)pyrrole



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 30.3 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.

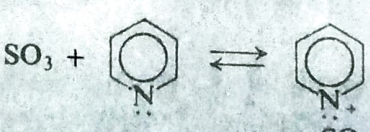


2-Furoic acid

Problem 30.4 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? (*Hint*: See Sec. 31.7.)

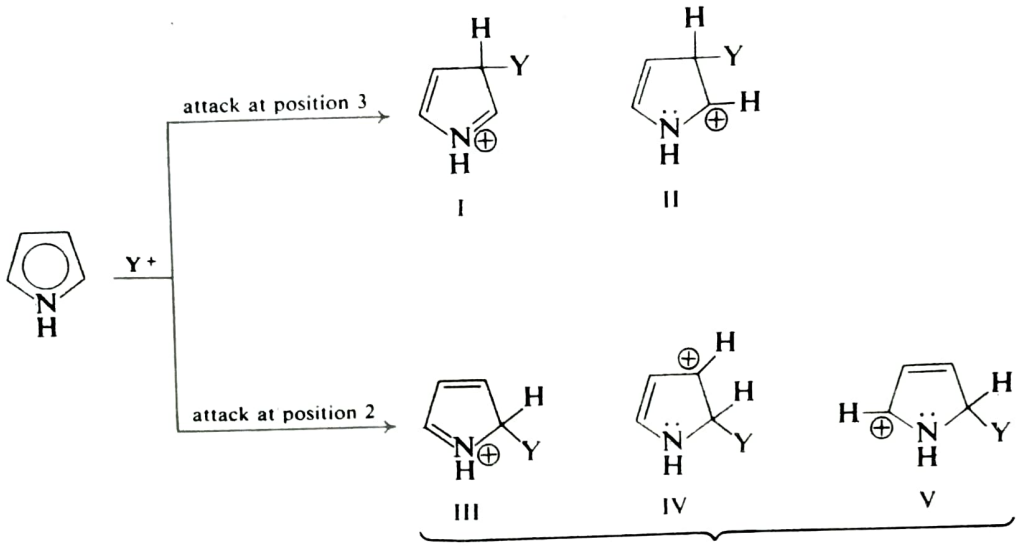
Problem 30.5 Predict the products from the treatment of furfural (2-furancarboxaldehyde) with concentrated aqueous NaOH.

Problem 30.6 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.



Pyridine

In our study of electrophilic aromatic substitution (Sec. 15.17), 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.



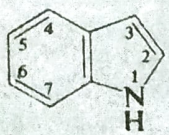
Attack at position 3 yields a carbocation that is a hybrid of structures I and II. Attack at position 2 yields a carbocation that is a hybrid not only of structures III and IV (analogous to I and II) but also of structure V; the extra stabilization conferred by V makes this ion the more stable one.

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

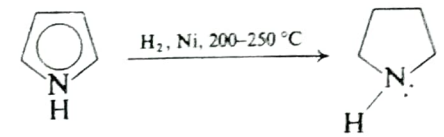


VI
Indole

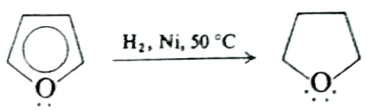
It undergoes electrophilic substitution, chiefly at position 3. Account (a) for the aromatic properties of indole, and (b) for the orientation in electrophilic substitution. (*Hint*: See Sec. 15.21.)

30.5 Saturated five-membered heterocycles

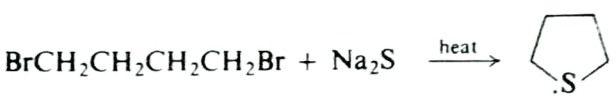
Catalytic hydrogenation converts pyrrole and furan into the corresponding saturated heterocycles, *pyrrolidine* and *tetrahydrofuran*. Since thiophene poisons most catalysts, *tetrahydrothiophene* is made instead from open-chain compounds.



Pyrrole ($K_b \sim 10^{-14}$) Pyrrolidine ($K_b \sim 10^{-3}$)



Furan Tetrahydrofuran



Tetrahydrothiophene

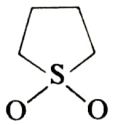
Saturation of these rings destroys the aromatic structure and, with it, the aromatic properties. Each of the saturated heterocycles has the properties we would expect of it: the properties of a secondary aliphatic amine, an aliphatic ether, or an aliphatic sulfide. With nitrogen's extra pair of electrons 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. 30.2.)

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

Figure 30.2 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 (Fig. 14.7, p. 506), with which it is isoelectronic. Pyrrolidine, on the other hand, is clearly aliphatic, and closely resembles cyclopentane (Fig. 13.8, p. 459), 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 (Sec. 26.4), and in hydroborations. Oxidation of tetrahydrothiophene yields *tetramethylene sulfone* (or *sulfolane*), also used as an aprotic solvent (Sec. 7.4).



Tetramethylene sulfone
(Sulfolane)

We have encountered pyrrolidine as a secondary amine commonly used in making enamines (Sec. 25.8). The pyrrolidine ring occurs naturally in a number of alkaloids (Sec. 4.27), providing the basicity that gives these compounds their name (*alkali-like*).

Problem 30.8 An older process for the synthesis of both the adipic acid and the hexamethylenediamine needed in the manufacture of nylon-6,6 (Sec. 31.7) started with tetrahydrofuran. Using only familiar chemical reactions, suggest possible steps in their synthesis.

Problem 30.9 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 30.10 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:

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

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

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

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

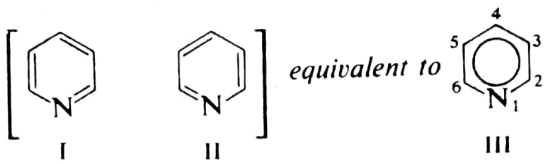
SIX-MEMBERED RINGS

30.6 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.



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. 30.3).

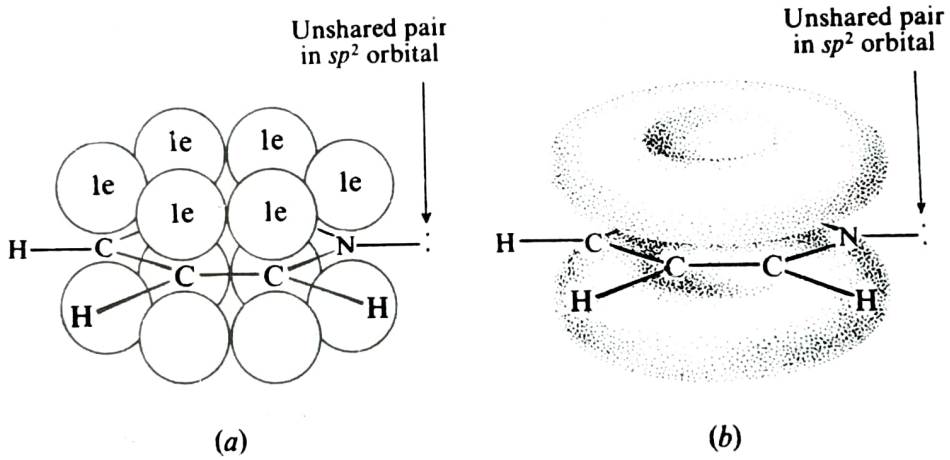


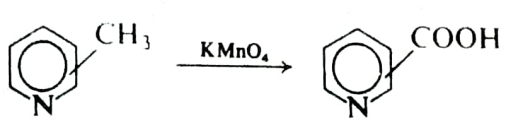
Figure 30.3 Pyridine molecule. (*a*) One electron in each *p* orbital; two electrons in an sp^2 orbital of nitrogen. (*b*) The *p* orbitals overlap to form π clouds above and below the plane of the ring; two unshared electrons are still in an sp^2 orbital of nitrogen.

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.

30.7 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.



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)

30.8 Reactions of pyridine

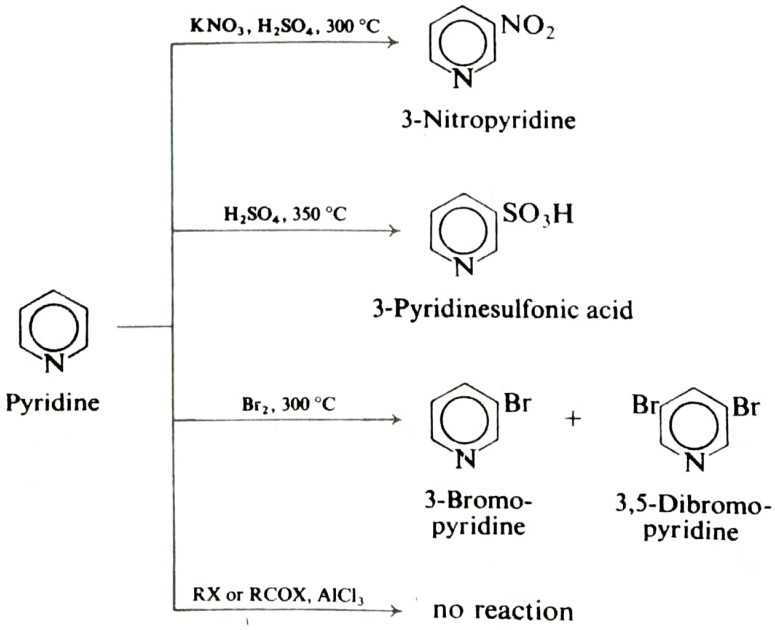
The chemical properties of pyridine are those we would expect on the basis of its structure. The ring undergoes the substitution, both electrophilic and nucleophilic, typical of aromatic rings; our interest will lie chiefly in the way the nitrogen atom affects these reactions.

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.

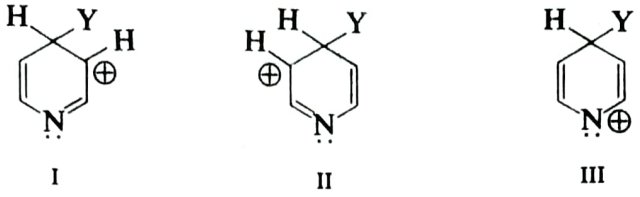
30.9 Electrophilic substitution in pyridine

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.

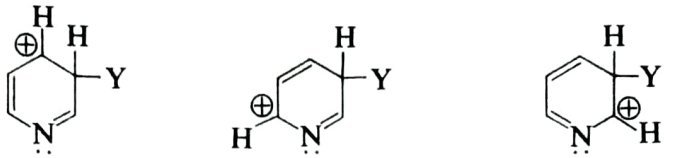


I II III

Especially unstable: nitrogen has sextet

Electrophilic attack at 4-position

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



IV V VI

Electrophilic attack at 3-position

(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 (see Sec. 30.4) 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.

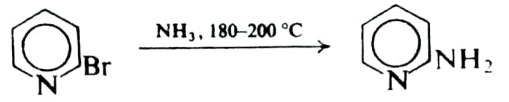
Problem 30.11 2-Aminopyridine can be nitrated or sulfonated under much milder conditions than pyridine itself; substitution occurs chiefly at the 5-position. Account for these facts.

Problem 30.12 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.

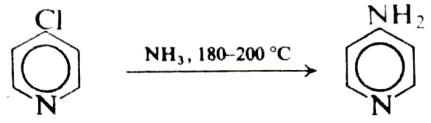
Problem 30.13 Account for the following: (a) treatment of quinoline (Sec. 30.1) with HNO_3 and H_2SO_4 gives 5- and 8-nitroquinolines; (b) oxidation with $KMnO_4$ gives 2,3-pyridinedicarboxylic acid. (*Hint*: See Sec. 15.21.)

30.10 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:

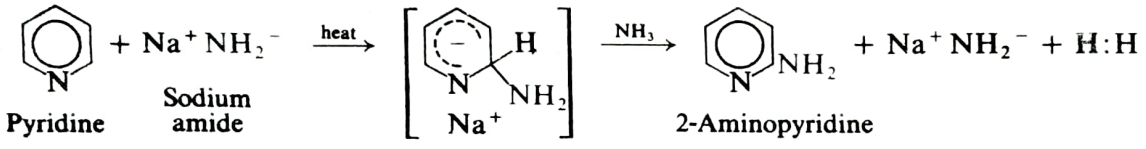


2-Bromopyridine 2-Aminopyridine

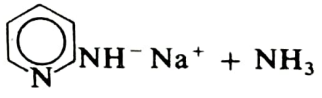


4-Chloropyridine 4-Aminopyridine

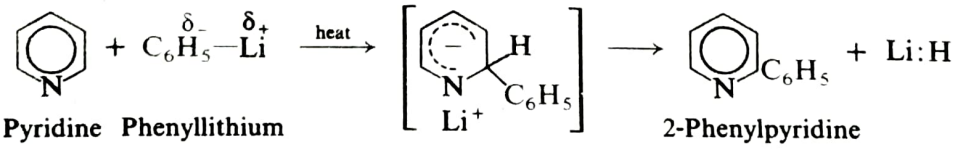
The reactivity of pyridine toward nucleophilic substitution is so great that even the powerfully basic hydride ion, $:H^-$, can be displaced. Two important examples of this reaction are amination by sodium amide (**Chichibabin reaction**), and alkylation or arylation by organolithium compounds.



Pyridine Sodium amide 2-Aminopyridine



Sodium salt of 2-aminopyridine



Pyridine Phenyllithium 2-Phenylpyridine

As we have seen (Sec. 26.8), 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.

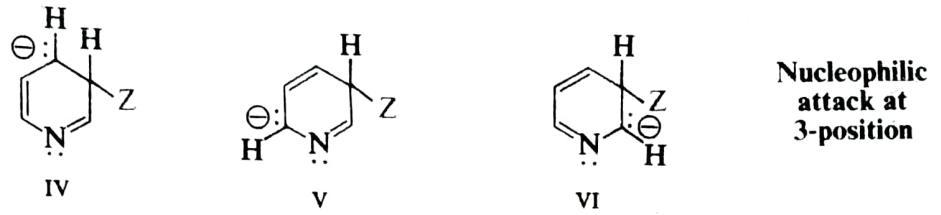
Nucleophilic attack at the 4-position yields a carbanion that is a hybrid of structures I, II, and III:

I II III

Nucleophilic attack at 4-position

Especially stable: negative charge on nitrogen

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



IV V VI

Nucleophilic attack at 3-position

(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.

30.11 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, and use the approach of Secs. 6.12 and 12.11.

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.

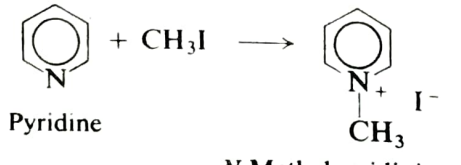
Pyridine bears the same relationship to an aliphatic amine as the phenyl anion bears to an alkyl anion. The pair of electrons that gives pyridine its basicity occupies an sp^2 orbital; it is held more tightly and is less available for sharing with acids than the pair of electrons of an aliphatic amine,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

Problem 30.14 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 (Sec. 20.8).

Problem 30.15 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)

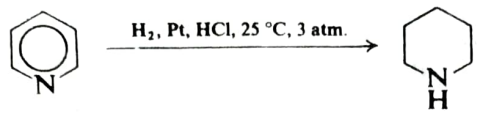
Problem 30.16 Like any other tertiary amine, pyridine can be converted (by peroxybenzoic acid) into its *N*-oxide. In contrast to pyridine itself, pyridine *N*-oxide readily undergoes nitration, chiefly in the 4-position. How do you account for this reactivity and orientation?

Pyridine *N*-oxide

Problem 30.17 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?

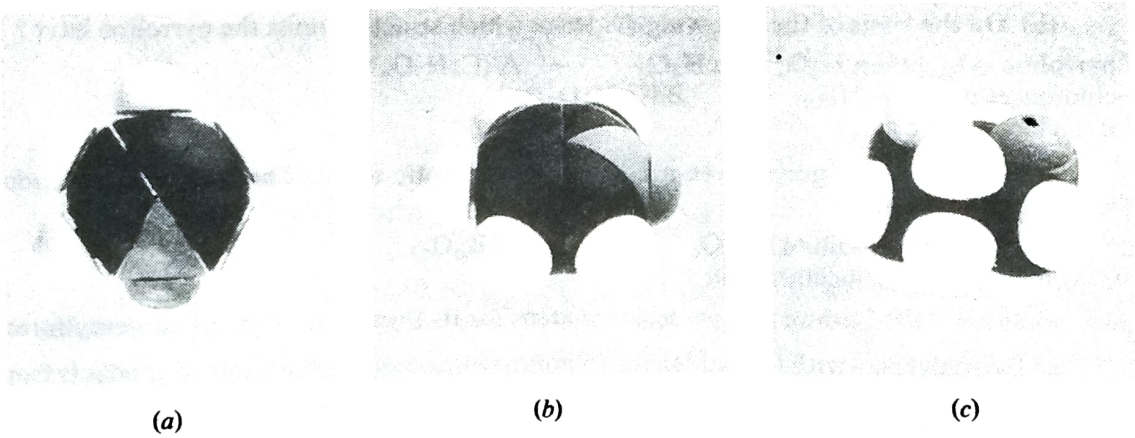
30.12 Reduction of pyridine

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



Pyridine ($K_b = 2.3 \times 10^{-9}$) Piperidine ($K_b = 2 \times 10^{-3}$)

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. 30.4). Like pyridine, piperidine is often used as a basic catalyst in such reactions as the Michael addition (Sec. 27.7).



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

Figure 30.4 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 (Fig. 14.5, p. 503), with an unshared pair of electrons taking the place of one hydrogen. Piperidine has the familiar shape of chair cyclohexane (Fig. 13.5, p. 456), 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 30.18 Why can piperidine not be used in place of pyridine in the Schotten–Baumann procedure?

12. *Tropilidene*, 1,3,5-cycloheptatriene, has been made from tropinone (Problem 11). Show how this might have been done. (*Hint*: See Problem 24, p. 882.)

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 $\xrightarrow{\text{Dieckmann}}$ 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 guvacine give upon dehydrogenation?

15. Give the structures of compounds W through CC. (*Hint*: Sec. 31.7.)

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 ($C_{16}H_{22}S_2$)

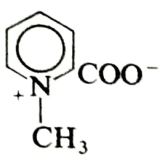
(+)-BB + H_2/Ni $\longrightarrow$ CC ($C_{16}H_{34}$), *optically inactive*

What is the significance of the optical inactivity of CC?

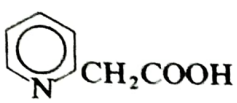
16. When heated in solution, 2-pyridinecarboxylic acid (I) loses carbon dioxide and forms pyridine. The rate of this decarboxylation is slowed down by addition of either acid or base. When decarboxylation is carried out in the presence of the ketone, R_2CO, there is obtained not only pyridine but also 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 both cases.)