24 Amines and Heterocycles

Organic KNOWLEDGE TOOLS

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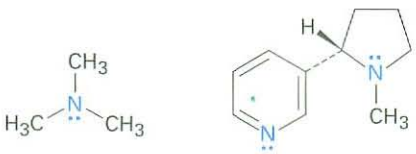
Online homework for this chapter may be assigned in Organic OWL.

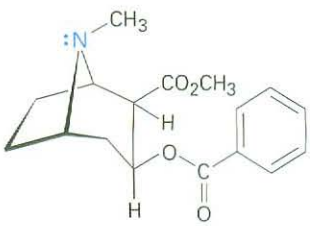
Amines are organic derivatives of ammonia in the same way that alcohols and ethers are organic derivatives of water. Like ammonia, amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic. We'll soon see, in fact, that most of the chemistry of amines depends on the presence of this lone pair of electrons.

Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish, nicotine is found in tobacco, and cocaine is a stimulant found in the South American coca bush. In addition, amino acids are the building blocks from which all proteins are made, and cyclic amine bases are constituents of nucleic acids.



Trimethylamine

Nicotine



Cocaine

WHY THIS CHAPTER?

By the end of this chapter, we will have seen all the common functional groups. Of those groups, amines and carbonyl compounds are the most abundant and have the richest chemistry. In addition to the proteins and nucleic acids already mentioned, the majority of pharmaceutical agents contain amine functional groups, and many of the common coenzymes necessary for biological catalysis are amines.

24.1 Naming Amines

Amines can be either alkyl-substituted (**alkylamines**) or aryl-substituted (**arylamines**). Although much of the chemistry of the two classes is similar, there are also substantial differences. Amines are classified as **primary** (RNH_2),

Sean Duggan

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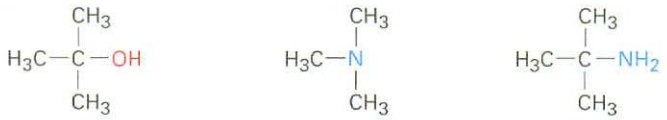
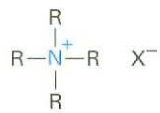
secondary (R_2NH), or **tertiary** (R_3N), depending on the number of organic substituents attached to nitrogen. Thus, methylamine (CH_3NH_2) is a primary amine, dimethylamine [$(CH_3)_2NH$] is a secondary amine, and trimethylamine [$(CH_3)_3N$] is a tertiary amine. Note that this usage of the terms *primary, secondary,* and *tertiary* is different from our previous usage. When we speak of a tertiary alcohol or alkyl halide, we refer to the degree of substitution at the alkyl carbon atom, but when we speak of a tertiary amine, we refer to the degree of substitution at the nitrogen atom.



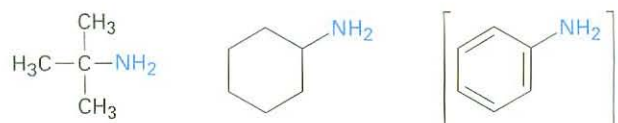
***tert*-Butyl alcohol (a tertiary alcohol)** **Trimethylamine (a tertiary amine)** ***tert*-Butylamine (a primary amine)**

Compounds containing a nitrogen atom with four attached groups also exist, but the nitrogen atom must carry a formal positive charge. Such compounds are called **quaternary ammonium salts**.



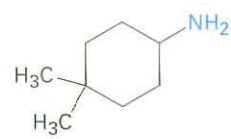
A quaternary ammonium salt

Primary amines are named in the IUPAC system in several ways. For simple amines, the suffix *-amine* is added to the name of the alkyl substituent. You might also recall from Chapter 15 that phenylamine, $C_6H_5NH_2$, has the common name *aniline*.

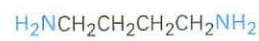


***tert*-Butylamine** **Cyclohexylamine** **Aniline**

Alternatively, the suffix *-amine* can be used in place of the final *-e* in the name of the parent compound.

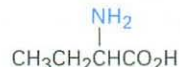


4,4-Dimethylcyclohexanamine



1,4-Butanediamine

Amines with more than one functional group are named by considering the $-NH_2$ as an *amino* substituent on the parent molecule.

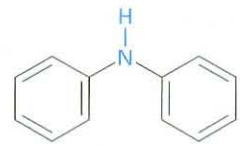


2-Aminobutanoic acid

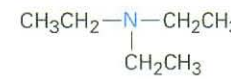
2,4-Diaminobenzoic acid

4-Amino-2-butanone

Symmetrical secondary and tertiary amines are named by adding the prefix *di-* or *tri-* to the alkyl group.

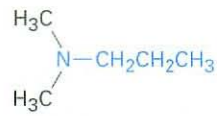


Diphenylamine

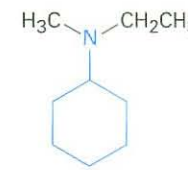


Triethylamine

Unsymmetrically substituted secondary and tertiary amines are named as *N*-substituted primary amines. The largest alkyl group is chosen as the parent name, and the other alkyl groups are *N*-substituents on the parent (*N* because they're attached to nitrogen).

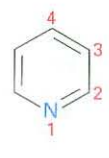


N,N-Dimethylpropylamine

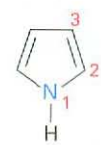


N-Ethyl-*N*-methylcyclohexylamine

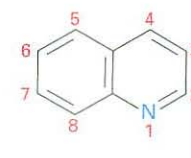
Heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.



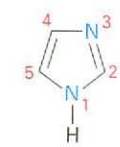
Pyridine



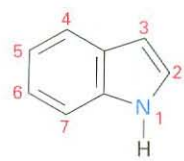
Pyrrole



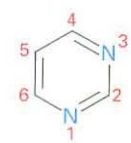
Quinoline



Imidazole



Indole

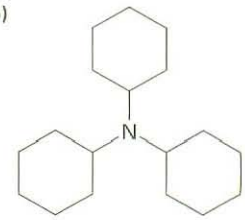
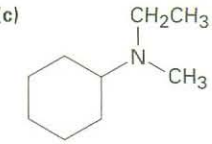


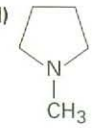
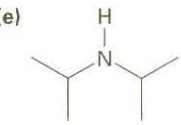
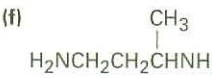
Pyrimidine

Pyrrolidine

Piperidine

Problem 24.1 Name the following compounds:

(a) $CH_3NHCH_2CH_3$ (b)  (c) 

(d)  (e)  (f) 

Problem 24.2 Draw structures corresponding to the following IUPAC names:

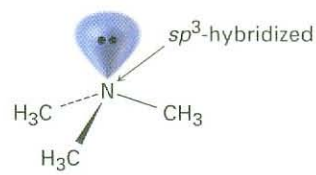
(a) Triisopropylamine
(b) Triallylamine
(c) *N*-Methylaniline
(d) *N*-Ethyl-*N*-methylcyclopentylamine
(e) *N*-Isopropylcyclohexylamine
(f) *N*-Ethylpyrrole

Problem 24.3 Draw structures for the following heterocyclic amines:

(a) 5-Methoxyindole
(b) 1,3-Dimethylpyrrole
(c) 4-(*N*,*N*-Dimethylamino)pyridine
(d) 5-Aminopyrimidine

24.2 Properties of Amines

The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp^3-hybridized, with the three substituents occupying three corners of a tetrahedron and the lone pair of electrons occupying the fourth corner. As you might expect, the C–N–C bond angles are close to the 109° tetrahedral value. For trimethylamine, the C–N–C bond angle is 108°, and the C–N bond length is 147 pm.



Trimethylamine

One consequence of tetrahedral geometry is that an amine with three different substituents on nitrogen is chiral, as we saw in Section 9.12. Unlike chiral carbon compounds, however, chiral amines can't usually be resolved because the two enantiomeric forms rapidly interconvert by a *pyramidal inversion*, much as an alkyl halide inverts in an S_N2 reaction. Pyramidal inversion occurs by a momentary rehybridization of the nitrogen atom to planar, sp^2 geometry, followed by rehybridization of the planar intermediate to tetrahedral, sp^3 geometry

(Figure 24.1). The barrier to inversion is about 25 kJ/mol (6 kcal/mol), an amount only twice as large as the barrier to rotation about a C–C single bond.

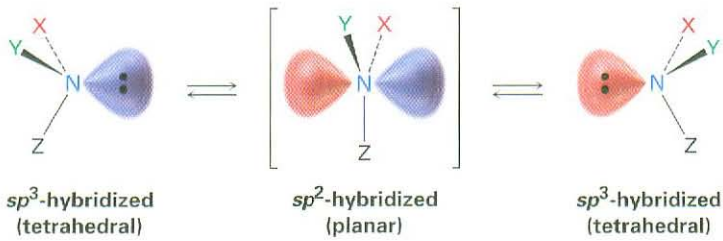
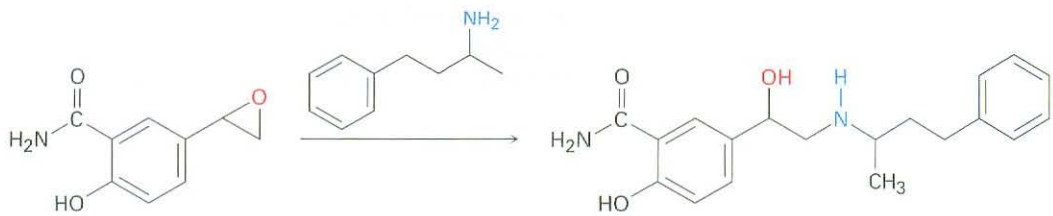


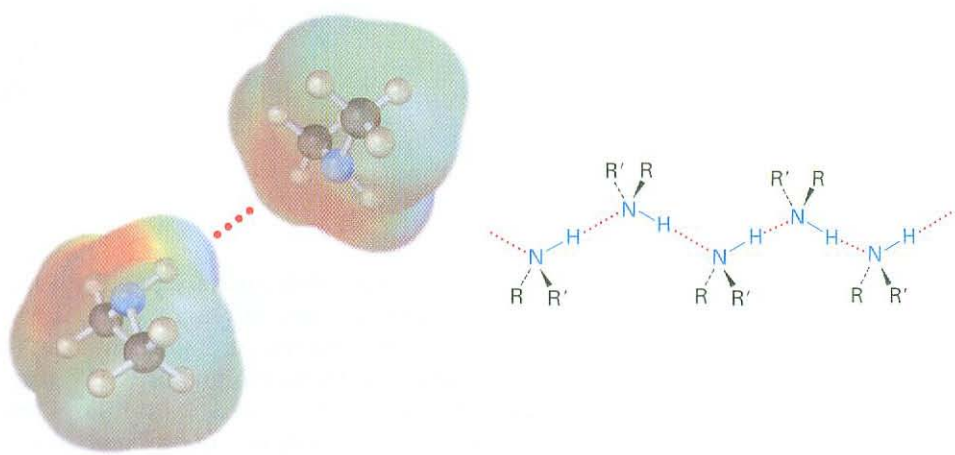
Figure 24.1 Pyramidal inversion rapidly interconverts the two mirror-image (enantiomeric) forms of an amine.

Alkylamines have a variety of applications in the chemical industry as starting materials for the preparation of insecticides and pharmaceuticals. Labetalol, for instance, a so-called β-blocker used for the treatment of high blood pressure, is prepared by S_N2 reaction of an epoxide with a primary amine. The substance marketed for drug use is a mixture of all four possible stereoisomers, but the biological activity derives primarily from the (*R*,*R*) isomer.



Labetalol

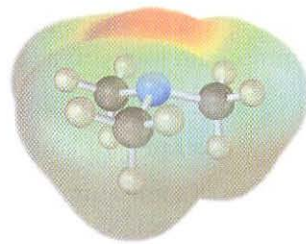
Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight. Diethylamine (MW = 73 amu) boils at 56.3 °C, for instance, while pentane (MW = 72 amu) boils at 36.1 °C.

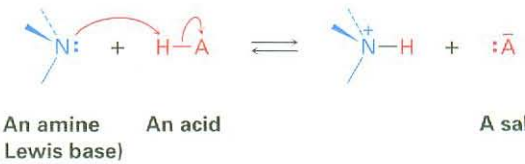


One other characteristic of amines is their odor. Low-molecular-weight amines such as trimethylamine have a distinctive fishlike aroma, while diamines such as 1,5-pentanediamine, commonly called cadaverine, have the appalling odors you might expect from their common names.

24.3 Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. They react with acids to form acid–base salts, and they react with electrophiles in many of the polar reactions seen in past chapters. Note in the following electrostatic potential map of trimethylamine how the negative (red) region corresponds to the lone-pair of electrons on nitrogen.





Amines are much stronger bases than alcohols and ethers, their oxygen-containing analogs. When an amine is dissolved in water, an equilibrium is established in which water acts as an acid and transfers a proton to the amine. Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2.8), the base strength of an amine can be measured by defining an analogous *basicity constant* K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

For the reaction

$$RNH_2 + H_2O \rightleftharpoons RNH_3^+ + OH^-$$

$$K_b = \frac{[RNH_3^+]\,[OH^-]}{[RNH_2]}$$

$$pK_b = -\log K_b$$

In practice, K_b values are not often used. Instead, the most convenient way to measure the *basicity* of an amine (RNH_2) is to look at the *acidity* of the corresponding ammonium ion (RNH_3^+).

For the reaction

$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^-$$

$$K_a = \frac{[RNH_2]\,[H_3O^+]}{[RNH_3^+]}$$

$$K_a \cdot K_b = \left[\frac{[RNH_2]\ [H_3O^+]}{[RNH_3^+]}\right]\left[\frac{[RNH_3^+]\ [OH^-]}{[RNH_2]}\right]$$

so

$$= [H_3O^+]\ [OH^-] = K_w = 1.00 \times 10^{-14}$$

Thus

$$K_a = \frac{K_w}{K_b} \quad \text{and} \quad K_b = \frac{K_w}{K_a}$$

and

$$pK_a + pK_b = 14$$

These equations say that the K_b of an amine multiplied by the K_a of the corresponding ammonium ion is equal to K_w, the ion-product constant for water (1.00×10^{-14}). Thus, if we know K_a for an ammonium ion, we also know K_b for the corresponding amine base because $K_b = K_w/K_a$. The more acidic the ammonium ion, the less tightly the proton is held and the weaker the corresponding base. That is, a weaker base has an ammonium ion with a smaller pK_a, and a stronger base has an ammonium ion with a larger pK_a.

Weaker base	Smaller pK_a for ammonium ion
Stronger base	Larger pK_a for ammonium ion

Table 24.1 lists pK_a values of some ammonium ions and indicates that there is a substantial range of amine basicities. Most simple alkylamines are similar in their base strength, with pK_a's for their ammonium ions in the narrow range 10 to 11. *Arylamines,* however, are considerably less basic than alkylamines, as are the heterocyclic amines pyridine and pyrrole.

In contrast with amines, *amides* ($RCONH_2$) are nonbasic. Amides don't undergo substantial protonation by aqueous acids, and they are poor nucleophiles. The main reason for this difference in basicity between amines and amides is that an amide is stabilized by delocalization of the nitrogen lone-pair electrons through orbital overlap with the carbonyl group. In resonance terms, amides are more stable and less reactive than amines because they are hybrids of two resonance forms. This amide resonance stabilization is lost when the nitrogen atom is protonated, so protonation is disfavored. Electrostatic potential maps show clearly the decreased electron density on the amide nitrogen.

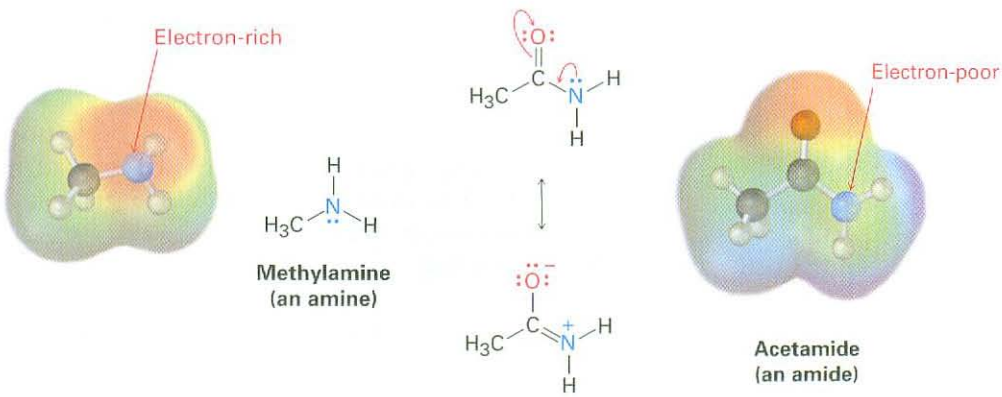
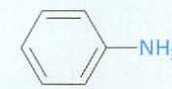
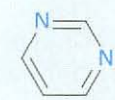
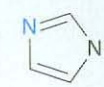


Table 24.1 Basicity of Some Common Amines

Name	Structure	pK_a of ammonium ion
Ammonia	NH_3	9.26
Primary alkylamine		
Methylamine	CH_3NH_2	10.64
Ethylamine	$CH_3CH_2NH_2$	10.75
Secondary alkylamine		
Diethylamine	$(CH_3CH_2)_2NH$	10.98
Pyrrolidine		11.27
Tertiary alkylamine		
Triethylamine	$(CH_3CH_2)_3N$	10.76
Arylamine		
Aniline		4.63
Heterocyclic amine		
Pyridine		5.25
Pyrimidine		1.3
Pyrrole		0.4
Imidazole		6.95

It's often possible to take advantage of their basicity to purify amines. For example, if a mixture of a basic amine and a neutral compound such as a ketone or alcohol is dissolved in an organic solvent and aqueous acid is added, the basic amine dissolves in the water layer as its protonated salt, while the neutral compound remains in the organic solvent layer. Separation of the water layer and neutralization of the ammonium ion by addition of NaOH then provides the pure amine (Figure 24.2).

In addition to their behavior as bases, primary and secondary amines can also act as very weak acids because an N–H proton can be removed by a sufficiently strong base. We've seen, for example, how diisopropylamine ($pK_a \approx 40$) reacts with butyllithium to yield lithium diisopropylamide (LDA; Section 22.5). Dialkylamine anions like LDA are extremely powerful bases that are often used

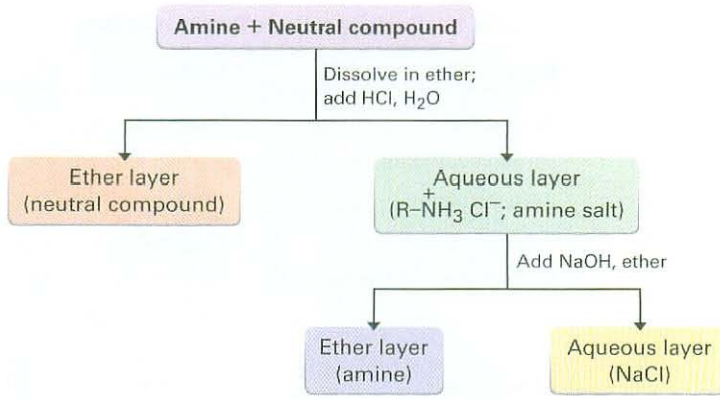
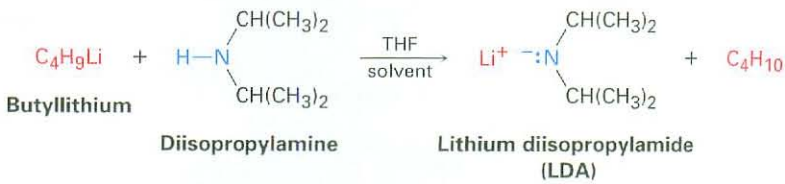


Figure 24.2 Separation and purification of an amine component from a mixture.

in laboratory organic chemistry for the generation of enolate ions from carbonyl compounds (Section 22.7).

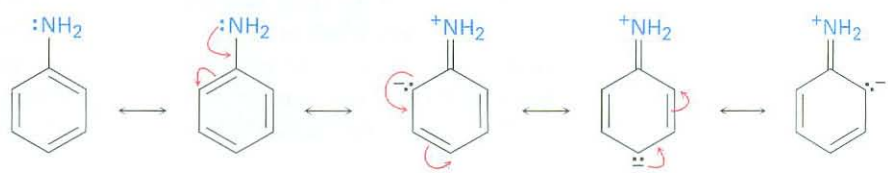


Problem 24.4 Which compound in each of the following pairs is more basic?
(a) $CH_3CH_2NH_2$ or $CH_3CH_2CONH_2$ (b) NaOH or CH_3NH_2
(c) CH_3NHCH_3 or pyridine

Problem 24.5 The benzylammonium ion ($C_6H_5CH_2NH_3^+$) has $pK_a = 9.33$, and the propylammonium ion has $pK_a = 10.71$. Which is the stronger base, benzylamine or propylamine? What are the pK_b's of benzylamine and propylamine?

24.4 Basicity of Substituted Arylamines

As noted previously, arylamines are generally less basic than alkylamines. Anilinium ion has $pK_a = 4.63$, for instance, whereas methylammonium ion has $pK_a = 10.64$. Arylamines are less basic than alkylamines because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic ring π electron system and are less available for bonding to H^+. In resonance terms, arylamines are stabilized relative to alkylamines because of their five resonance forms.



Much of the resonance stabilization is lost on protonation, however, so the energy difference between protonated and nonprotonated forms is higher for arylamines than it is for alkylamines. As a result, arylamines are less basic. Figure 24.3 illustrates the difference.

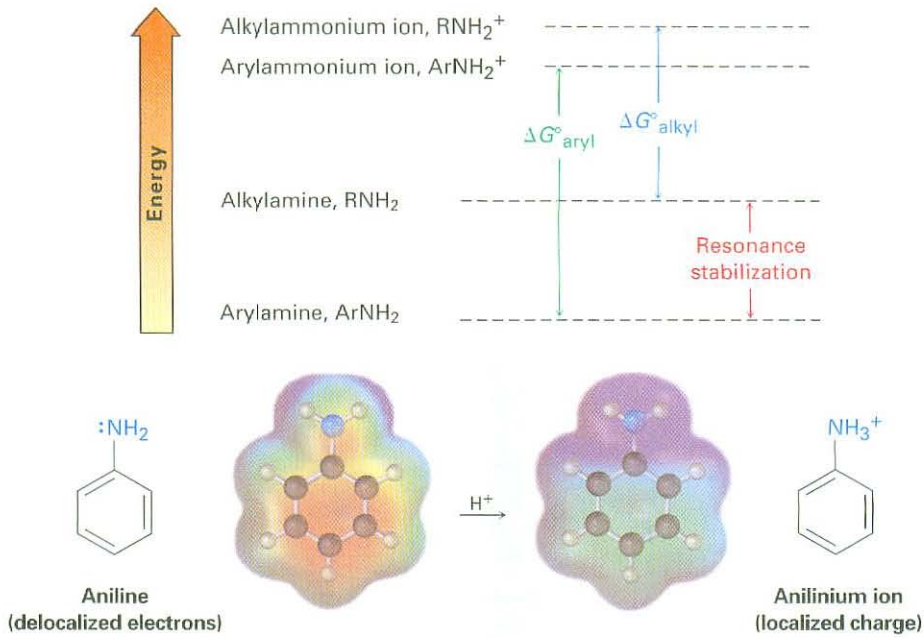


Figure 24.3 Arylamines have a larger positive $\Delta G°$ for protonation and are therefore less basic than alkylamines, primarily because of resonance stabilization of the ground state. Electrostatic potential maps show that lone-pair electron density is delocalized in the amine but the charge is localized in the corresponding ammonium ion.

Substituted arylamines can be either more basic or less basic than aniline, depending on the substituent. Electron-donating substituents, such as $-CH_3$, $-NH_2$, and $-OCH_3$, which increase the reactivity of an aromatic ring toward electrophilic substitution (Section 16.4), also increase the basicity of the corresponding arylamine. Electron-withdrawing substituents, such as $-Cl$, $-NO_2$, and $-CN$, which decrease ring reactivity toward electrophilic substitution, also decrease arylamine basicity. Table 24.2 considers only *p*-substituted anilines, but similar trends are observed for ortho and meta derivatives.

Problem 24.6 Without looking at Table 24.2, rank the following compounds in order of ascending basicity.

(a) *p*-Nitroaniline, *p*-aminobenzaldehyde, *p*-bromoaniline
(b) *p*-Chloroaniline, *p*-aminoacetophenone, *p*-methylaniline
(c) *p*-(Trifluoromethyl)aniline, *p*-methylaniline, *p*-(fluoromethyl)aniline

24.5 Biological Amines and the Henderson–Hasselbalch Equation

We saw in Section 20.3 that the extent of dissociation of a carboxylic acid HA in an aqueous solution buffered to a given pH can be calculated with the Henderson–Hasselbalch equation. Furthermore, we concluded that at the physiological

Table 24.2 Base Strength of Some *p*-Substituted Anilines

	Substituent, Y	pK_a	
Stronger base			
	—NH_2	6.15	
	—OCH_3	5.34	Activating groups
	—CH_3	5.08	
	—H	4.63	
	—Cl	3.98	
	—Br	3.86	
	—CN	1.74	Deactivating groups
Weaker base	—NO_2	1.00	

pH of 7.3 inside living cells, carboxylic acids are almost entirely dissociated into their carboxylate anions, RCO_2^-.

Henderson–Hasselbalch equation: $$pH = pK_a + \log\frac{[A^-]}{[HA]}$$

$$\log\frac{[A^-]}{[HA]} = pH - pK_a$$

What about amine bases? In what form do they exist at the physiological pH inside cells—as the amine ($A^- = RNH_2$), or as the ammonium ion ($HA = RNH_3^+$)? Let's take a 0.0010 M solution of methylamine at pH = 7.3, for example. According to Table 24.1, the pK_a of methylammonium ion is 10.64, so from the Henderson–Hasselbalch equation, we have

$$\log\frac{[RNH_2]}{[RNH_3^+]} = pH - pK_a = 7.3 - 10.64 = -3.34$$

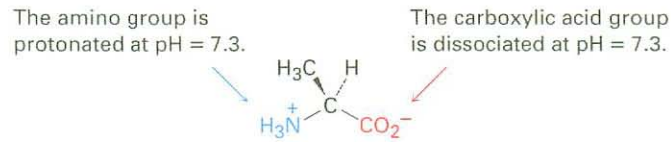
$$\frac{[RNH_2]}{[RNH_3^+]} = \text{antilog}(-3.34) = 4.6 \times 10^{-4}$$

$$[RNH_2] = (4.6 \times 10^{-4})[RNH_3^+]$$

In addition, we know that

$$[RNH_2] + [RNH_3^+] = 0.0010\ M$$

Solving the two simultaneous equations gives $[RNH_3^+] = 0.0010$ M and $[RNH_2] = 5 \times 10^{-7}$ M. In other words, at a physiological pH of 7.3, essentially 100% of the methylamine in a 0.0010 M solution exists in its protonated form as methylammonium ion. The same is true of other amine bases, so we write cellular amines in their protonated form and amino acids in their ammonium carboxylate form to reflect their structures at physiological pH.



Alanine (an amino acid)

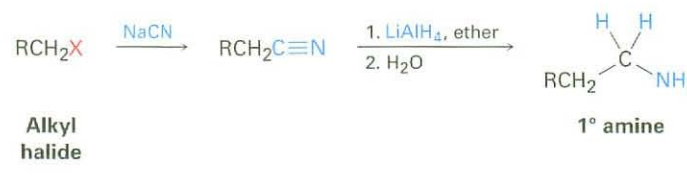
Problem 24.7 Calculate the percentages of neutral and protonated forms present in a solution of 0.0010 M pyrimidine at pH = 7.3. The pK_a of pyrimidinium ion is 1.3.

24.6 Synthesis of Amines

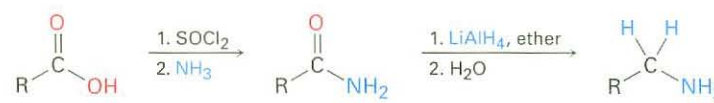
Reduction of Nitriles, Amides, and Nitro Compounds

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from a variety of reactions that yield amines.**

We've already seen in Sections 20.7 and 21.7 how amines can be prepared by reduction of nitriles and amides with $LiAlH_4$. The two-step sequence of S_N2 displacement with CN^- followed by reduction thus converts an alkyl halide into a primary alkylamine having one more carbon atom. Amide reduction converts carboxylic acids and their derivatives into amines with the same number of carbon atoms.



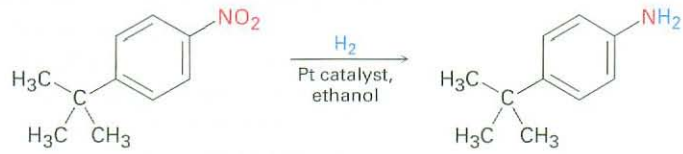
Alkyl halide **1° amine**



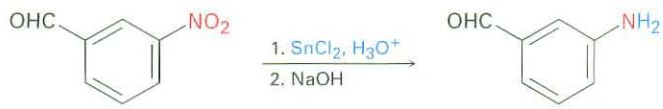
Carboxylic acid **1° amine**

Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group (Section 16.2). The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is often incompatible with

the presence elsewhere in the molecule of other reducible groups, such as C=C bonds or carbonyl groups. Iron, zinc, tin, and tin(II) chloride ($SnCl_2$) are also effective when used in acidic aqueous solution. Tin(II) chloride is particularly mild and is often used when other reducible functional groups are present.



***p*-*tert*-Butylnitrobenzene** ***p*-*tert*-Butylaniline (100%)**



***m*-Nitrobenzaldehyde** ***m*-Aminobenzaldehyde (90%)**

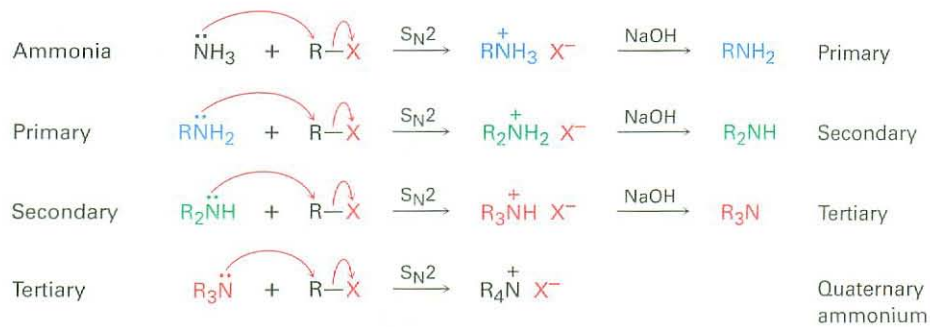
Problem 24.8 Propose structures for either a nitrile or an amide that might be a precursor of each of the following amines:

(a) $CH_3CH_2CH_2NH_2$ (b) $(CH_3CH_2CH_2)_2NH$

(c) Benzylamine, $C_6H_5CH_2NH_2$ (d) *N*-Ethylaniline

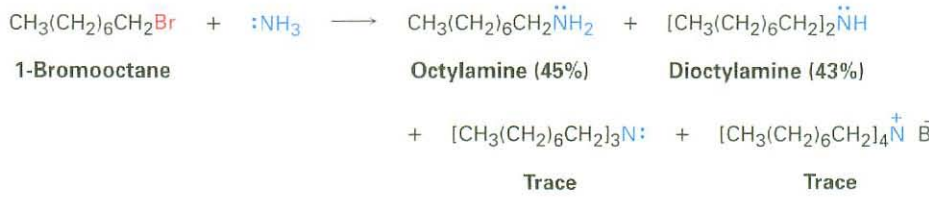
S_N2 Reactions of Alkyl Halides

Ammonia and other amines are good nucleophiles in S_N2 reactions. As a result, the simplest method of alkylamine synthesis is by S_N2 alkylation of ammonia or an alkylamine with an alkyl halide. If ammonia is used, a primary amine results; if a primary amine is used, a secondary amine results; and so on. Even tertiary amines react rapidly with alkyl halides to yield quaternary ammonium salts, $R_4N^+ X^-$.



Unfortunately, these reactions don't stop cleanly after a single alkylation has occurred. Because ammonia and primary amines have similar reactivity, the initially formed monoalkylated substance often undergoes further reaction to yield a mixture of products. Even secondary and tertiary amines undergo further alkylation, although to a lesser extent. For example, treatment of 1-bromooctane with

a twofold excess of ammonia leads to a mixture containing only 45% of octylamine. A nearly equal amount of dioctylamine is produced by double alkylation, along with smaller amounts of trioctylamine and tetraoctylammonium bromide.

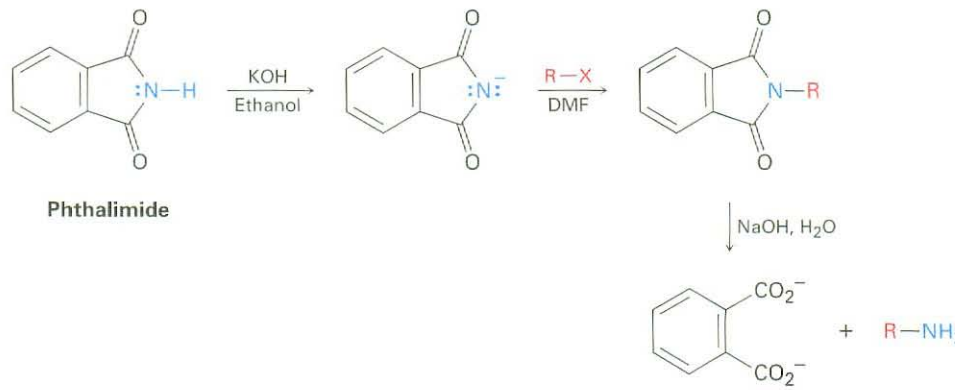


A better method for preparing primary amines is to use the *azide synthesis*, in which azide ion, N_3^-, is used for S_N2 reaction with a primary or secondary alkyl halide to give an alkyl azide, RN_3. Because alkyl azides are not nucleophilic, overalkylation can't occur. Subsequent reduction of the alkyl azide, either by catalytic hydrogenation over a palladium catalyst or by reaction with $LiAlH_4$, then leads to the desired primary amine. Although the method works well, low-molecular-weight alkyl azides are explosive and must be handled carefully.

Siegmund Gabriel

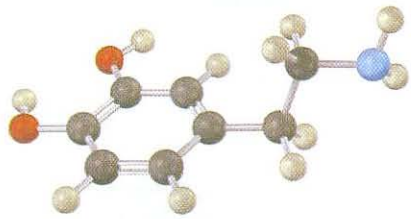
Siegmund Gabriel (1851–1924) was born in Berlin, Germany, and received his Ph.D. in 1874 at the University of Berlin, working with August von Hofmann. After further work with Robert Bunsen, he became professor of chemistry at the University of Berlin.

Another alternative for preparing a primary amine from an alkyl halide is the **Gabriel amine synthesis**, which uses a *phthalimide* alkylation. An **imide** (−CONHCO−) is similar to a β-keto ester in that the acidic N−H hydrogen is flanked by two carbonyl groups. Thus, imides are deprotonated by such bases as KOH, and the resultant anions are readily alkylated in a reaction similar to the acetoacetic ester synthesis (Section 22.7). Basic hydrolysis of the *N*-alkylated imide then yields a primary amine product. The imide hydrolysis step is analogous to the hydrolysis of an amide (Section 21.7).



Problem 24.9 Write the mechanism of the last step in the Gabriel amine synthesis, the base-promoted hydrolysis of a phthalimide to yield an amine plus phthalate ion.

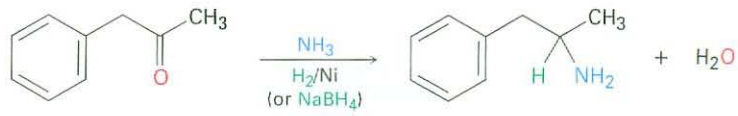
Problem 24.10 Show two methods for the synthesis of dopamine, a neurotransmitter involved in regulation of the central nervous system. Use any alkyl halide needed.



Dopamine

Reductive Amination of Aldehydes and Ketones

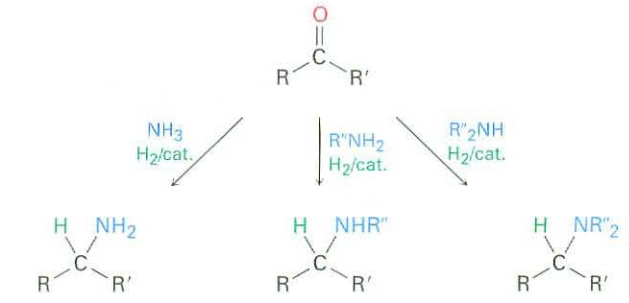
Amines can be synthesized in a single step by treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent, a process called **reductive amination**. For example, amphetamine, a central nervous system stimulant, is prepared commercially by reductive amination of phenyl-2-propanone with ammonia, using hydrogen gas over a nickel catalyst as the reducing agent.



Phenyl-2-propanone Amphetamine

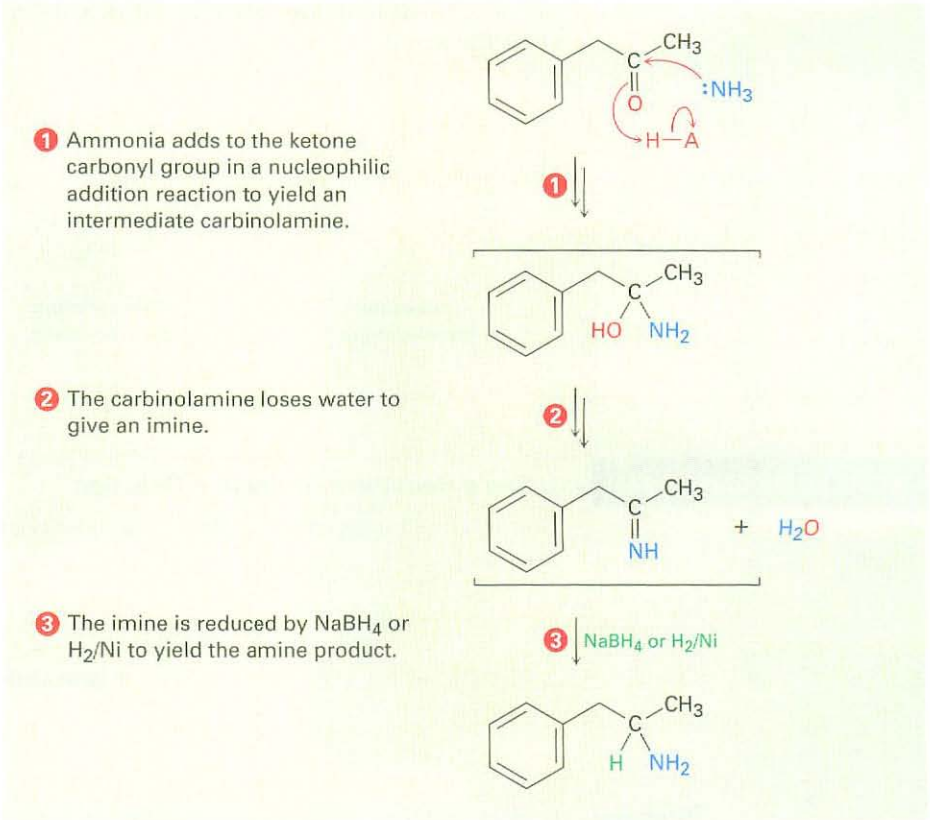
Reductive amination takes place by the pathway shown in Figure 24.4. An imine intermediate is first formed by a nucleophilic addition reaction (Section 19.8), and the C=N bond of the imine is then reduced.

Ammonia, primary amines, and secondary amines can all be used in the reductive amination reaction, yielding primary, secondary, and tertiary amines, respectively.

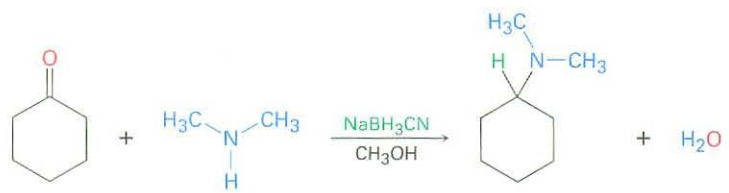


Primary amine Secondary amine Tertiary amine

Active Figure 24.4
MECHANISM: Mechanism of reductive amination of a ketone to yield an amine. Details of the imine-forming step were shown in Figure 19.8 on page 711. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*



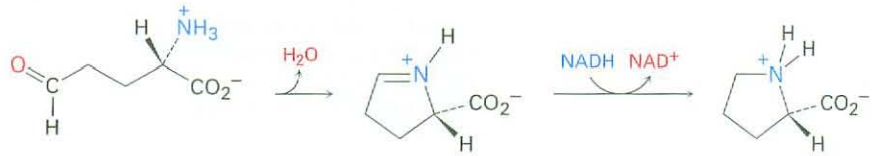
Many different reducing agents are effective, but the most common choice in the laboratory is sodium cyanoborohydride, $NaBH_3CN$. Sodium cyanoborohydride is similar in reactivity to sodium borohydride ($NaBH_4$) but is more stable in weak acid solution.



Cyclohexanone **N,N-Dimethylcyclohexylamine (85%)**

Reductive aminations also occur in various biological pathways. In the biosynthesis of the amino acid proline, for instance, glutamate 5-semialdehyde undergoes internal imine formation to give 1-pyrrolinium 5-carboxylate, which is then reduced by nucleophilic addition of hydride ion to the C=N bond.

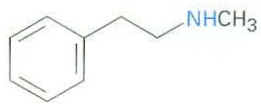
Reduced nicotinamide adenine dinucleotide, NADH, acts as the biological reducing agent.



Glutamate 5-semialdehyde **1-Pyrrolinium 5-carboxylate** **Proline**

WORKED EXAMPLE 24.1 *Using a Reductive Amination Reaction*

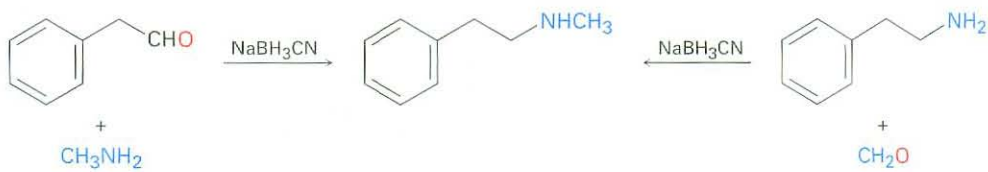
How might you prepare *N*-methyl-2-phenylethylamine using a reductive amination reaction?



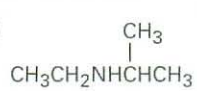
***N*-Methyl-2-phenylethylamine**

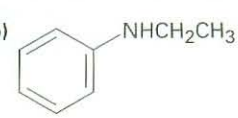
Strategy Look at the target molecule, and identify the groups attached to nitrogen. One of the groups must be derived from the aldehyde or ketone component, and the other must be derived from the amine component. In the case of *N*-methyl-2-phenylethylamine, there are two combinations that can lead to the product: phenylacetaldehyde plus methylamine or formaldehyde plus 2-phenylethylamine. In general, it's usually better to choose the combination with the simpler amine component—methylamine in this case—and to use an excess of that amine as reactant.

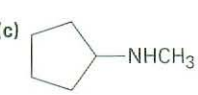
Solution



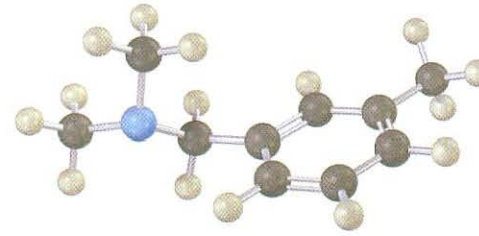
Problem 24.11 How might the following amines be prepared using reductive amination reactions? Show all precursors if more than one is possible.

(a) 

(b) 

(c) 

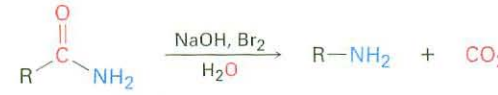
Problem 24.12 How could you prepare the following amine using a reductive amination reaction?



Hofmann and Curtius Rearrangements

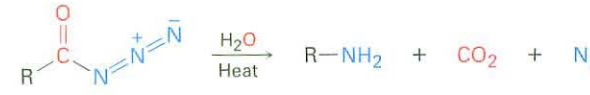
Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both the **Hofmann rearrangement** and the **Curtius rearrangement**. Although the Hofmann rearrangement involves a primary amide and the Curtius rearrangement involves an acyl azide, both proceed through similar mechanisms.

Hofmann rearrangement



An amide

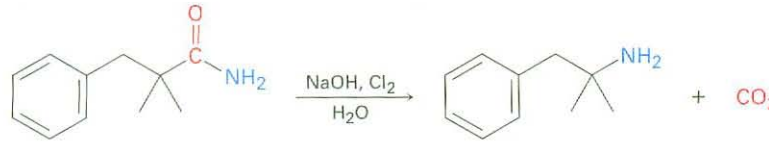
Curtius rearrangement



An acyl azide

Hofmann rearrangement occurs when a primary amide, $RCONH_2$, is treated with Br_2 and base (Figure 24.5). The overall mechanism is lengthy, but most of the individual steps have been encountered before. Thus, the bromination of an amide in steps 1 and 2 is analogous to the base-promoted bromination of a ketone enolate ion (Section 22.6), and the rearrangement of the bromoamide anion in step 4 is analogous to a carbocation rearrangement (Section 6.11). Nucleophilic addition of water to the isocyanate carbonyl group in step 5 is a typical carbonyl-group process (Section 19.4), as is the final decarboxylation step (Section 22.7).

Despite its mechanistic complexity, the Hofmann rearrangement often gives high yields of both arylamines and alkylamines. For example, the appetite-suppressant drug phentermine is prepared commercially by Hofmann rearrangement of a primary amide. Commonly known by the name *Fen-Phen*, the combination of phentermine with another appetite-suppressant, fenfluramine, is suspected of causing heart damage.



2,2-Dimethyl-3-phenylpropanamide **Phetermine**

August Wilhelm von Hofmann

August Wilhelm von Hofmann (1818–1892) was born in Giessen, Germany, the son of the architect who designed the chemistry building at the university there. After receiving his doctorate working with Justus von Liebig at the University of Giessen, he served as the first director of the new Royal College of Chemistry in London from 1845 to 1864 and then moved to the University of Berlin as professor (1865–1892). Among his many contributions to chemistry, he was one of the founders of the German dye industry, was the discoverer of formaldehyde, and was a cofounder of the German Chemical Society.

Theodor Curtius

Theodor Curtius (1857–1928) was born in Duisberg, Germany, and received his doctorate at the University of Leipzig working with Herman Kolbe. He was professor at the universities of Kiel, Bonn, and Heidelberg (1898–1926).

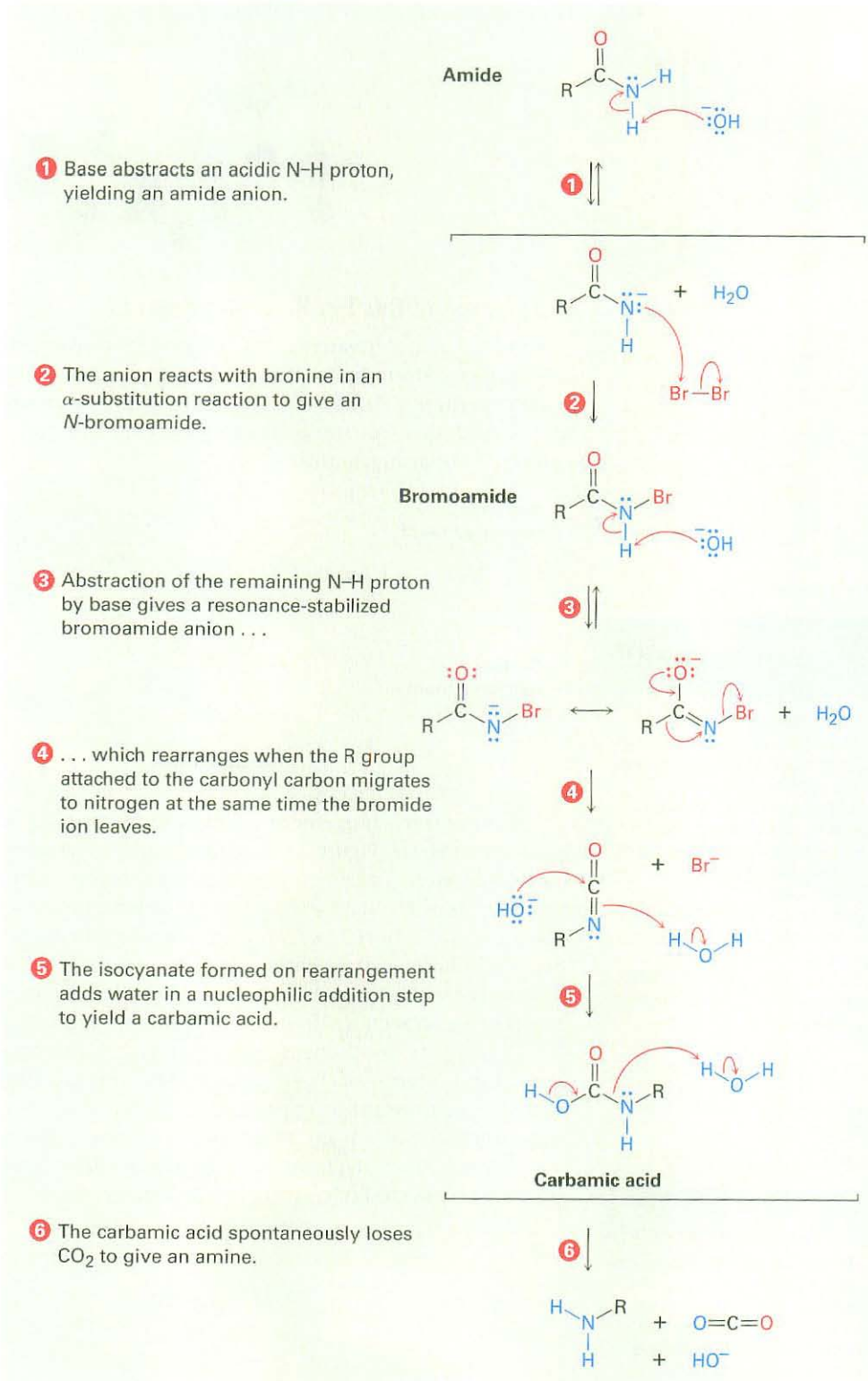
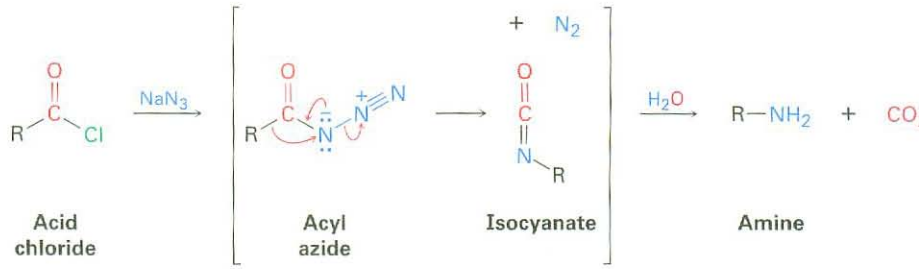
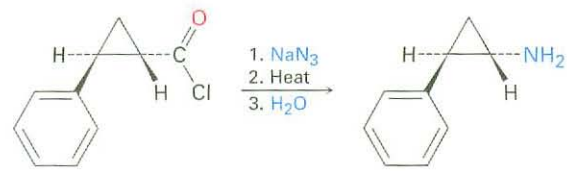


Figure 24.5 MECHANISM: Mechanism of the Hofmann rearrangement of an amide to an amine. Each step is analogous to a reaction studied previously.

The Curtius rearrangement, like the Hofmann rearrangement, involve migration of an −R group from the C=O carbon atom to the neighboring nitro gen with simultaneous loss of a leaving group. The reaction takes place on heat ing an acyl azide that is itself prepared by nucleophilic acyl substitution of ar acid chloride.



Like the Hofmann rearrangement, the Curtius rearrangement is often used commercially. For example, the antidepressant drug tranylcypromine is made by Curtius rearrangement of 2-phenylcyclopropanecarbonyl chloride.



trans-2-Phenylcyclopropanecarbonyl chloride

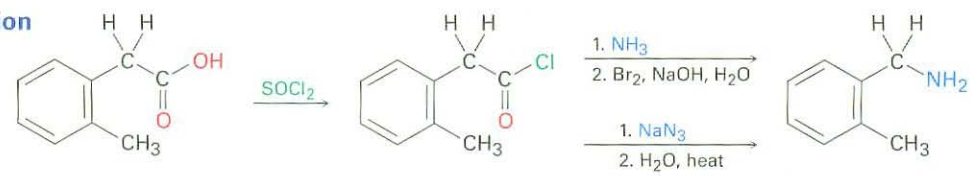
Tranylcypromine

WORKED EXAMPLE 24.2 ***Using the Hofmann and Curtius Reactions***

How would you prepare *o*-methylbenzylamine from a carboxylic acid, using both Hofmann and Curtius rearrangements?

Strategy Both Hofmann and Curtius rearrangements convert a carboxylic acid derivative—either an amide (Hofmann) or an acid chloride (Curtius)—into a primary amine with loss of one carbon, RCOY → RNH_2. Both reactions begin with the same carboxylic acid, which can be identified by replacing the $-NH_2$ group of the amine product by a $-CO_2H$ group. In the present instance, *o*-methylphenylacetic acid is needed.

Solution

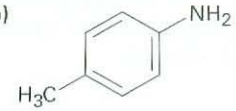


o-Methylphenylacetic acid

o-Methylbenzylamine

Problem 24.13 How would you prepare the following amines, using both Hofmann and Curtius rearrangements on a carboxylic acid derivative?

(a) $CH_3CH_2CH_2CH_2NH_2$ with a CH_3 group on the second carbon

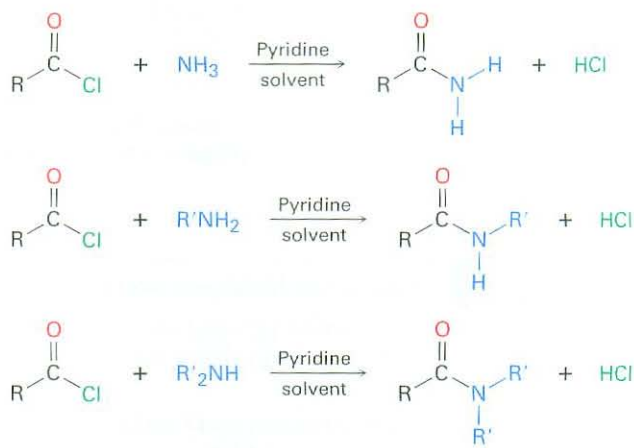
(b) 

24.7 Reactions of Amines

Alkylation and Acylation

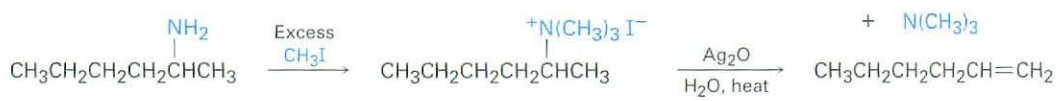
ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from a variety of reactions involving amines.**

We've already studied the two most general reactions of amines—alkylation and acylation. As we saw earlier in this chapter, primary, secondary, and tertiary amines can be alkylated by reaction with a primary alkyl halide. Alkylations of primary and secondary amines are difficult to control and often give mixtures of products, but tertiary amines are cleanly alkylated to give quaternary ammonium salts. Primary and secondary (but not tertiary) amines can also be acylated by nucleophilic acyl substitution reaction with an acid chloride or an acid anhydride to yield an amide (Sections 21.4 and 21.5). Note that overacylation of the nitrogen does not occur because the amide product is much less nucleophilic and less reactive than the starting amine.



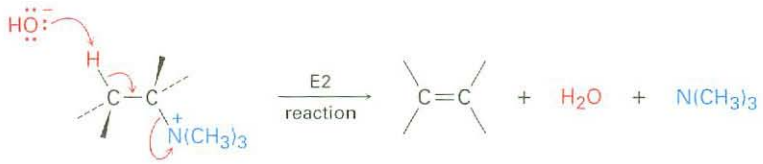
Hofmann Elimination

Like alcohols, amines can be converted into alkenes by an elimination reaction. Because an amide ion, NH_2^-, is such a poor leaving group, however, it must first be converted into a better leaving group. In the **Hofmann elimination reaction**, an amine is methylated by reaction with excess iodomethane to produce a quaternary ammonium salt, which then undergoes elimination to give an alkene on heating with a base, typically silver oxide, Ag_2O. For example, 1-methylpentylamine is converted into 1-hexene in 60% yield.



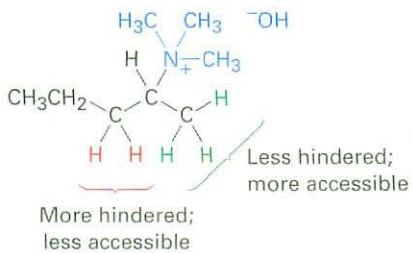
1-Methylpentylamine → **(1-Methylpentyl)trimethylammonium iodide** → **1-Hexene (60%)**

Silver oxide acts by exchanging hydroxide ion for iodide ion in the quaternary salt, thus providing the base necessary to cause elimination. The actual elimination step is an E2 reaction (Section 11.8) in which hydroxide ion removes a proton at the same time that the positively charged nitrogen atom leaves.



Quaternary ammonium salt **Alkene**

An interesting feature of the Hofmann elimination is that it gives products different from those of most other E2 reactions. Whereas the *more* highly substituted alkene product generally predominates in the E2 reaction of an alkyl halide (Zaitsev's rule; Section 11.7), the *less* highly substituted alkene predominates in the Hofmann elimination of a quaternary ammonium salt. The reason for this selectivity is probably steric. Because of the large size of the trialkylamine leaving group, the base must abstract a hydrogen from the most sterically accessible, least hindered position.

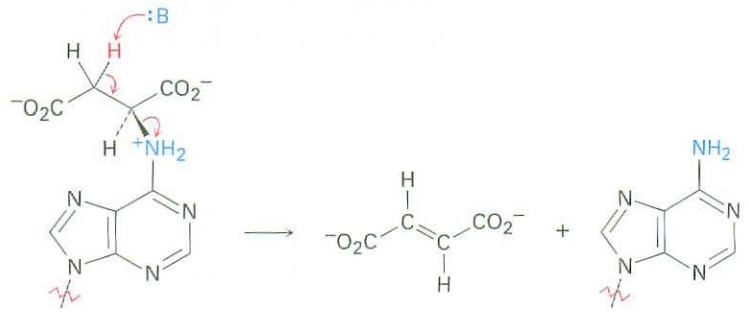


(1-Methylbutyl)trimethylammonium hydroxide

1-Pentene (94%) **2-Pentene (6%)**

The Hofmann elimination reaction is not often used today in the laboratory, but analogous biological eliminations occur frequently, although usually with protonated ammonium ions rather than quaternary ammonium salts. In the biosynthesis of nucleic acids, for instance, a substance called adenylosuccinate

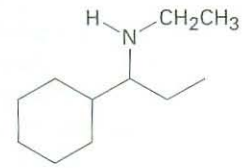
undergoes an elimination of a positively charged nitrogen to give fumarate plus adenosine monophosphate.



Adenylosuccinate **Fumarate** **Adenosine monophosphate**

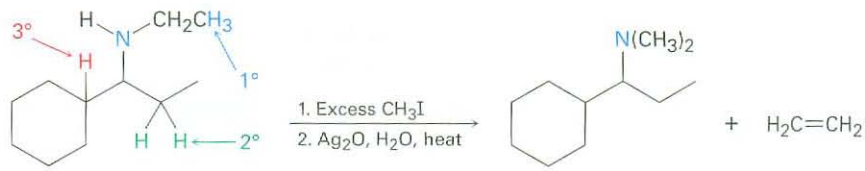
WORKED EXAMPLE 24.3 ***Predicting the Product of a Hofmann Elimination***

What product would you expect from Hofmann elimination of the following amine?



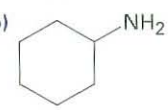
Strategy The Hofmann elimination is an E2 reaction that converts an amine into an alkene and occurs with non-Zaitsev regiochemistry to form the least highly substituted double bond. To predict the product, look at the reactant and identify the positions from which elimination might occur (the positions two carbons removed from nitrogen). Then carry out an elimination using the most accessible hydrogen. In the present instance, there are three possible positions from which elimination might occur—one primary, one secondary, and one tertiary. The primary position is the most accessible and leads to the least highly substituted alkene, ethylene.

Solution

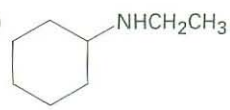


Problem 24.14 What products would you expect from Hofmann elimination of the following amines? If more than one product is formed, indicate which is major.

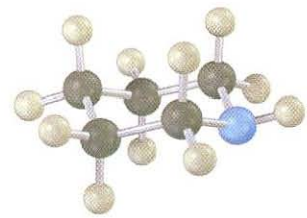
(a) $CH_3CH_2CH_2CH(NH_2)CH_2CH_2CH_2CH_3$

(b) 

(c) $CH_3CH_2CH_2CH(NH_2)CH_2CH_2CH_3$

(d) 

Problem 24.15 What product would you expect from Hofmann elimination of a heterocyclic amine such as piperidine? Write all the steps.



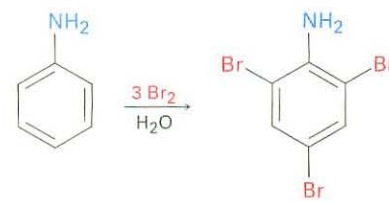
Piperidine

24.8 Reactions of Arylamines

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from a variety of reactions involving arylamines.**

Electrophilic Aromatic Substitution

An amino group is strongly activating and ortho- and para-directing in electrophilic aromatic substitution reactions (Section 16.4). This high reactivity can be a drawback at times because it's often difficult to prevent polysubstitution. For instance, reaction of aniline with Br_2 takes place rapidly and yields the 2,4,6-tribrominated product. The amino group is so strongly activating that it's not possible to stop at the monobromo stage.

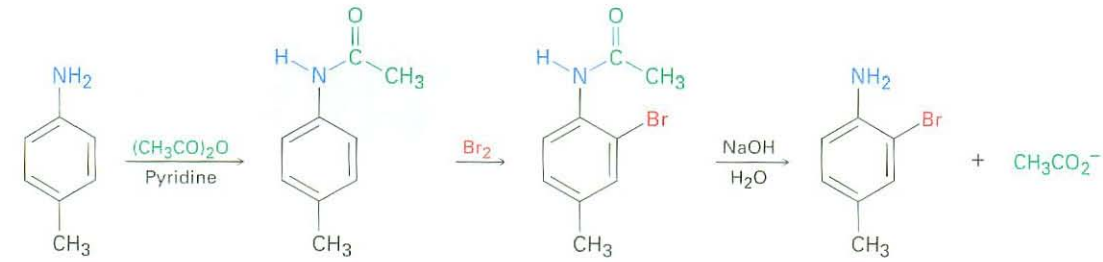


Aniline **2,4,6-Tribromoaniline (100%)**

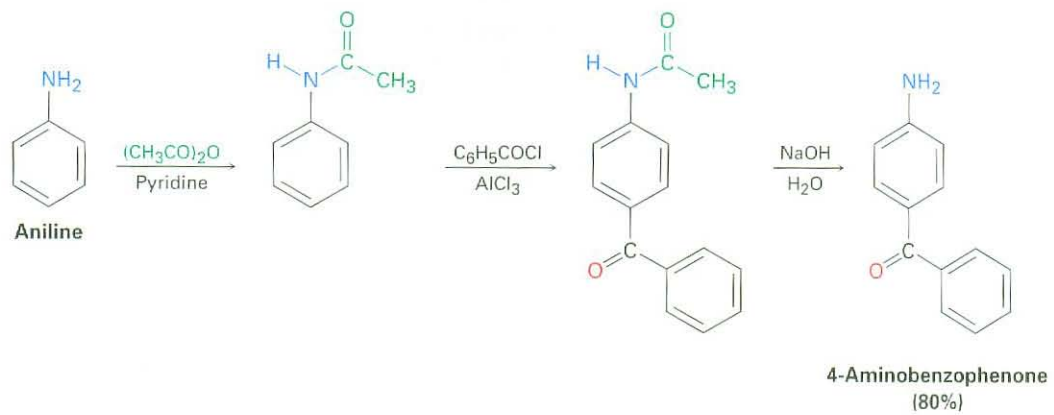
Another drawback to the use of amino-substituted benzenes in electrophilic aromatic substitution reactions is that Friedel–Crafts reactions are not successful (Section 16.3). The amino group forms an acid–base complex with the $AlCl_3$ catalyst, which prevents further reaction from occurring. Both drawbacks can be overcome, however, by carrying out electrophilic aromatic substitution reactions on the corresponding *amide* rather than on the free amine.

As we saw in Section 21.5, treatment of an amine with acetic anhydride yields the corresponding acetyl amide, or acetamide. Although still activating and ortho-, para-directing, amido substituents (−NHCOR) are less strongly activating and less basic than amino groups because their nitrogen lone-pair electrons are delocalized by the neighboring carbonyl group. As a result, bromination of an *N*-arylamide occurs cleanly to give a monobromo product, and hydrolysis with aqueous base then gives the free amine. For example, *p*-toluidine (4-methylaniline) can be acetylated, brominated, and hydrolyzed

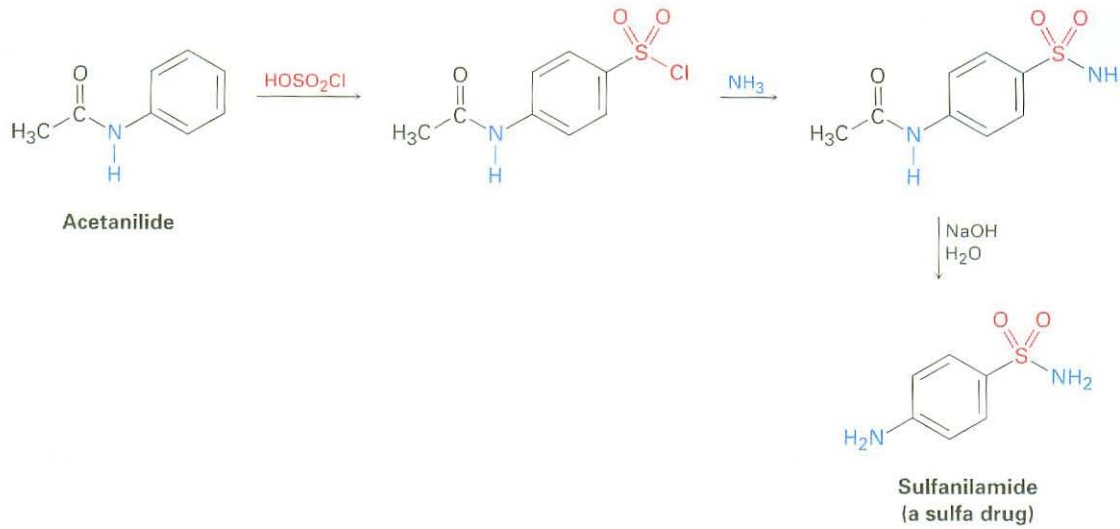
to yield 2-bromo-4-methylaniline. None of the 2,6-dibrominated product is obtained.



Friedel–Crafts alkylations and acylations of *N*-arylamides also proceed normally. For example, benzoylation of acetanilide (*N*-acetylaniline) under Friedel–Crafts conditions gives 4-aminobenzophenone in 80% yield after hydrolysis.



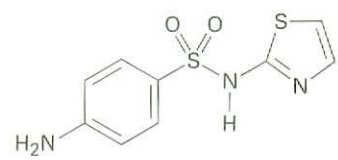
Modulating the reactivity of an amino-substituted benzene by forming an amide is a useful trick that allows many kinds of electrophilic aromatic substitutions to be carried out that would otherwise be impossible. A good example is the preparation of the sulfa drugs. Sulfa drugs, such as sulfanilamide, were among the first pharmaceutical agents to be used clinically against bacterial infection. Although they have largely been replaced by safer and more powerful antibiotics, sulfa drugs are credited with saving the lives of thousands of wounded during World War II, and they are still prescribed for infections of the urinary tract. They are prepared by chlorosulfonation of acetanilide, followed by reaction of *p*-(*N*-acetylamino)benzenesulfonyl chloride with ammonia or some other amine to give a sulfonamide. Hydrolysis of the amide then yields the sulfa drug. Note that this amide hydrolysis can be carried out in the presence of the sulfonamide group because sulfonamides hydrolyze very slowly.



Acetanilide

Sulfanilamide (a sulfa drug)

Problem 24.16 Propose a synthesis of the drug sulfathiazole from benzene and any necessary amine.



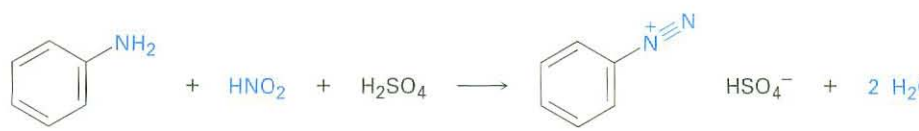
Sulfathiazole

Problem 24.17 Propose syntheses of the following compounds from benzene:

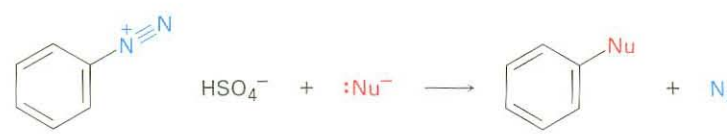
(a) *N,N*-Dimethylaniline **(b)** *p*-Chloroaniline
(c) *m*-Chloroaniline **(d)** 2,4-Dimethylaniline

Diazonium Salts: The Sandmeyer Reaction

Primary arylamines react with nitrous acid, HNO_2, to yield stable **arenediazonium salts**, $Ar-\overset{+}{N}\equiv N\ X^-$, a process called a **diazotization reaction.** *Alkyl*amines also react with nitrous acid, but the alkanediazonium products of these reactions are so reactive they can't be isolated. Instead, they lose nitrogen instantly to yield carbocations. The analogous loss of N_2 from an arenediazonium ion to yield an aryl cation is disfavored by the instability of the cation.



Arenediazonium salts are extremely useful because the diazonio group (N_2) can be replaced by a nucleophile in a substitution reaction.

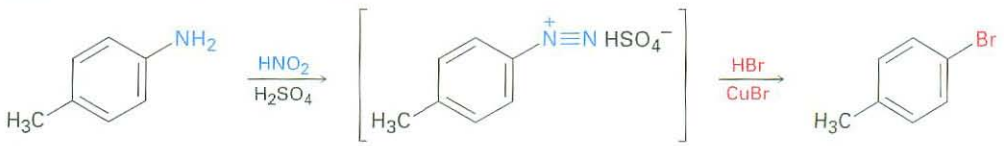


Traugott Sandmeyer

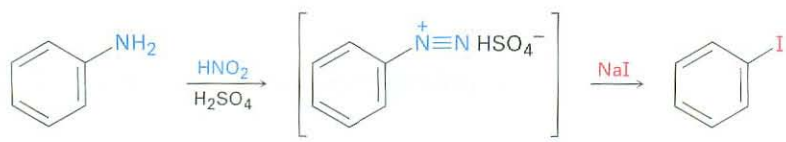
Traugott Sandmeyer (1854–1922) was born in Wettingen, Switzerland, and received his Ph.D. at the University of Heidelberg. He spent his professional career doing pharmaceutical research at the Geigy Company in Basel, Switzerland.

Many different nucleophiles—halide, hydride, cyanide, and hydroxide among others—react with arenediazonium salts, yielding many different kinds of substituted benzenes. The overall sequence of (1) nitration, (2) reduction, (3) diazotization, and (4) nucleophilic substitution is perhaps the single most versatile method of aromatic substitution.

Aryl chlorides and bromides are prepared by reaction of an arenediazonium salt with the corresponding copper(I) halide, CuX, a process called the **Sandmeyer reaction**. Aryl iodides can be prepared by direct reaction with NaI without using a copper(I) salt. Yields generally fall between 60 and 80%.

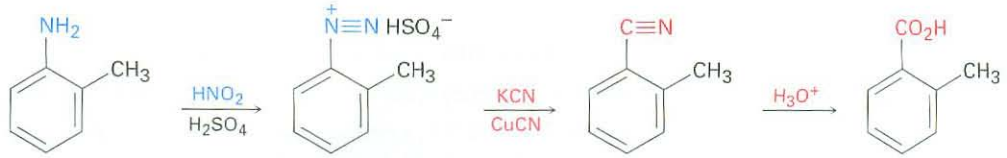


p-Methylaniline — *p*-Bromotoluene (73%)



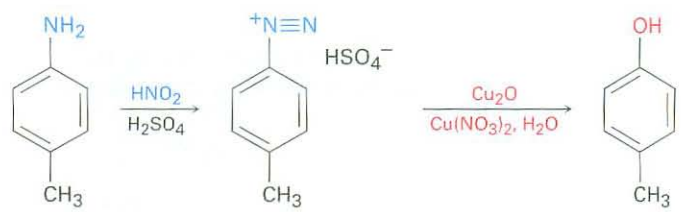
Aniline — Iodobenzene (67%)

Similar treatment of an arenediazonium salt with CuCN yields the nitrile, ArCN, which can then be further converted into other functional groups such as carboxyl. For example, Sandmeyer reaction of *o*-methylbenzenediazonium bisulfate with CuCN yields *o*-methylbenzonitrile, which can be hydrolyzed to give *o*-methylbenzoic acid. This product can't be prepared from *o*-xylene by the usual side-chain oxidation route because both methyl groups would be oxidized.



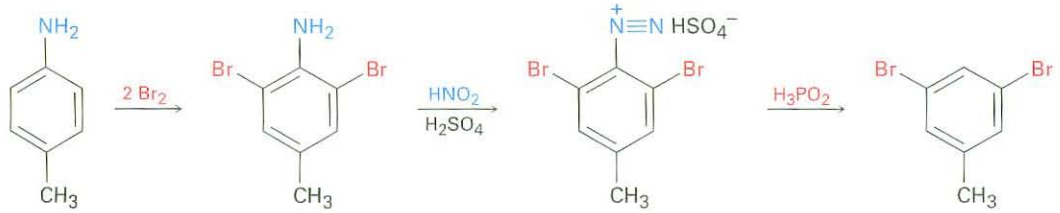
o-Methylaniline — *o*-Methylbenzenediazonium bisulfate — *o*-Methylbenzonitrile — *o*-Methylbenzoic acid

The diazonio group can also be replaced by −OH to yield a phenol and by −H to yield an arene. A phenol is prepared by reaction of the arenediazonium salt with copper(I) oxide in an aqueous solution of copper(II) nitrate, a reaction that is especially useful because few other general methods exist for introducing an −OH group onto an aromatic ring.

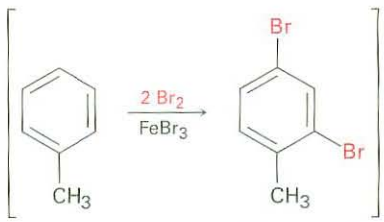


p-Methylaniline (*p*-Toluidine) — *p*-Cresol (93%)

Reduction of a diazonium salt to give an arene occurs on treatment with hypophosphorous acid, H_3PO_2. This reaction is used primarily when there is a need for temporarily introducing an amino substituent onto a ring to take advantage of its directing effect. Suppose, for instance, that you needed to make 3,5-dibromotoluene. The product can't be made by direct bromination of toluene because reaction would occur at positions 2 and 4. Starting with *p*-methylaniline (*p*-toluidine), however, dibromination occurs ortho to the strongly directing amino substituent, and diazotization followed by treatment with H_3PO_2 yields the desired product.

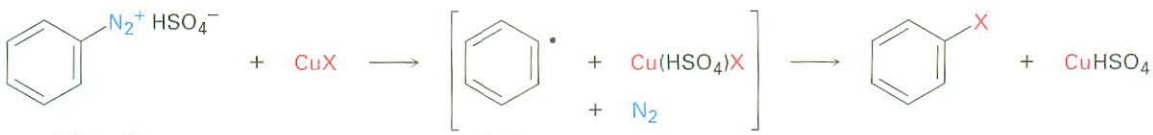


***p*-Methylaniline** **3,5-Dibromotoluene**



Toluene **2,4-Dibromotoluene**

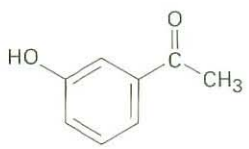
Mechanistically, these diazonio replacement reactions occur through radical rather than polar pathways. In the presence of a copper(I) compound, for instance, it's thought that the arenediazonium ion is first converted to an aryl radical plus copper(II), followed by subsequent reaction to give product plus regenerated copper(I) catalyst.



Diazonium compound **Aryl radical**

WORKED EXAMPLE 24.4 ***Using Diazonium Replacement Reactions***

How would you prepare *m*-hydroxyacetophenone from benzene, using a diazonium replacement reaction in your scheme?

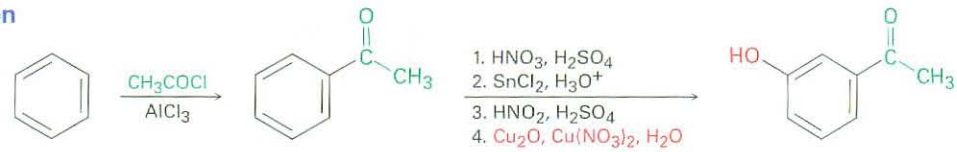


***m*-Hydroxyacetophenone**

Strategy As always, organic syntheses are planned by working backward from the final product, one step at a time. First, identify the functional groups in the product and recall how those groups can be synthesized. *m*-Hydroxyacetophenone has an $-OH$ group and a $-COCH_3$ group in a meta relationship on a benzene ring. A hydroxyl group is generally introduced onto an aromatic ring by a four-step sequence of nitration, reduction, diazotization, and diazonio replacement. An acetyl group is introduced by a Friedel–Crafts acylation reaction.

Next, ask yourself what an immediate precursor of the target might be. Since an acetyl group is a meta director while a hydroxyl group is an ortho and para director, acetophenone might be a precursor of *m*-hydroxyacetophenone. Benzene, in turn, is a precursor of acetophenone.

Solution



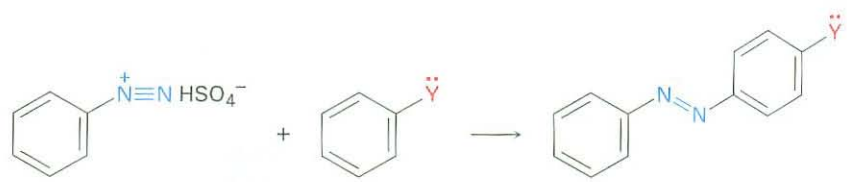
Benzene Acetophenone *m*-Hydroxyacetophenone

Problem 24.18 How would you prepare the following compounds from benzene, using a diazonium replacement reaction in your scheme?

(a) *p*-Bromobenzoic acid (b) *m*-Bromobenzoic acid
(c) *m*-Bromochlorobenzene (d) *p*-Methylbenzoic acid
(e) 1,2,4-Tribromobenzene

Diazonium Coupling Reactions

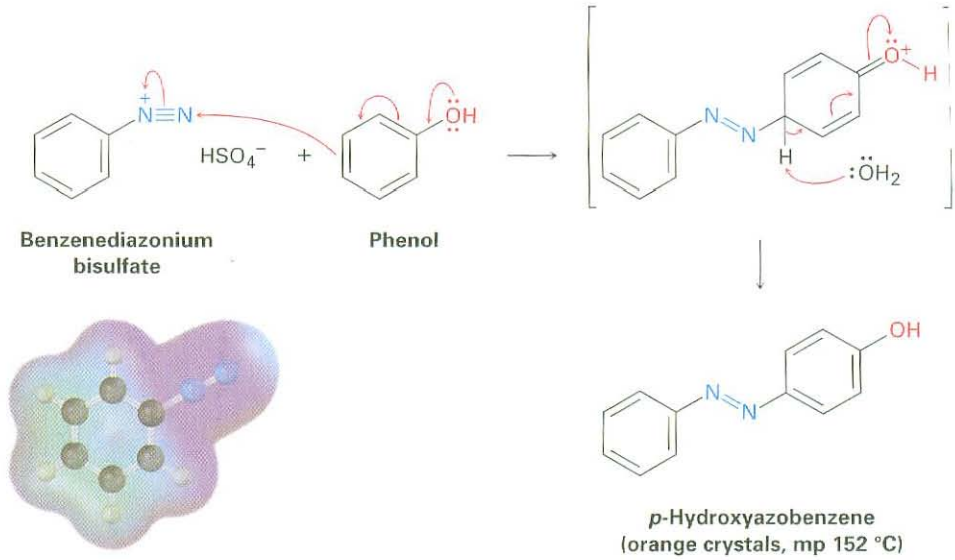
Arenediazonium salts undergo a coupling reaction with activated aromatic rings such as phenols and arylamines to yield brightly colored **azo compounds**, $Ar—N{=}N—Ar'$.



An azo compound

where Y = $-OH$ or $-NR_2$

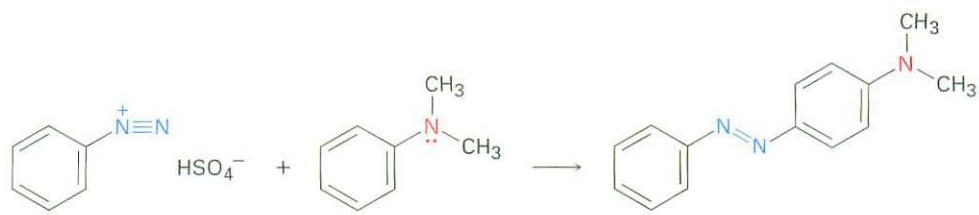
Diazonium coupling reactions are typical electrophilic aromatic substitutions in which the positively charged diazonium ion is the electrophile that reacts with the electron-rich ring of a phenol or arylamine. Reaction usually occurs at the para position, although ortho reaction can take place if the para position is blocked.



Benzenediazonium bisulfate **Phenol**

p-Hydroxyazobenzene (orange crystals, mp 152 °C)

Azo-coupled products are widely used as dyes for textiles because their extended conjugated π electron system causes them to absorb in the visible region of the electromagnetic spectrum (Section 14.9). *p*-(Dimethylamino)azobenzene, for instance, is a bright yellow compound that was at one time used as a coloring agent in margarine.



Benzenediazonium bisulfate ***N,N*-Dimethylaniline** ***p*-(Dimethylamino)azobenzene (yellow crystals, mp 127 °C)**

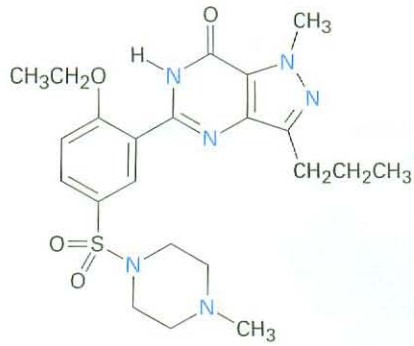
Problem 24.19 Propose a synthesis of *p*-(dimethylamino)azobenzene from benzene as your only organic starting material.

24.9 Heterocycles

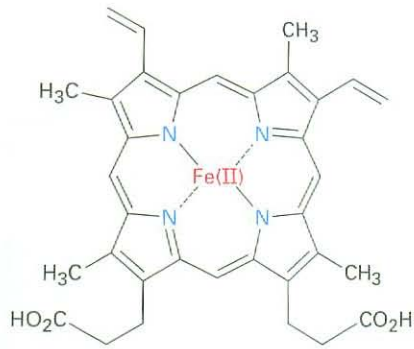
A **heterocycle** is a cyclic compound that contains atoms of two or more elements in its ring, usually carbon along with nitrogen, oxygen, or sulfur. Heterocyclic amines are particularly common, and many have important biological properties. Pyridoxal phosphate, a coenzyme; sildenafil (Viagra),

a well-known pharmaceutical; and heme, the oxygen carrier in blood, are examples.

Pyridoxal phosphate (a coenzyme)



Sildenafil (Viagra)

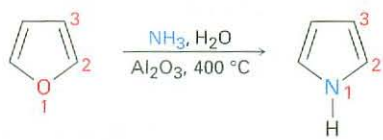


Heme

Most heterocycles have the same chemistry as their open-chain counterparts. Lactones and acyclic esters behave similarly, lactams and acyclic amides behave similarly, and cyclic and acyclic ethers behave similarly. In certain cases, however, particularly when the ring is unsaturated, heterocycles have unique and interesting properties.

Pyrrole and Imidazole

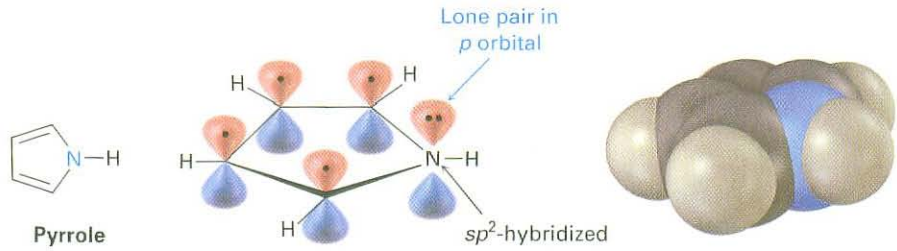
Pyrrole, the simplest five-membered unsaturated heterocyclic amine, is obtained commercially by treatment of furan with ammonia over an alumina catalyst at 400 °C. Furan, the oxygen-containing analog of pyrrole, is obtained by acid-catalyzed dehydration of the five-carbon sugars found in oat hulls and corncobs.



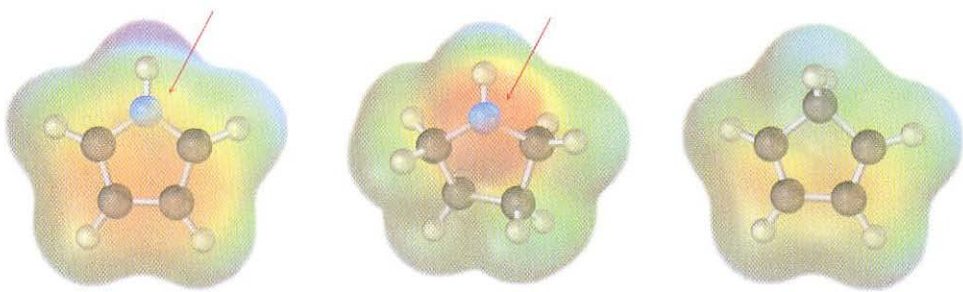
Furan **Pyrrole**

Although pyrrole appears to be both an amine and a conjugated diene, its chemical properties are not consistent with either of these structural features. Unlike most other amines, pyrrole is not basic—the pK_a of the pyrrolinium ion is 0.4; unlike most other conjugated dienes, pyrrole undergoes electrophilic substitution reactions rather than additions. The reason for both these properties, as noted previously in Section 15.5, is that pyrrole has six π electrons and is aromatic. Each of the four carbons contributes one

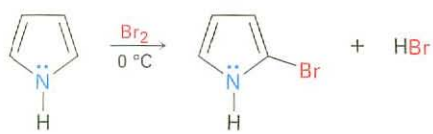
π electron, and the sp^2-hybridized nitrogen contributes two more from its lone pair.



Because the nitrogen lone pair is a part of the aromatic sextet, protonation on nitrogen would destroy the aromaticity of the ring. The nitrogen atom in pyrrole is therefore less electron-rich, less basic, and less nucleophilic than the nitrogen in an aliphatic amine. By the same token, the *carbon* atoms of pyrrole are *more* electron-rich and more nucleophilic than typical double-bond carbons. The pyrrole ring is therefore reactive toward electrophiles in the same way that enamines are (Section 23.11). Electrostatic potential maps show how the pyrrole nitrogen is electron-poor (less red) compared with the nitrogen in its saturated counterpart pyrrolidine, while the pyrrole carbon atoms are electron-rich (more red) compared with the carbons in 1,3-cyclopentadiene.



The chemistry of pyrrole is similar to that of activated benzene rings. In general, however, the heterocycles are more reactive toward electrophiles than benzene rings are, and low temperatures are often necessary to control the reactions. Halogenation, nitration, sulfonation, and Friedel–Crafts acylation can all be accomplished. For example:



Electrophilic substitutions normally occur at C2, the position next to the nitrogen, because reaction at this position leads to a more stable intermediate cation having three resonance forms, whereas reaction at C3 gives a less stable cation with only two resonance forms (Figure 24.6).

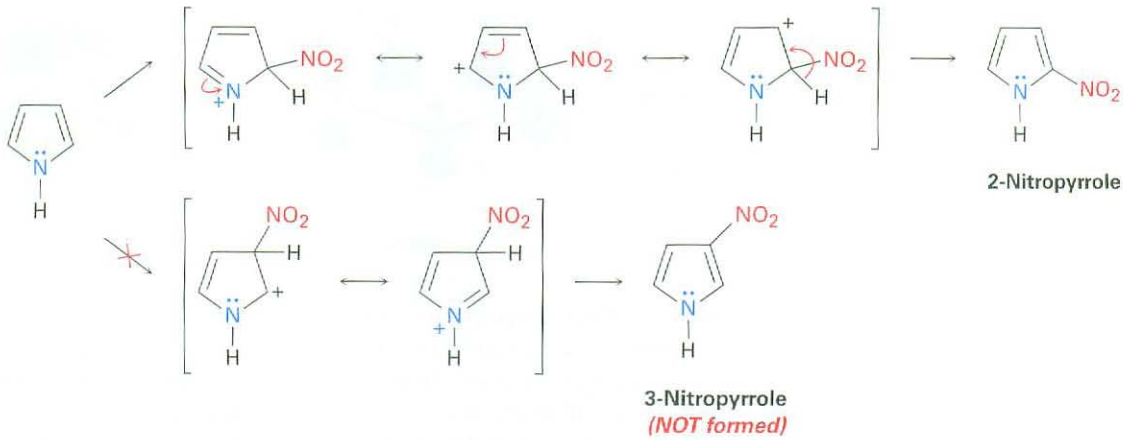
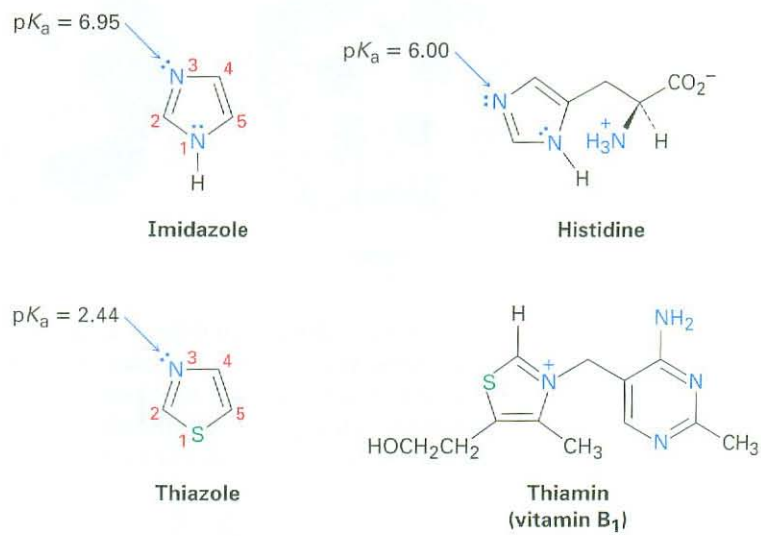


Figure 24.6 Electrophilic nitration of pyrrole. The intermediate produced by reaction at C2 is more stable than that produced by reaction at C3.

Other common five-membered heterocyclic amines include imidazole and thiazole. Imidazole, a constituent of the amino acid histidine, has two nitrogens, only one of which is basic. Thiazole, the five-membered ring system on which the structure of thiamin (vitamin B_1) is based, also contains a basic nitrogen that is alkylated in thiamin to form a quaternary ammonium ion.



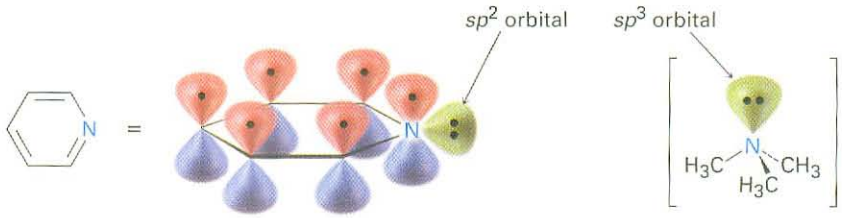
Problem 24.20 Draw an orbital picture of thiazole. Assume that both the nitrogen and sulfur atoms are sp^2-hybridized, and show the orbitals that the lone pairs occupy.

Problem 24.21 What is the percent protonation of the imidazole nitrogen atom in histidine at a physiological pH of 7.3? (See Section 24.5.)

Pyridine and Pyrimidine

Pyridine is the nitrogen-containing heterocyclic analog of benzene. Like ben zene, pyridine is a flat, aromatic molecule, with bond angles of 120° and C–(bond lengths of 139 pm, intermediate between typical single and double bond: The five carbon atoms and the sp^2-hybridized nitrogen atom each contribut one π electron to the aromatic sextet, and the lone-pair electrons occupy a sp^2 orbital in the plane of the ring (Section 15.5).

As shown in Table 24.1, pyridine ($pK_a = 5.25$) is a stronger base than pyrrol but a weaker base than alkylamines. The diminished basicity of pyridine com pared with an alkylamine is due to the fact that the lone-pair electrons on th pyridine nitrogen are in an sp^2 orbital, while those on an alkylamine nitroge are in an sp^3 orbital. Because *s* orbitals have their maximum electron density a the nucleus but *p* orbitals have a node at the nucleus, electrons in an orbital wit more *s* character are held more closely to the positively charged nucleus and ar less available for bonding. As a result, the sp^2-hybridized nitrogen atom (33% *s* character) in pyridine is less basic than the sp^3-hybridized nitrogen in an alkylamine (25% *s* character).



Pyridine

Unlike benzene, pyridine undergoes electrophilic aromatic substitution reactions with great difficulty. Halogenation can be carried out under drastic conditions, but nitration occurs in very low yield, and Friedel–Crafts reactions are not successful. Reactions usually give the 3-substituted product.

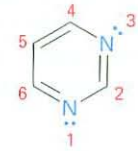
Pyridine **3-Bromopyridine (30%)**

The low reactivity of pyridine toward electrophilic aromatic substitution is caused by a combination of factors. One is that acid–base complexation between the basic ring nitrogen atom and the incoming electrophile places a positive charge on the ring, thereby deactivating it. Equally important is that the electron density of the ring is decreased by the electron-withdrawing induc tive effect of the electronegative nitrogen atom. Thus, pyridine has a substantial dipole moment ($\mu = 2.26$ D), with the ring carbons acting as the positive end of

the dipole. Reaction of an electrophile with the positively polarized carbon atoms is therefore difficult.

μ = 2.26 D

In addition to pyridine, the six-membered diamine pyrimidine is also found commonly in biological molecules, particularly as a constituent of nucleic acids. With a pK_a of 1.3, pyrimidine is substantially less basic than pyridine because of the inductive effect of the second nitrogen.

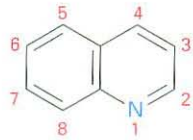


Pyrimidine
pK_a = 1.3

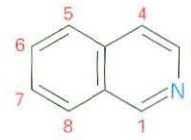
Problem 24.22 Electrophilic aromatic substitution reactions of pyridine normally occur at C3. Draw the carbocation intermediates resulting from reaction of an electrophile at C1, C2, and C3, and explain the observed result.

Polycyclic Heterocycles

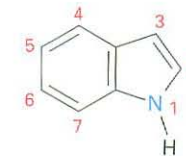
As we saw in Section 15.7, quinoline, isoquinoline, indole, and purine are common polycyclic heterocycles. The first three contain both a benzene ring and a heterocyclic aromatic ring, while purine contains two heterocyclic rings joined together. All four ring systems occur commonly in nature, and many compounds with these rings have pronounced physiological activity. The quinoline alkaloid quinine, for instance, is widely used as an antimalarial drug, tryptophan is a common amino acid, and the purine adenine is a constituent of nucleic acids.



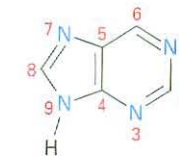
Quinoline



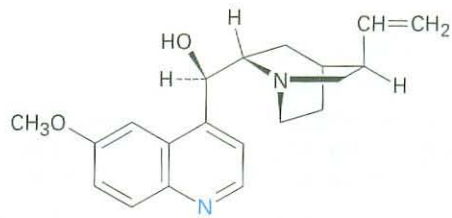
Isoquinoline



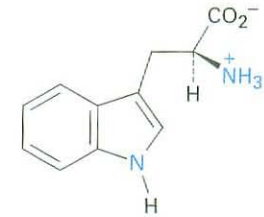
Indole



Purine



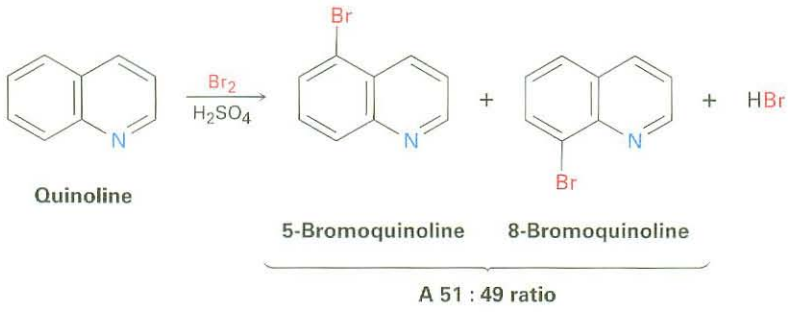
Quinine
(antimalarial)



Tryptophan
(amino acid)

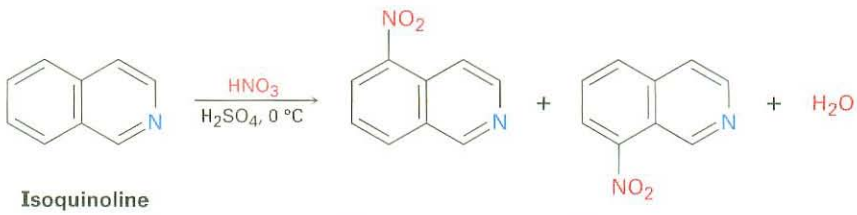
Adenine
(DNA constituent)

The chemistry of these polycyclic heterocycles is just what you might expect from a knowledge of the simpler heterocycles pyridine and pyrrole. Quinoline and isoquinoline both have basic, pyridine-like nitrogen atoms, and both undergo electrophilic substitutions, although less easily than benzene. Reaction occurs on the benzene ring rather than on the pyridine ring, and a mixture of substitution products is obtained.



Quinoline **5-Bromoquinoline** **8-Bromoquinoline**

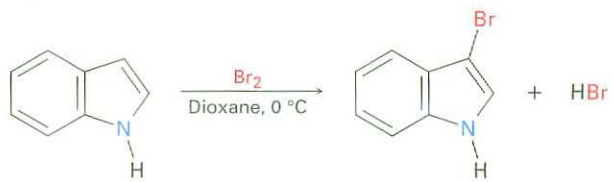
A 51 : 49 ratio



Isoquinoline **5-Nitroisoquinoline** **8-Nitroisoquinoline**

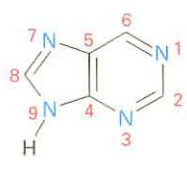
A 90 : 10 ratio

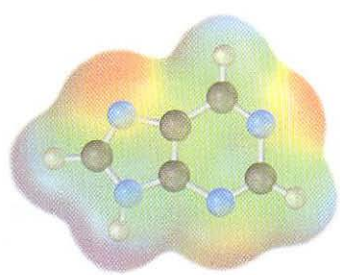
Indole has a nonbasic, pyrrole-like nitrogen and undergoes electrophilic substitution more easily than benzene. Substitution occurs at C3 of the electron-rich pyrrole ring, rather than on the benzene ring.



Indole **3-Bromoindole**

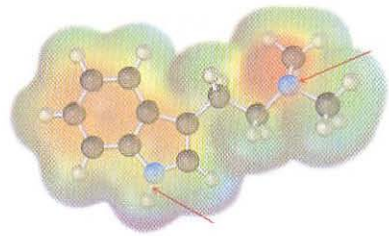
Purine has three basic, pyridine-like nitrogens with lone-pair electrons in sp^2 orbitals in the plane of the ring. The remaining purine nitrogen is nonbasic and pyrrole-like, with its lone-pair electrons as part of the aromatic π electron system.





Purine

Problem 24.23 Which nitrogen atom in the hallucinogenic indole alkaloid *N,N*-dimethyltryptamine is more basic? Explain.



***N,N*-Dimethyltryptamine**

Problem 24.24 Indole reacts with electrophiles at C3 rather than at C2. Draw resonance forms of the intermediate cations resulting from reaction at C2 and C3, and explain the observed results.

24.10 Spectroscopy of Amines

Infrared Spectroscopy

Primary and secondary amines can be identified by a characteristic N–H stretching absorption in the 3300 to 3500 cm^{-1} range of the IR spectrum. Alcohols also absorb in this range (Section 17.11), but amine absorption bands are generally sharper and less intense than hydroxyl bands. Primary amines show a pair of bands at about 3350 and 3450 cm^{-1}, and secondary amines show a single band at 3350 cm^{-1}. Tertiary amines have no absorption in this region because they have no N–H bonds. An IR spectrum of cyclohexylamine is shown in Figure 24.7.

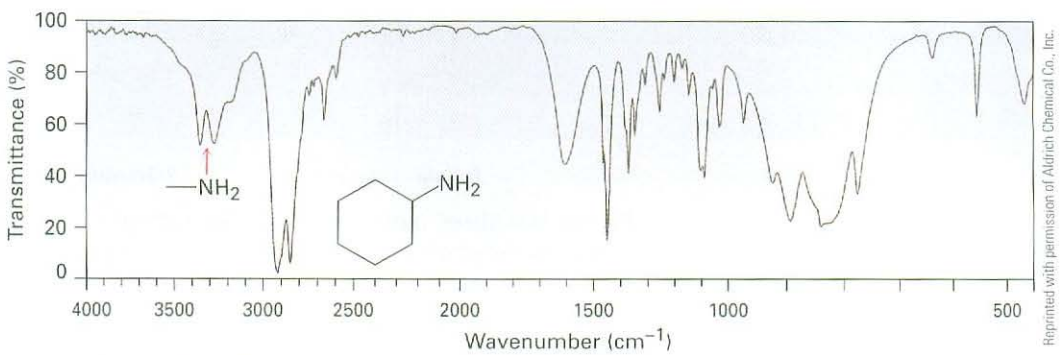


Figure 24.7 IR spectrum of cyclohexylamine.

In addition to looking for a characteristic N–H absorption, there is also a simple trick for telling whether a compound is an amine. Addition of a small amount of HCl produces a broad and strong ammonium band in the 2200 to 3000 cm^{-1} range if the sample contains an amino group. Figure 24.8 gives an example.

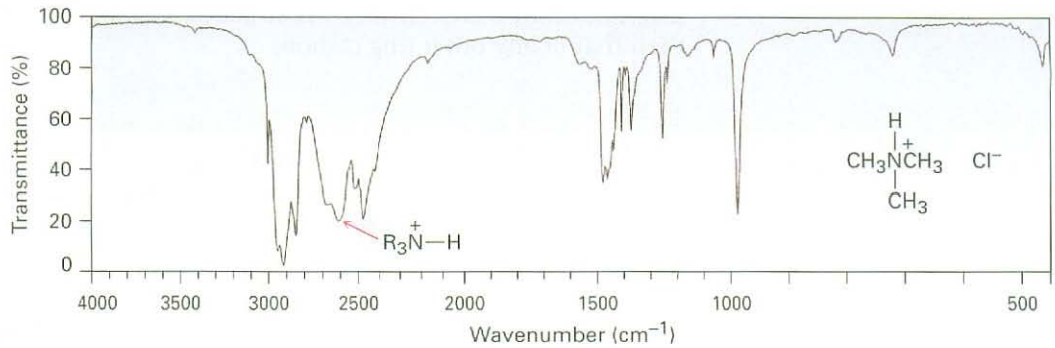
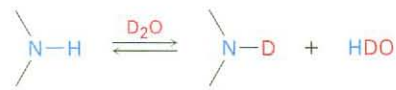


Figure 24.8 IR spectrum of trimethylammonium chloride.

Nuclear Magnetic Resonance Spectroscopy

Amines are difficult to identify solely by ^{1}H NMR spectroscopy because N–H hydrogens tend to appear as broad signals without clear-cut coupling to neighboring C–H hydrogens. As with O–H absorptions (Section 17.11), amine N–H absorptions can appear over a wide range and are best identified by adding a small amount of D_2O to the sample tube. Exchange of N–D for N–H occurs, and the N–H signal disappears from the NMR spectrum.



Hydrogens on the carbon next to nitrogen are deshielded because of the electron-withdrawing effect of the nitrogen, and they therefore absorb at lower field than alkane hydrogens. *N*-Methyl groups are particularly distinctive because they absorb as a sharp three-proton singlet at 2.2 to 2.6 δ. This *N*-methyl resonance at 2.42 δ is easily seen in the ^{1}H NMR spectrum of *N*-methylcyclohexylamine (Figure 24.9).

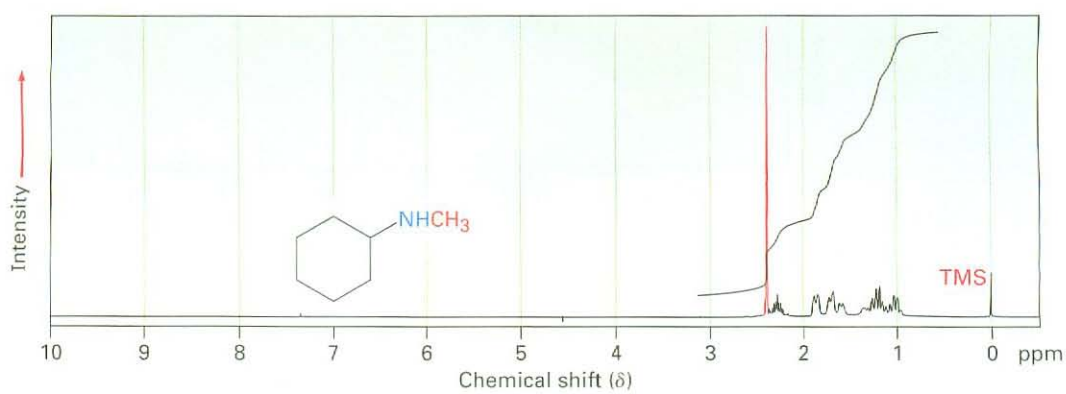
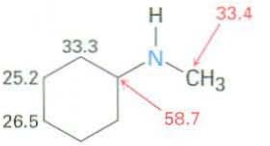


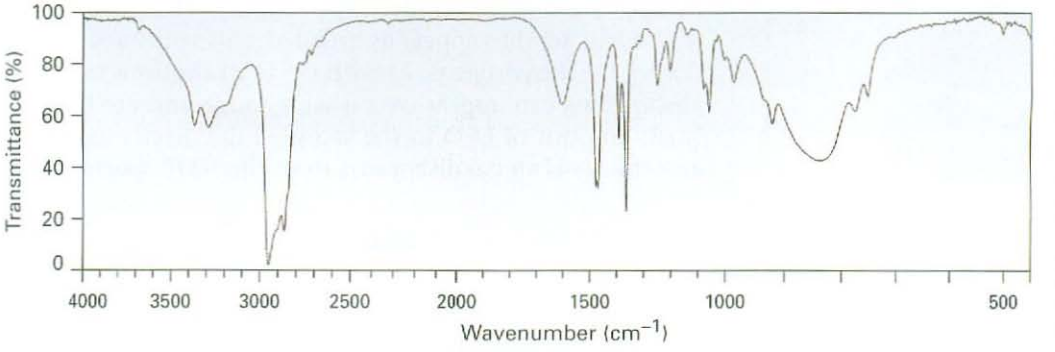
Figure 24.9 Proton NMR spectrum of *N*-methylcyclohexylamine.

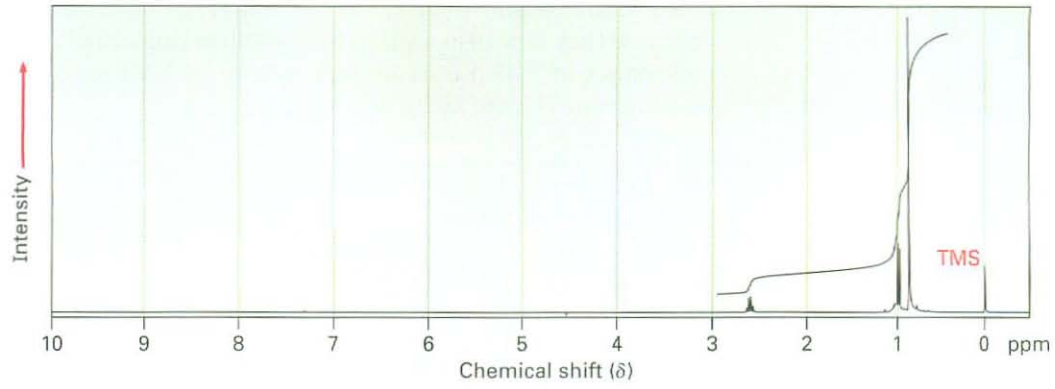
Carbons next to amine nitrogens are slightly deshielded in the ^{13}C NMR spectrum and absorb about 20 ppm downfield from where they would absorb in an alkane of similar structure. In *N*-methylcyclohexylamine, for example, the

ring carbon to which nitrogen is attached absorbs at a position 24 ppm lower than that of any other ring carbon.



Problem 24.25 Compound **A**, $C_6H_{12}O$, has an IR absorption at 1715 cm^{-1} and gives compound **B**, $C_6H_{15}N$, when treated with ammonia and $NaBH_3CN$. The IR and ^1H NMR spectra of **B** are shown. What are the structures of **A** and **B**?



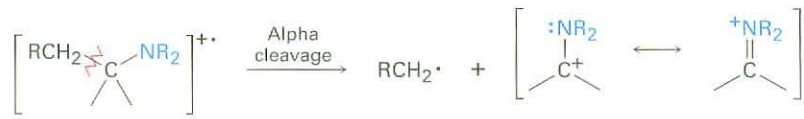


Mass Spectrometry

The *nitrogen rule* of mass spectrometry says that a compound with an odd number of nitrogen atoms has an odd-numbered molecular weight. Thus, the presence of nitrogen in a molecule is detected simply by observing its mass spectrum. An odd-numbered molecular ion usually means that the unknown

compound has one or three nitrogen atoms, and an even-numbered molecular ion usually means that a compound has either zero or two nitrogen atoms. The logic behind the rule derives from the fact that nitrogen is trivalent, thus requiring an odd number of hydrogen atoms. For example, morphine has the formula $C_{17}H_{19}NO_3$ and a molecular weight of 285 amu.

Alkylamines undergo a characteristic α cleavage in the mass spectrometer, similar to the cleavage observed for alcohols (Section 17.11). A C–C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a resonance-stabilized, nitrogen-containing cation.



As an example, the mass spectrum of *N*-ethylpropylamine shown in Figure 24.10 has peaks at $m/z = 58$ and $m/z = 72$, corresponding to the two possible modes of α cleavage.

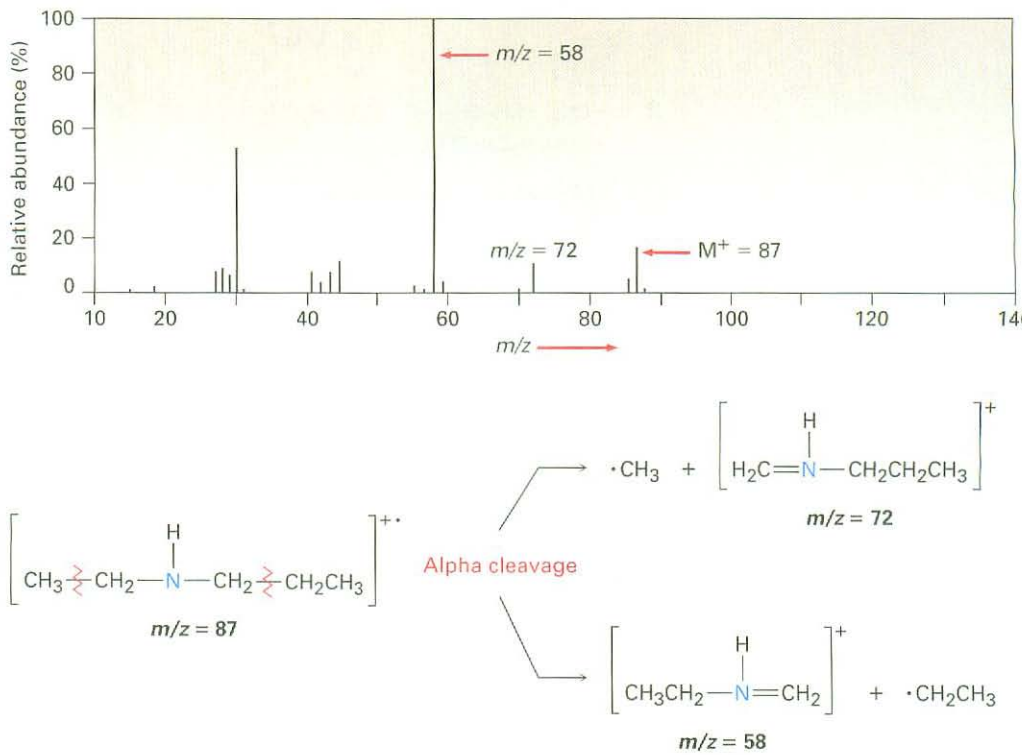


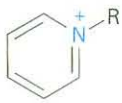
Figure 24.10 Mass spectrum of *N*-ethylpropylamine. The two possible modes of α cleavage lead to the observed fragment ions at $m/z = 58$ and $m/z = 72$.

Focus On . . .

Green Chemistry II: Ionic Liquids

Liquids made of ions? Usually when we think of ionic compounds, we think of high-melting solids: sodium chloride, magnesium sulfate, lithium carbonate, and so forth. But yes, there also ionic compounds that are liquid at room temperature, and they are gaining importance as reaction solvents, particularly for use in green chemistry processes (see the Chapter 11 *Focus On*).

Ionic liquids have been known for nearly a century; the first to be discovered was ethylammonium nitrate, $CH_3CH_2NH_3^+\ NO_3^-$, with a melting point of 12 °C. More generally, however, the ionic liquids in use today are salts in which the cation is unsymmetrical and in which one or both of the ions are bulky so that the charges are dispersed over a large volume. Both factors minimize the crystal lattice energy and disfavor formation of the solid. Typical cations are quaternary ammonium ions from heterocyclic amines, either 1,3-dialkylimidazolium ions, *N*-alkylpyridinium ions, or ring-substituted *N*-alkylpyridinium ions.



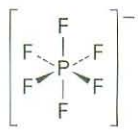
$[R = -CH_3, -CH_2CH_3, -CH_2CH_2CH_2CH_3, -CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3]$

1,3-Dialkylimidazolium ions

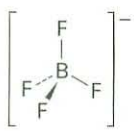
$[R = -CH_2CH_3, -CH_2CH_2CH_2CH_3, -CH_2CH_2CH_2CH_2CH_2CH_3]$

***N*-Alkylpyridinium ions**

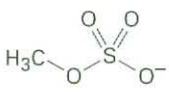
Anions are just as varied as the cations, and more than 250 different ionic liquids with different anion/cation combinations are commercially available. Hexafluorophosphate, tetrafluoroborate, alkyl sulfates, trifluoromethanesulfonates (triflates), and halides are some anion possibilities.



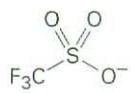
Hexafluorophosphate



Tetrafluoroborate



Methyl sulfate



Trifluoromethanesulfonate

Cl^-, Br^-, I^-

Halide

(continued)

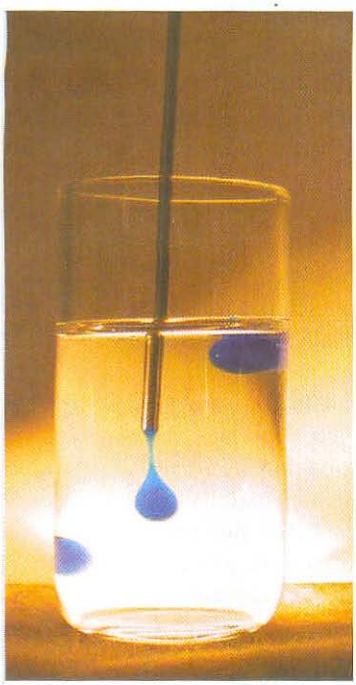


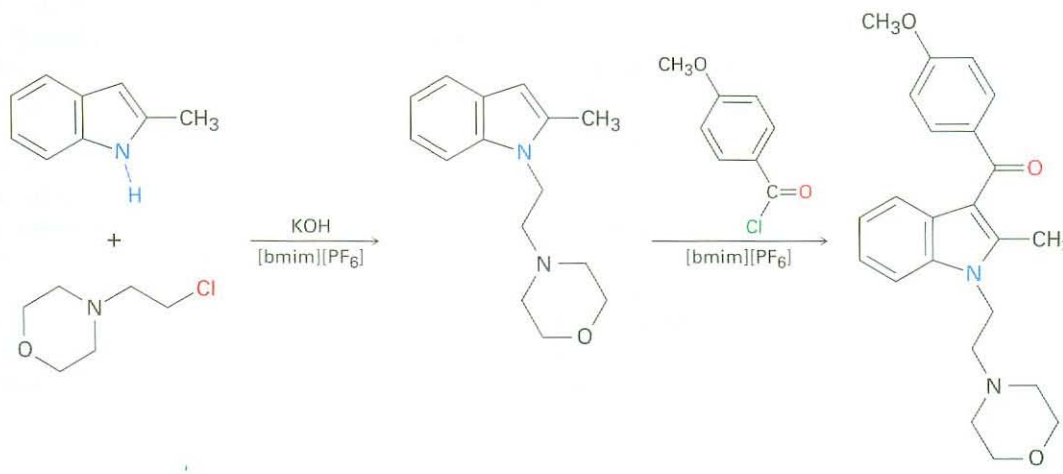
Image provided by Peg Williams, USAFA, Dept. of Chemistry Research Center

Yes, these liquids really do consist of ionic rather than molecular substances.

Ionic liquids have several important features that make them attractive for use as solvents, particularly in green chemistry:

- They dissolve both polar and nonpolar organic compounds, giving high solute concentrations and thereby minimizing the amount of solvent needed.
- They can be optimized for specific reactions by varying cation and anion structures.
- They are nonflammable.
- They are thermally stable.
- They have negligible vapor pressures and do not evaporate.
- They are generally recoverable and can be reused many times.

As an example of their use in organic chemistry, the analgesic drug Pravadoline has been synthesized in two steps using 1-butyl-3-methylimidazolium hexafluorophosphate, abbreviated [bmim][PF_6], as the solvent for both steps. The first step is a base-induced S_N2 reaction of 2-methylindole with a primary alkyl halide, and the second is a Friedel–Crafts acylation. Both steps take place in 95% yield, and the ionic solvent is recovered simply by washing the reaction mixture, first with toluene and then with water. We'll be hearing a lot more about ionic solvents in coming years.



Pravadoline

SUMMARY AND KEY WORDS

Amines are organic derivatives of ammonia. They are named in the IUPAC system either by adding the suffix *-amine* to the name of the alkyl substituent or by considering the amino group as a substituent on a more complex parent molecule.

The chemistry of amines is dominated by the lone-pair electrons on nitrogen, which makes amines both basic and nucleophilic. The base strength of **arylamines** is generally lower than that of **alkylamines** because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic π system. Electron-withdrawing substituents on the aromatic ring further weaken the basicity of a substituted aniline, while electron-donating substituents increase basicity. Alkylamines are sufficiently basic that they exist almost entirely in their protonated form at the physiological pH of 7.3 inside cells.

Heterocyclic amines are compounds that contain one or more nitrogen atoms as part of a ring. Saturated heterocyclic amines usually have the same chemistry as their open-chain analogs, but unsaturated heterocycles such as pyrrole, imidazole, pyridine, and pyrimidine are aromatic. All four are unusually stable, and all undergo aromatic substitution on reaction with electrophiles. Pyrrole is nonbasic because its nitrogen lone-pair electrons are part of the aromatic π system. Fused-ring heterocycles such as quinoline, isoquinoline, indole, and purine are also commonly found in biological molecules.

Arylamines are prepared by nitration of an aromatic ring followed by reduction. Alkylamines are prepared by S_N2 reaction of ammonia or an amine with an alkyl halide. This method often gives poor yields, however, and an alternative such as the **Gabriel amine synthesis** is preferred. Amines can also be prepared by a number of reductive methods, including $LiAlH_4$ reduction of amides, nitriles, and azides. Also important is the **reductive amination** reaction in which a ketone or an aldehyde is treated with an amine in the presence of a reducing agent such as $NaBH_3CN$. In addition, amines result from the **Hofmann** and **Curtius rearrangements** of carboxylic acid derivatives. Both methods involve migration of the $-R$ group bonded to the carbonyl carbon and yield a product that has one less carbon atom than the starting material.

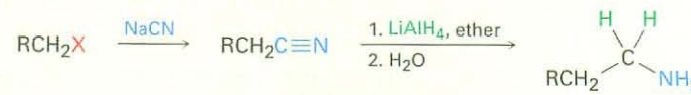
Many of the reactions of amines are familiar from past chapters. Thus, amines react with alkyl halides in S_N2 reactions and with acid chlorides in nucleophilic acyl substitution reactions. Amines also undergo E2 elimination to yield alkenes if they are first quaternized by treatment with iodomethane and then heated with silver oxide, a process called the **Hofmann elimination**.

Arylamines are converted by diazotization with nitrous acid into **arenediazonium salts**, $ArN_2^+\ X^-$. The diazonio group can then be replaced by many other substituents in the **Sandmeyer reaction** to give a wide variety of substituted aromatic compounds. Aryl chlorides, bromides, iodides, and nitriles can be prepared from arenediazonium salts, as can arenes and phenols. In addition to their reactivity toward substitution reactions, diazonium salts undergo coupling with phenols and arylamines to give brightly colored azo dyes.

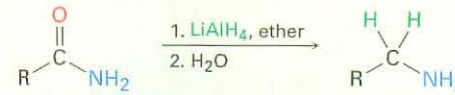
SUMMARY OF REACTIONS

1. Synthesis of amines (Section 24.6)

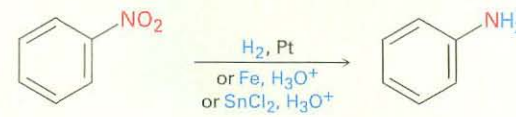
(a) Reduction of nitriles



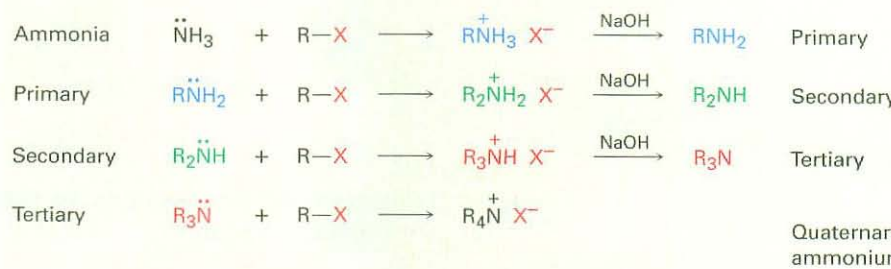
(b) Reduction of amides



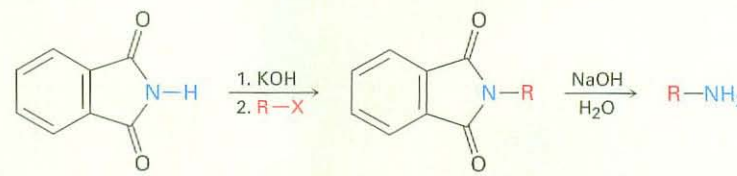
(c) Reduction of nitrobenzenes



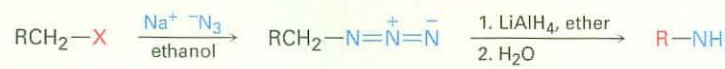
(d) S_N2 Alkylation of alkyl halides



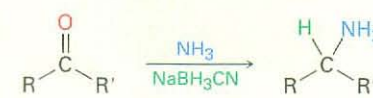
(e) Gabriel amine synthesis



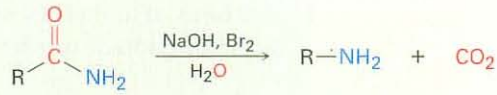
(f) Reduction of azides



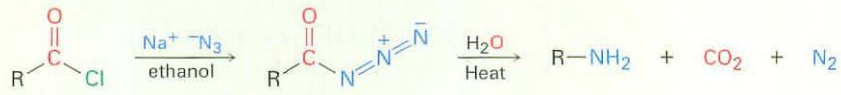
(g) Reductive amination of aldehydes/ketones



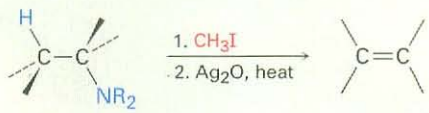
(h) Hofmann rearrangement of amides



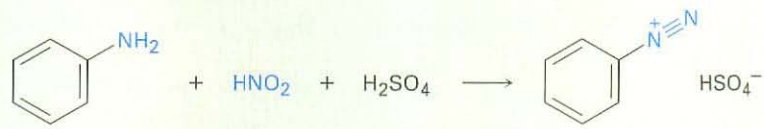
(i) Curtius rearrangement of acyl azides



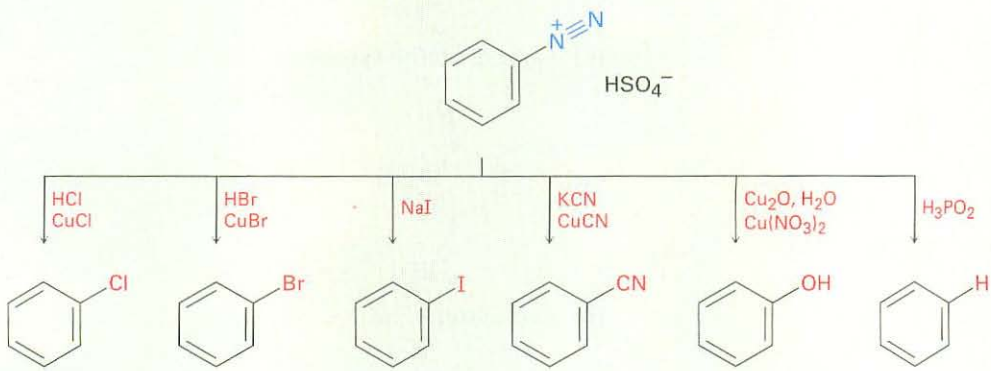
2. Reactions of amines
   (a) Alkylation with alkyl halides; see reaction 1(d)
   (b) Hofmann elimination (Section 24.7)



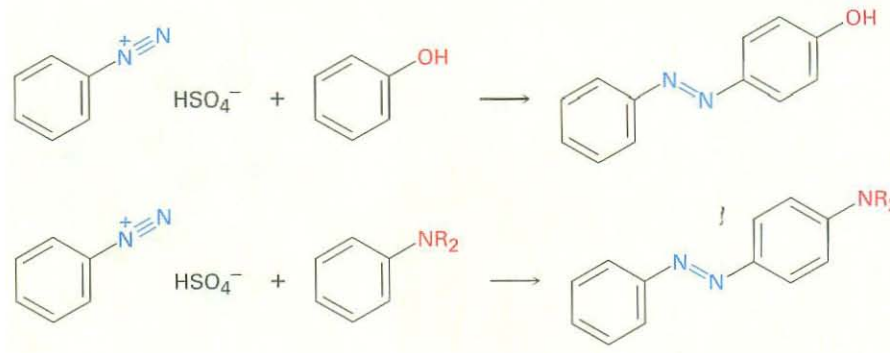
(c) Diazotization (Section 24.8)



3. Reactions of arenediazonium salts (Section 24.8)
   (a) Nucleophilic substitutions



(b) Diazonium coupling



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

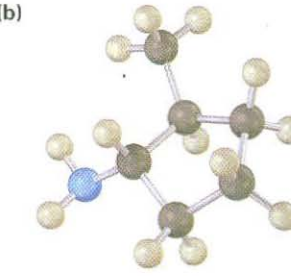
VISUALIZING CHEMISTRY

(Problems 24.1–24.25 appear within the chapter.)

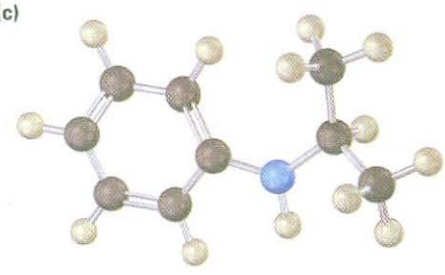
24.26 ■ Name the following amines, and identify each as primary, secondary, or tertiary:

(a)

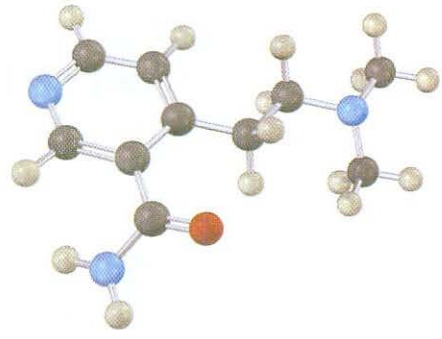
(b)



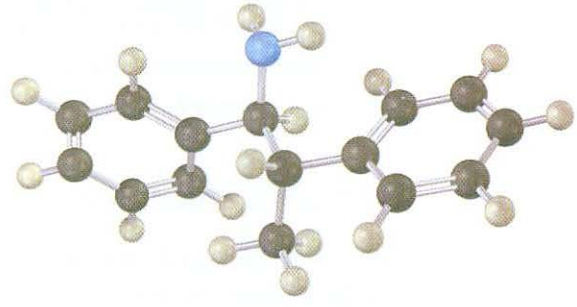
(c)



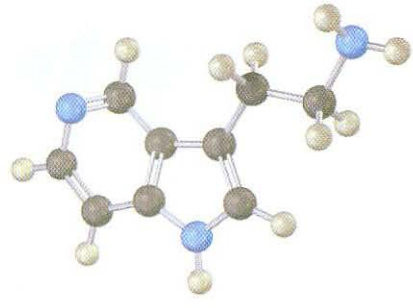
24.27 ■ The following compound contains three nitrogen atoms. Rank them in order of increasing basicity.



24.28 Name the following amine, including *R,S* stereochemistry, and draw the product of its reaction with excess iodomethane followed by heating with Ag_2O (Hofmann elimination). Is the stereochemistry of the alkene product *Z* or *E*? Explain.

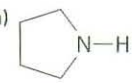


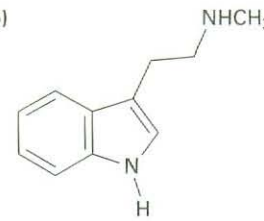
24.29 Which nitrogen atom in the following compound is more basic? Explain.

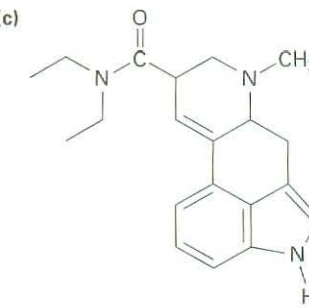


ADDITIONAL PROBLEMS

24.30 Classify each of the amine nitrogen atoms in the following substances as primary, secondary, or tertiary:

(a) 

(b) 

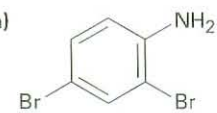
(c) 

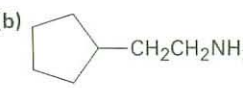
Lysergic acid diethylamide

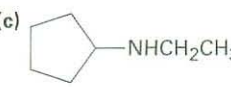
24.31 ■ Draw structures corresponding to the following IUPAC names:

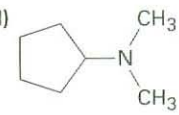
(a) *N*,*N*-Dimethylaniline
(b) (Cyclohexylmethyl)amine
(c) *N*-Methylcyclohexylamine
(d) (2-Methylcyclohexyl)amine
(e) 3-(*N*,*N*-Dimethylamino)propanoic acid

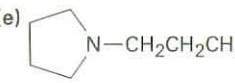
24.32 ■ Name the following compounds:

(a) 

(b) 

(c) 

(d) 

(e) 

(f) $H_2NCH_2CH_2CH_2CN$

24.33 ■ Give the structures of the major organic products you would expect from reaction of *m*-toluidine (*m*-methylaniline) with the following reagents:

(a) Br_2 (1 equivalent)
(b) CH_3I (excess)
(c) CH_3COCl in pyridine
(d) The product of (c), then HSO_3Cl

24.34 ■ Show the products from reaction of *p*-bromoaniline with the following reagents:

(a) CH_3I (excess)
(b) HCl
(c) HNO_2, H_2SO_4
(d) CH_3COCl
(e) CH_3MgBr
(f) CH_3CH_2Cl, $AlCl_3$
(g) Product of (c) with CuCl, HCl
(h) Product of (d) with CH_3CH_2Cl, $AlCl_3$

24.35 ■ How would you prepare the following substances from 1-butanol?

(a) Butylamine
(b) Dibutylamine
(c) Propylamine
(d) Pentylamine
(e) *N*,*N*-Dimethylbutylamine
(f) Propene

24.36 ■ How would you prepare the following substances from pentanoic acid?

(a) Pentanamide
(b) Butylamine
(c) Pentylamine
(d) 2-Bromopentanoic acid
(e) Hexanenitrile
(f) Hexylamine

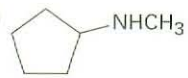
24.37 ■ How would you prepare aniline from the following starting materials?
(a) Benzene (b) Benzamide (c) Toluene

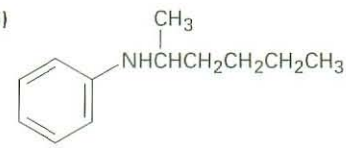
24.38 ■ How would you convert aniline into each of the products listed in Problem 24.37?

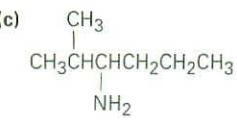
24.39 How would you prepare benzylamine, $C_6H_5CH_2NH_2$, from benzene? More than one step is needed.

24.40 ■ How might you prepare pentylamine from the following starting materials?
(a) Pentanamide (b) Pentanenitrile (c) 1-Butene
(d) Hexanamide (e) 1-Butanol (f) 5-Decene
(g) Pentanoic acid

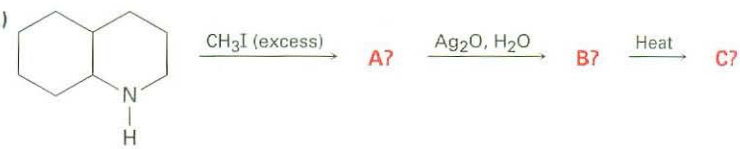
24.41 ■ What are the major products you would expect from Hofmann elimination of the following amines?

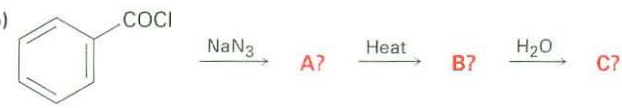
(a) 

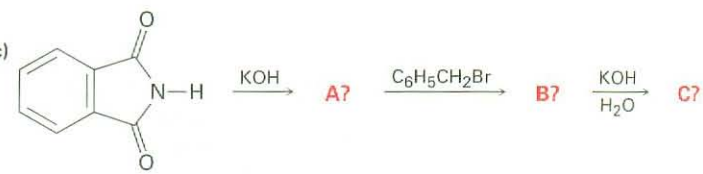
(b) 

(c) 

24.42 ■ Predict the product(s) of the following reactions. If more than one product is formed, tell which is major.

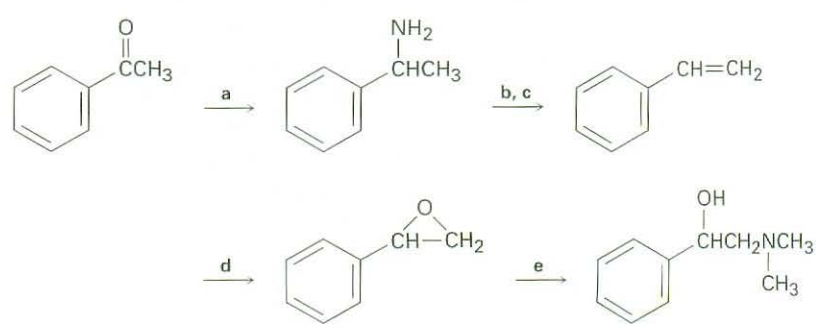
(a) 

(b) 

(c) 

(d) $BrCH_2CH_2CH_2CH_2Br$ + 1 equiv CH_3NH_2 $\xrightarrow[H_2O]{NaOH}$?

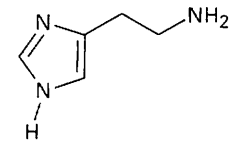
24.43 Fill in the missing reagents a–e in the following scheme:



■ Assignable in OWL

24.44 Although pyrrole is a much weaker base than most other amines, it is a much stronger acid ($pK_a \approx 15$ for the pyrrole versus 35 for diethylamine). The N–H proton is readily abstracted by base to yield the pyrrole anion, $C_4H_4N^-$. Explain.

24.45 Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms. List them in order of increasing basicity, and explain your ordering.

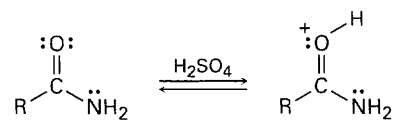


Histamine

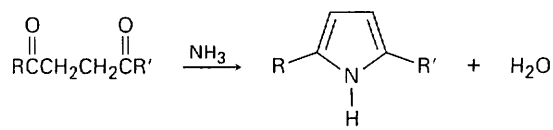
24.46 Oxazole is a five-membered aromatic heterocycle. Would you expect oxazole to be more basic or less basic than pyrrole? Explain.

Oxazole

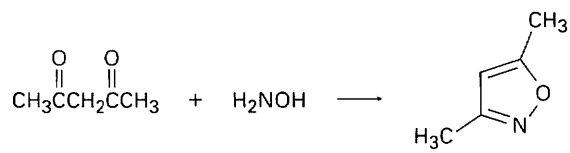
24.47 Protonation of an amide using strong acid occurs on oxygen rather than on nitrogen. Suggest a reason for this behavior, taking resonance into account.



24.48 Substituted pyrroles are often prepared by treatment of a 1,4-diketone with ammonia. Propose a mechanism.



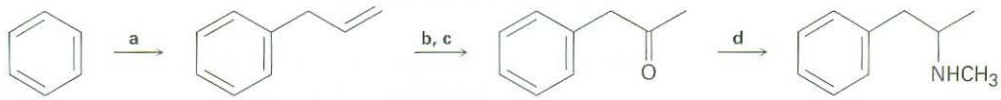
24.49 3,5-Dimethylisoxazole is prepared by reaction of 2,4-pentanedione with hydroxylamine. Propose a mechanism.



3,5-Dimethylisoxazole

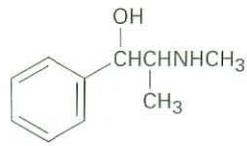
24.50 Account for the fact that *p*-nitroaniline ($pK_a = 1.0$) is less basic than *m*-nitroaniline ($pK_a = 2.5$) by a factor of 30. Draw resonance structures to support your argument. (The pK_a values refer to the corresponding ammonium ions.)

24.51 Fill in the missing reagents **a–d** in the following synthesis of racemic methamphetamine from benzene.



(*R,S*)-Methamphetamine

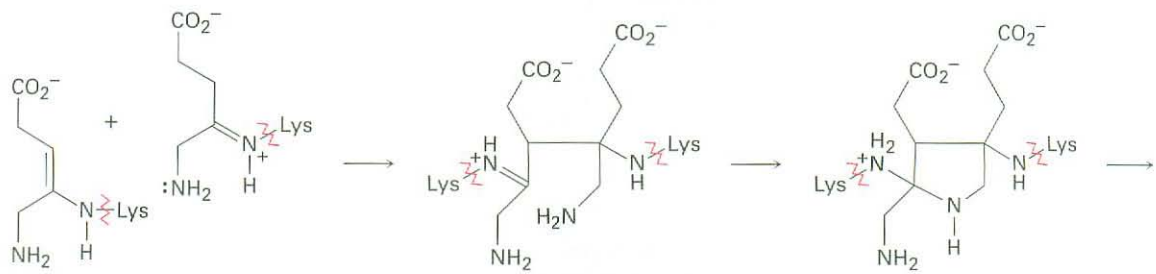
24.52 How might a reductive amination be used to synthesize ephedrine, an amino alcohol that is widely used for the treatment of bronchial asthma?



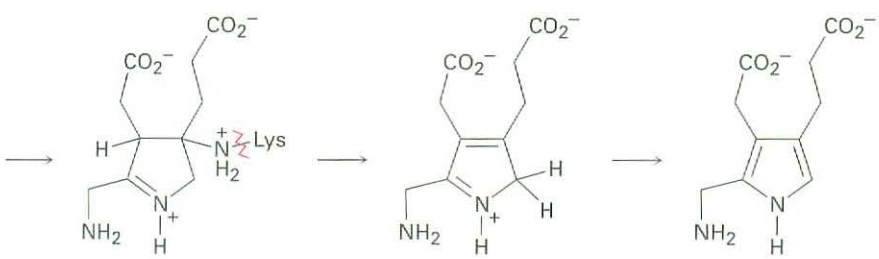
Ephedrine

24.53 One problem with reductive amination as a method of amine synthesis is that by-products are sometimes obtained. For example, reductive amination of benzaldehyde with methylamine leads to a mixture of *N*-methylbenzylamine and *N*-methyldibenzylamine. How do you suppose the tertiary amine by-product is formed? Propose a mechanism.

24.54 Chlorophyll, heme, vitamin B_{12}, and a host of other substances are biosynthesized from porphobilinogen (PBG), which is itself formed from condensation of two molecules of 5-aminolevulinate. The two 5-aminolevulinates are bound to lysine (Lys) amino acids in the enzyme, one in the enamine form and one in the imine form, and their condensation is thought to occur by the following steps. Using curved arrows, show the mechanism of each step.



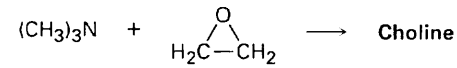
Enzyme-bound 5-aminolevulinate



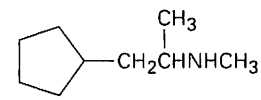
Porphobilinogen (PBG)

■ Assignable in OWL

24.55 Choline, a component of the phospholipids in cell membranes, can be prepared by S_N2 reaction of trimethylamine with ethylene oxide. Show the structure of choline, and propose a mechanism for the reaction.

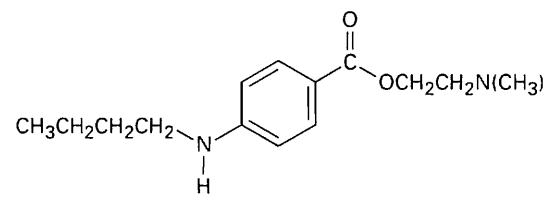


24.56 Cyclopentamine is an amphetamine-like central nervous system stimulant. Propose a synthesis of cyclopentamine from materials of five carbons or less.



Cyclopentamine

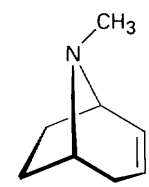
24.57 Tetracaine is a substance used medicinally as a spinal anesthetic during lumbar punctures (spinal taps).



Tetracaine

(a) How would you prepare tetracaine from the corresponding aniline derivative, $ArNH_2$?
(b) How would you prepare tetracaine from *p*-nitrobenzoic acid?
(c) How would you prepare tetracaine from benzene?

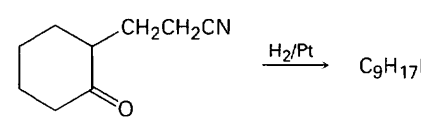
24.58 Atropine, $C_{17}H_{23}NO_3$, is a poisonous alkaloid isolated from the leaves and roots of *Atropa belladonna*, the deadly nightshade. In small doses, atropine acts as a muscle relaxant; 0.5 ng (nanogram, 10^{-9} g) is sufficient to cause pupil dilation. On basic hydrolysis, atropine yields tropic acid, $C_6H_5CH(CH_2OH)CO_2H$, and tropine, $C_8H_{15}NO$. Tropine is an optically inactive alcohol that yields tropidene on dehydration with H_2SO_4. Propose a structure for atropine.



Tropidene

24.59 Tropidene (Problem 24.58) can be converted by a series of steps into tropilidene (1,3,5-cycloheptatriene). How would you accomplish this conversion?

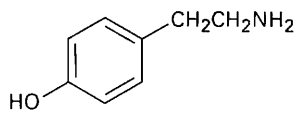
24.60 Propose a structure for the product with formula $C_9H_{17}N$ that results when 2-(2-cyanoethyl)cyclohexanone is reduced catalytically.



24.61 Coniine, $C_8H_{17}N$, is the toxic principle of the poison hemlock drunk by Socrates. When subjected to Hofmann elimination, coniine yields 5-(*N*,*N*-dimethylamino)-1-octene. If coniine is a secondary amine, what is its structure?

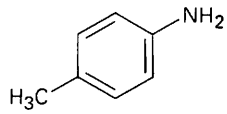
24.62 How would you synthesize coniine (Problem 24.61) from acrylonitrile ($H_2C{=}CHCN$) and ethyl 3-oxohexanoate ($CH_3CH_2CH_2COCH_2CO_2Et$)? (Hint: See Problem 24.60.)

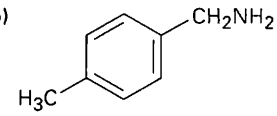
24.63 Tyramine is an alkaloid found, among other places, in mistletoe and ripe cheese. How would you synthesize tyramine from benzene? From toluene?

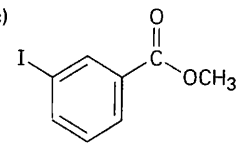


Tyramine

24.64 How would you prepare the following compounds from toluene? A diazonio replacement reaction is needed in some instances.

(a) 

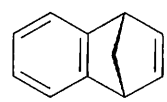
(b) 

(c) 

24.65 Reaction of anthranilic acid (*o*-aminobenzoic acid) with HNO_2 and H_2SO_4 yields a diazonium salt that can be treated with base to yield a neutral diazonium carboxylate.

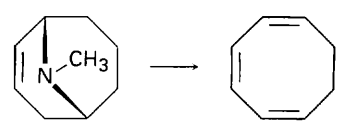
(a) What is the structure of the neutral diazonium carboxylate?

(b) Heating the diazonium carboxylate results in the formation of CO_2, N_2, and an intermediate that reacts with 1,3-cyclopentadiene to yield the following product:



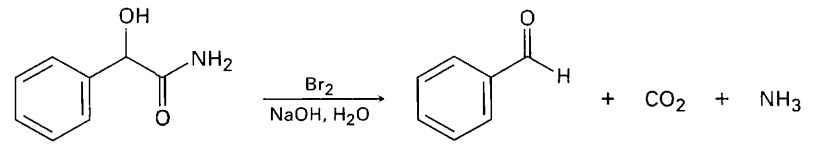
What is the structure of the intermediate, and what kind of reaction does it undergo with cyclopentadiene?

24.66 Cyclooctatetraene was first synthesized in 1911 by a route that involved the following transformation:

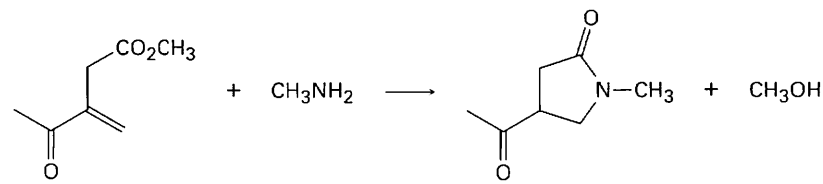


How might you use the Hofmann elimination to accomplish this reaction? How would you finish the synthesis by converting cyclooctatriene into cyclooctatetraene?

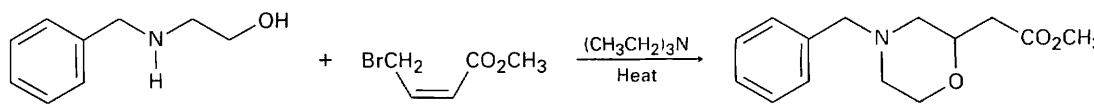
24.67 When an α-hydroxy amide is treated with Br_2 in aqueous NaOH under Hofmann rearrangement conditions, loss of CO_2 occurs and a chain-shortened aldehyde is formed. Propose a mechanism.



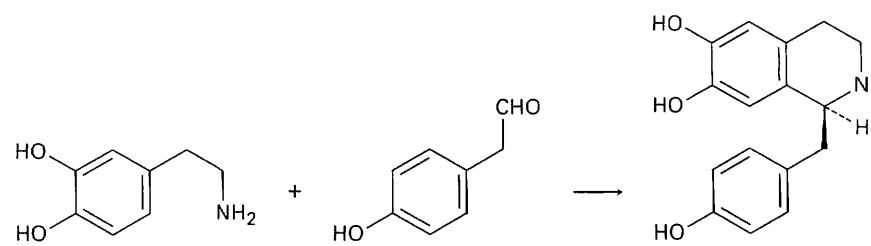
24.68 The following transformation involves a conjugate nucleophilic addition reaction (Section 19.13) followed by an intramolecular nucleophilic acyl substitution reaction (Section 21.2). Show the mechanism.



24.69 Propose a mechanism for the following reaction:

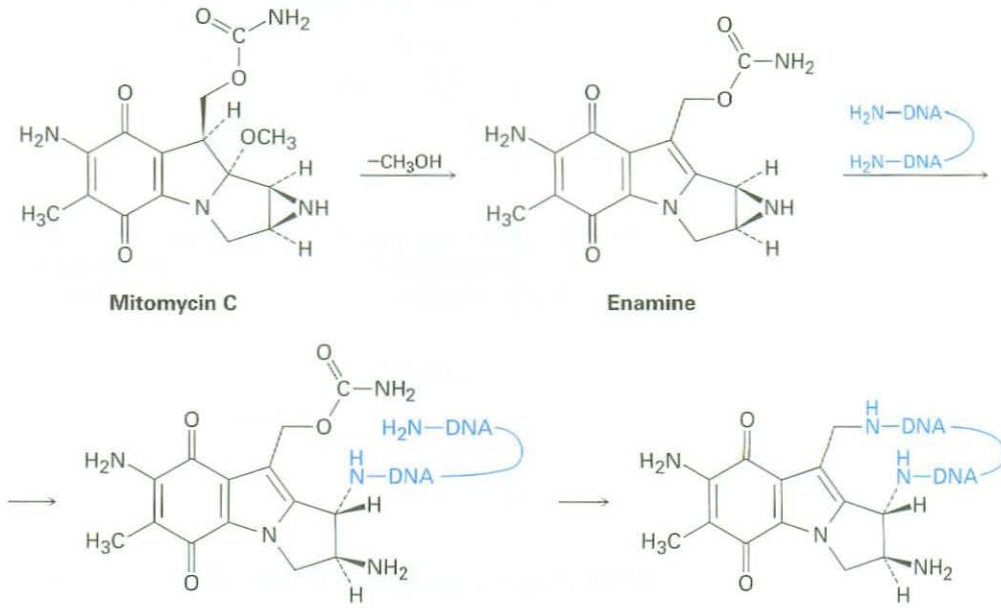


24.70 One step in the biosynthesis of morphine is the reaction of dopamine with *p*-hydroxyphenylacetaldehyde to give (*S*)-norcoclaurine. Assuming that the reaction is acid-catalyzed, propose a mechanism.



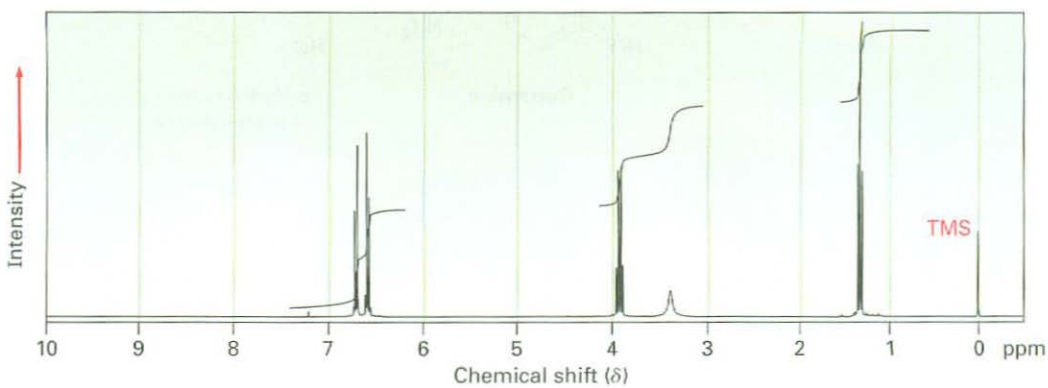
Dopamine | ***p*-Hydroxyphenylacetaldehyde** | **(*S*)-Norcoclaurine**

24.71 The antitumor antibiotic mitomycin C functions by forming cross-links in DNA chains.

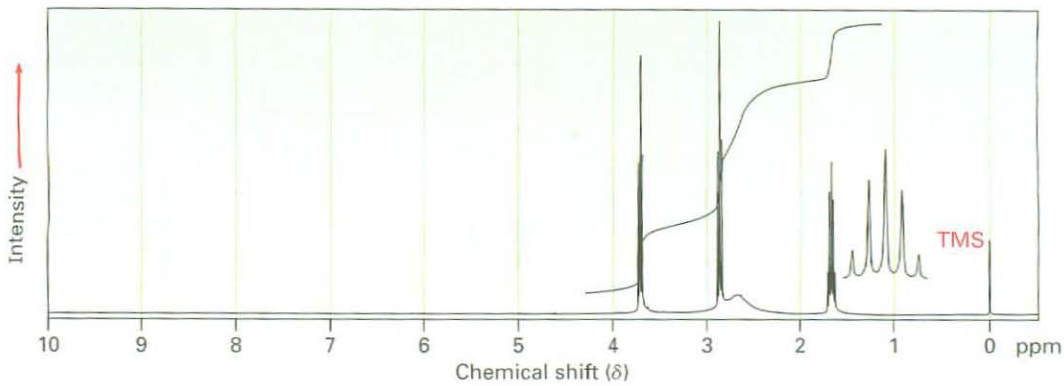


(a) The first step is loss of methoxide and formation of an iminium ion intermediate that is deprotonated to give an enamine. Show the mechanism.
(b) The second step is reaction of the enamine with DNA to open the three-membered, nitrogen-containing (aziridine) ring. Show the mechanism.
(c) The third step is loss of carbamate ($NH_2CO_2^-$) and formation of an unsaturated iminium ion, followed by a conjugate addition of another part of the DNA chain. Show the mechanism.

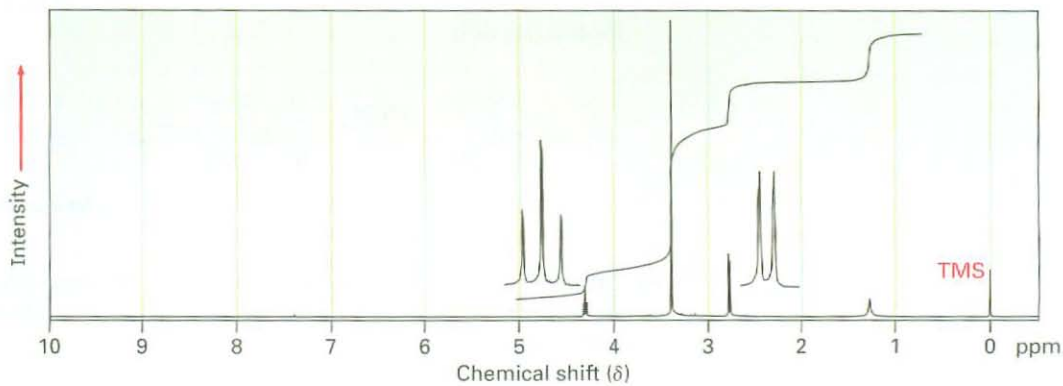
24.72 Phenacetin, a substance formerly used in over-the-counter headache remedies, has the formula $C_{10}H_{13}NO_2$. Phenacetin is neutral and does not dissolve in either acid or base. When warmed with aqueous NaOH, phenacetin yields an amine, $C_8H_{11}NO$, whose ^1H NMR spectrum is shown. When heated with HI, the amine is cleaved to an aminophenol, C_6H_7NO. What is the structure of phenacetin, and what are the structures of the amine and the aminophenol?



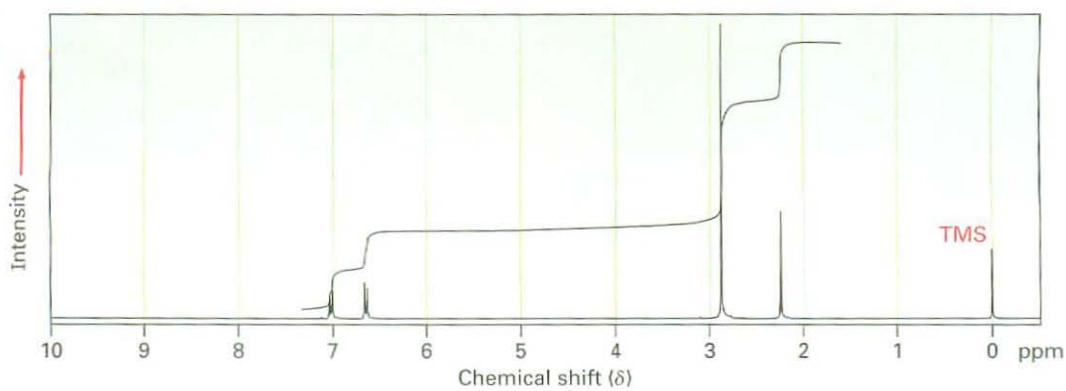
24.73 Propose structures for amines with the following ^{1}H NMR spectra:
(a) C_3H_9NO



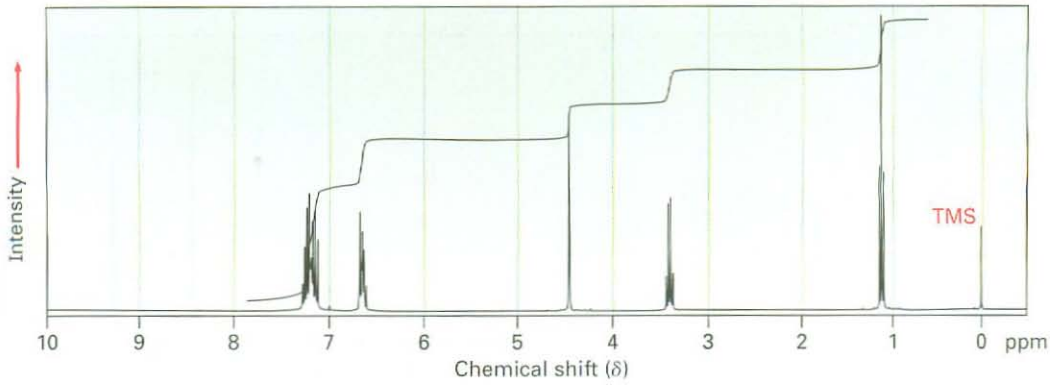
(b) $C_4H_{11}NO_2$



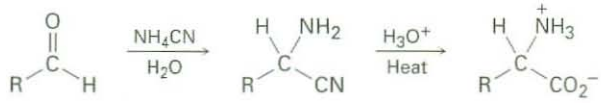
24.74 Propose structures for compounds that show the following ^{1}H NMR spectra.
(a) $C_9H_{13}N$



(b) $C_{15}H_{17}N$

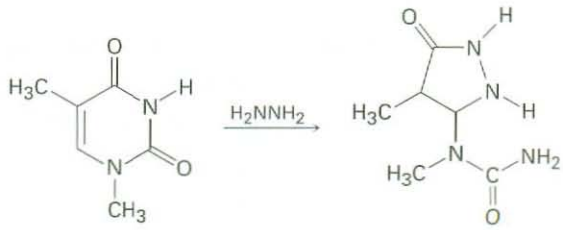


24.75 α-Amino acids can be prepared by the *Strecker synthesis*, a two-step process in which an aldehyde is treated with ammonium cyanide followed by hydrolysis of the amino nitrile intermediate with aqueous acid. Propose a mechanism for the reaction.



An α-amino acid

24.76 One of the reactions used in determining the sequence of nucleotides in a strand of DNA is reaction with hydrazine. Propose a mechanism for the following reaction, which occurs by an initial conjugate addition followed by internal amide formation.



■ Assignable in OWL