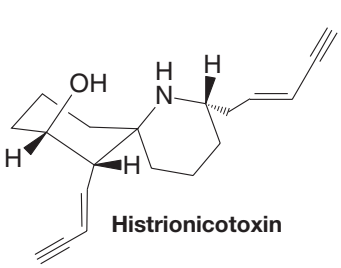
CHAPTER

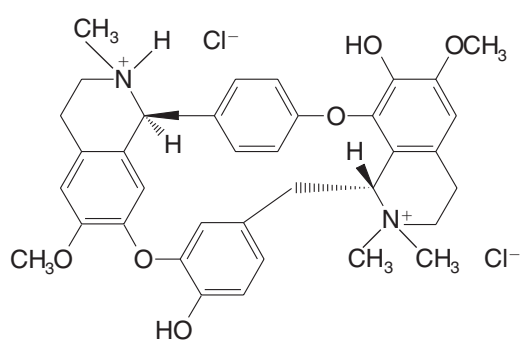
# 20

# Amines

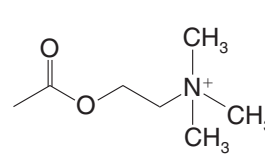
Amine-containing compounds have an incredible range of biochemical properties. Some, like acetylcholine, act as neurotransmitters, control muscle function, enhance sensory perceptions, and sustain attention span. Others, however, can play far more sinister roles. Colombian poison dart frogs, for example, are tiny and beautiful, but they are also deadly. They produce a compound known as histrionicotoxin, an amine that causes paralysis and eventually death through suffocation. The respiratory muscles cease to function because acetylcholine cannot act, preventing it from initiating the electrical signaling that makes the muscles of our lungs function. Similarly, Amazon tribes have long used a mixture of compounds




**Histrionicotoxin**




***d*-Tubocurarine chloride**




**Acetylcholine**

from a woody vine called curare for hunting game and for self-protection; this material includes another paralytic neurotoxin called *d*-tubocurarine, which also blocks acetylcholine function. As we shall see, these examples represent just the tip of the iceberg for what amines do.

**IN THIS CHAPTER, WE WILL CONSIDER:**

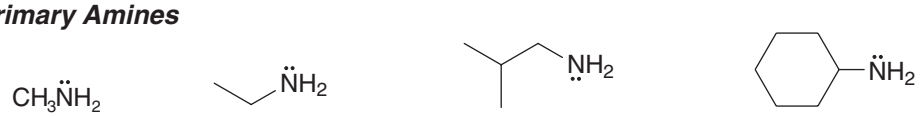
- the properties, structure, and nomenclature of amines
- the ability of amines to act as bases, salts, and resolving agents
- the synthesis and reactivity of amines

**[ WHY DO THESE TOPICS MATTER? ]** At the end of this chapter we will show you how amine-containing compounds led not only to the genesis of a revolutionary idea for how small molecules can treat disease, but also to the identification of the world's first therapies for pneumonia and gastrointestinal infections.

## 20.1 NOMENCLATURE

In common nomenclature most primary amines are named as *alkylamines*. In systematic nomenclature (blue names in parentheses below) they are named by adding the suffix *-amine* to the name of the chain or ring system to which the $NH_2$ group is attached with replacement of the final *-e*. Amines are classified as being **primary** (**1°**), **secondary** (**2°**), or **tertiary** (**3°**) on the basis of the number of organic groups attached to the nitrogen (Section 2.8).

### *Primary Amines*



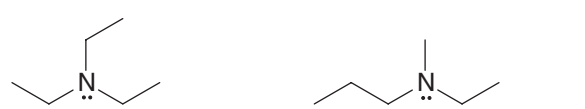
**Methylamine** (methanamine) | **Ethylamine** (ethanamine) | **Isobutylamine** (2-methyl-1-propanamine) | **Cyclohexylamine** (cyclohexanamine)

Most **secondary** and **tertiary amines** are named in the same general way. In common nomenclature we either designate the organic groups individually if they are different or use the prefixes di- or tri- if they are the same. In systematic nomenclature we use the locant *N* to designate substituents attached to a nitrogen atom.

### *Secondary Amines*

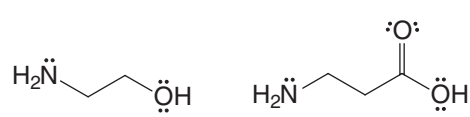
**Ethylmethylamine** (*N*-methylethanamine) | **Diethylamine** (*N*-ethylethanamine)

### *Tertiary Amines*



**Triethylamine** (*N*,*N*-diethylethanamine) | **Ethylmethylpropylamine** (*N*-ethyl-*N*-methyl-1-propanamine)

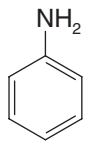
In the IUPAC system, the substituent —$NH_2$ is called the *amino* group. We often use this system for naming amines containing an OH group or a $CO_2H$ group:



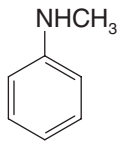
**2-Aminoethanol** | **3-Aminopropanoic acid**

## 20.1A Arylamines

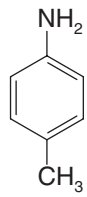
Some common **arylamines** have the following names:



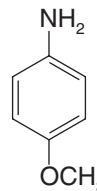
**Aniline**
(benzenamine)



***N*-Methylaniline**
(*N*-methyl-benzenamine)



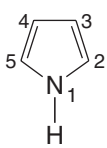
***p*-Toluidine**
(4-methyl-benzenamine)



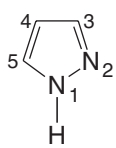
***p*-Anisidine**
(4-methoxy-benzenamine)

## 20.1B Heterocyclic Amines

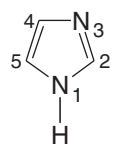
The important **heterocyclic amines** all have common names. In systematic replacement nomenclature the prefixes *aza-*, *diaza-*, and *triaza-* are used to indicate that nitrogen atoms have replaced carbon atoms in the corresponding hydrocarbon. A nitrogen atom in the ring (or the highest atomic weight heteroatom, as in the case of thiazole) is designated position 1 and numbering proceeds to give the lowest overall set of locants to the heteroatoms:



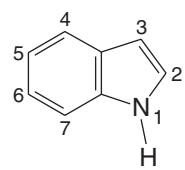
**Pyrrole**
(1-azacyclopenta-2,4-diene)



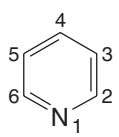
**Pyrazole**
(1,2-diazacyclopenta-2,4-diene)



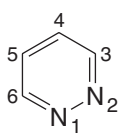
**Imidazole**
(1,3-diazacyclopenta-2,4-diene)



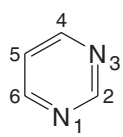
**Indole**
(1-azaindene)



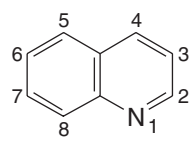
**Pyridine**
(azabenzene)



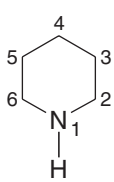
**Pyridazine**
(1,2-diazabenzene)



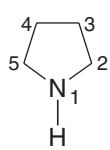
**Pyrimidine**
(1,3-diazabenzene)



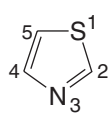
**Quinoline**
(1-azanaphthalene)



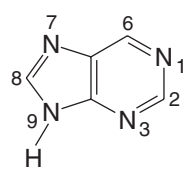
**Piperidine**
(azacyclohexane)



**Pyrrolidine**
(azacyclopentane)



**Thiazole**
(1-thia-3-azacyclopenta-2,4-diene)



**Purine**

# 20.2 PHYSICAL PROPERTIES AND STRUCTURE OF AMINES

## 20.2A Physical Properties

Amines are moderately polar substances; they have boiling points that are higher than those of alkanes but generally lower than those of alcohols of comparable molecular weight. Molecules of primary and secondary amines can form strong hydrogen bonds

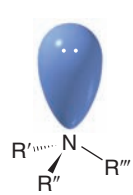
to each other and to water. Molecules of tertiary amines cannot form hydrogen bonds to each other, but they can form hydrogen bonds to molecules of water or other hydroxylic solvents. As a result, tertiary amines generally boil at lower temperatures than primary and secondary amines of comparable molecular weight, but all low-molecular-weight amines are very water soluble. Table 20.1 lists the physical properties of some common amines.

**TABLE 20.1 PHYSICAL PROPERTIES OF AMINES**

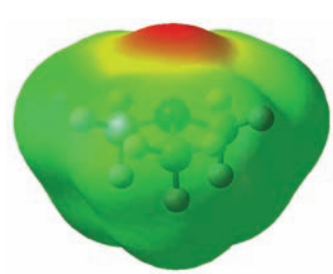
| Name | Structure | mp (°C) | bp (°C) | Water Solubility (25 °C) (g 100 mL$^{-1}$) | p$K_a$ (aminium ion) |
|---|---|---|---|---|---|
| **Primary Amines** | | | | | |
| Methylamine | $CH_3NH_2$ | −94 | −6 | Very soluble | 10.64 |
| Ethylamine | $CH_3CH_2NH_2$ | −81 | 17 | Very soluble | 10.75 |
| Isopropylamine | $(CH_3)_2CHNH_2$ | −101 | 33 | Very soluble | 10.73 |
| Cyclohexylamine | Cyclo-$C_6H_{11}NH_2$ | −18 | 134 | Slightly soluble | 10.64 |
| Benzylamine | $C_6H_5CH_2NH_2$ | 10 | 185 | Slightly soluble | 9.30 |
| Aniline | $C_6H_5NH_2$ | −6 | 184 | 3.7 | 4.58 |
| 4-Methylaniline | 4-$CH_3C_6H_4NH_2$ | 44 | 200 | Slightly soluble | 5.08 |
| 4-Nitroaniline | 4-$NO_2C_6H_4NH_2$ | 148 | 332 | Insoluble | 1.00 |
| **Secondary Amines** | | | | | |
| Dimethylamine | $(CH_3)_2NH$ | −92 | 7 | Very soluble | 10.72 |
| Diethylamine | $(CH_3CH_2)_2NH$ | −48 | 56 | Very soluble | 10.98 |
| Diphenylamine | $(C_6H_5)_2NH$ | 53 | 302 | Insoluble | 0.80 |
| **Tertiary Amines** | | | | | |
| Trimethylamine | $(CH_3)_3N$ | −117 | 3 | Very soluble | 9.70 |
| Triethylamine | $(CH_3CH_2)_3N$ | −115 | 90 | 14 | 10.76 |
| *N*,*N*-Dimethylaniline | $C_6H_5N(CH_3)_2$ | 3 | 194 | Slightly soluble | 5.06 |

## 20.2B Structure of Amines

The nitrogen atom of most amines is like that of ammonia; it is approximately $sp^3$ hybridized. The three alkyl groups (or hydrogen atoms) occupy corners of a tetrahedron; the $sp^3$ orbital containing the unshared electron pair is directed toward the other corner. We describe the shape of the amine by the location of the atoms as being **trigonal pyramidal** (Section 1.16B). However, if we were to consider the unshared electron pair as being a group we would describe the geometry of the amine as being tetrahedral. The electrostatic potential map for the van der Waals surface of trimethylamine indicates localization of negative charge where the nonbonding electrons are found on the nitrogen:



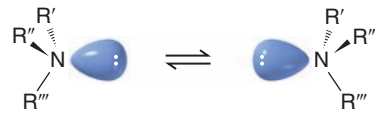

**Structure of an amine.**



**A calculated structure for trimethylamine. The electrostatic potential map shows charge associated with the nitrogen unshared electron pair.**

The bond angles are what one would expect of a tetrahedral structure; they are very close to 109.5°. The bond angles for trimethylamine, for example, are 108°.

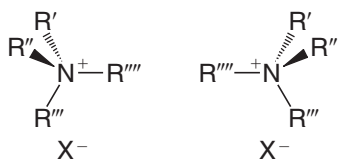
If the alkyl groups of a tertiary amine are all different, the amine will be chiral. There will be two enantiomeric forms of the tertiary amine, and, theoretically, we ought to be able to resolve (separate) these enantiomers. In practice, however, resolution is usually impossible because the enantiomers interconvert rapidly:



**Interconversion of amine enantiomers**

This interconversion occurs through what is called a **pyramidal** or **nitrogen inversion**. The barrier to the interconversion is about 25 kJ $mol^{-1}$ for most simple amines, low enough to occur readily at room temperature. In the transition state for the inversion, the nitrogen atom becomes $sp^2$ hybridized with the unshared electron pair occupying a $p$ orbital.

Ammonium salts cannot undergo nitrogen inversion because they do not have an unshared pair. Therefore, those **quaternary ammonium salts** with four different groups are chiral and can be resolved into separate (relatively stable) enantiomers:



**Quaternary ammonium salts such as these can be resolved.**

## 20.3 BASICITY OF AMINES: AMINE SALTS

- Amines are relatively weak bases. Most are stronger bases than water but are far weaker bases than hydroxide ions, alkoxide ions, and alkanide anions.

A convenient way to compare the **base strengths** of amines is to compare the p$K_a$ values of their conjugate acids, the corresponding alkylaminium ions (Sections 3.6C and 20.3D).

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

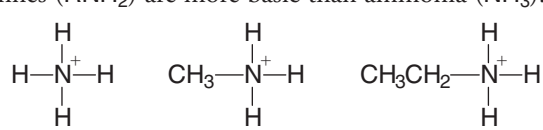
$$K_a = \frac{[RNH_2][H_3O^+]}{[RNH_3^+]}$$

$$pK_a = -\log K_a$$

The equilibrium for an amine that is relatively more basic will lie more toward the left in the above chemical equation than for an amine that is less basic.

- The aminium ion of a more basic amine will have a larger p$K_a$ than the aminium ion of a less basic amine.

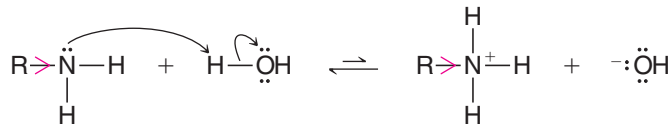
When we compare aminium ion acidities in terms of this equilibrium, we see that most primary alkylaminium ions ($RNH_3^+$) are less acidic than ammonium ion ($NH_4^+$). In other words, primary alkylamines ($RNH_2$) are more basic than ammonia ($NH_3$):



| Aminium ion p$K_a$ | 9.26 | 10.64 | 10.75 |
|---|---|---|---|

We can account for this on the basis of the electron-releasing ability of an alkyl group. An alkyl group releases electrons, and it *stabilizes* the alkylaminium ion that results from the

acid–base reaction *by dispersing its positive charge*. It stabilizes the alkylaminium ion to a greater extent than it stabilizes the amine:

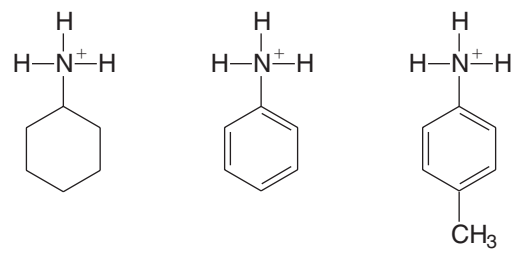


**By releasing electrons, R → stabilizes the alkylaminium ion through dispersal of charge.**

## 20.3A Basicity of Arylamines

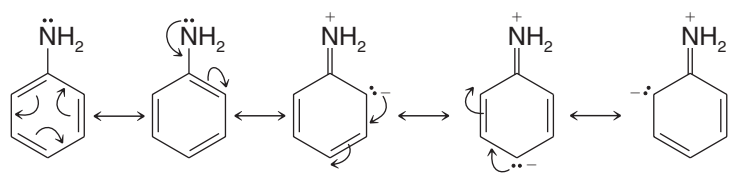
- Aromatic amines are much weaker bases than alkylamines.

Considering amine basicity from the perspective of aminium ion acidity, when we examine the p$K_a$ values of the conjugate acids of aromatic amines (e.g., aniline and 4-methylaniline) in Table 20.1, we see that they are much weaker bases than the nonaromatic amine, cyclohexylamine:



| | | | |
|---|---|---|---|
| **Aminium ion p$K_a$** | **10.64** | **4.58** | **5.08** |

We can account for this effect, in part, on the basis of resonance contributions to the overall hybrid of an arylamine. For aniline, the following contributors are important:



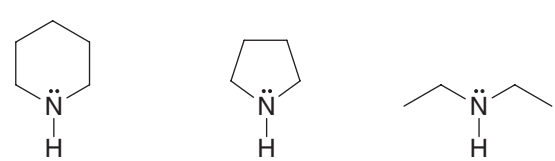
**1** **2** **3** **4** **5**

Structures **1** and **2** are the Kekulé structures that contribute to any benzene derivative. Structures **3–5**, however, *delocalize* the unshared electron pair of the nitrogen over the ortho and para positions of the ring. This delocalization of the electron pair makes it less available to a proton, and *delocalization of the electron pair stabilizes aniline*.

Another important effect in explaining the lower basicity of aromatic amines is the **electron-withdrawing effect of a phenyl group**. Because the carbon atoms of a phenyl group are $sp^2$ hybridized, they are more electronegative (and therefore more electron withdrawing) than the $sp^3$-hybridized carbon atoms of alkyl groups. We shall discuss this effect further in Section 21.5A.

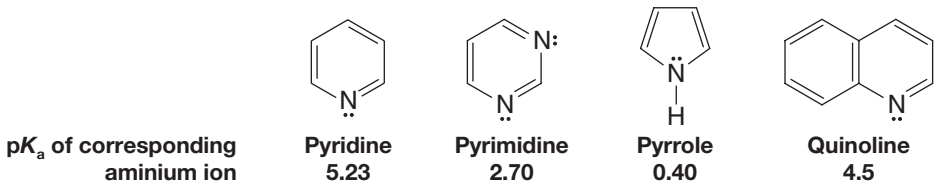
## 20.3B Basicity of Heterocyclic Amines

Nonaromatic heterocyclic amines have basicities that are approximately the same as those of acyclic amines:



| | | | |
|---|---|---|---|
| **p$K_a$ of corresponding aminium ion** | **Piperidine** **11.20** | **Pyrrolidine** **11.11** | **Diethylamine** **10.98** |

In aqueous solution, aromatic heterocyclic amines such as pyridine, pyrimidine, and pyrrole are much weaker bases than nonaromatic amines or ammonia.

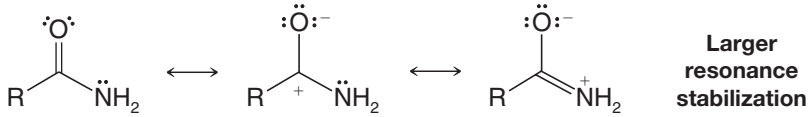



## 20.3C Amines versus Amides

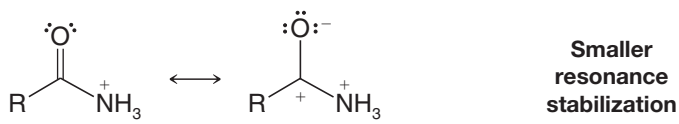
- Amides are far less basic than amines (even less basic than arylamines). The p$K_a$ of the conjugate acid of a typical amide is about zero.

The lower basicity of amides when compared to amines can be understood in terms of resonance and inductive effects. An amide is stabilized by resonance involving the nonbonding pair of electrons on the nitrogen atom. However, an amide protonated on its nitrogen atom lacks this type of resonance stabilization. This is shown in the following resonance structures:

***Amide***

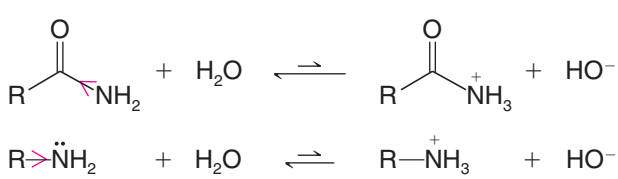



***N-Protonated Amide***

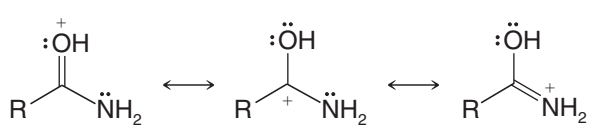


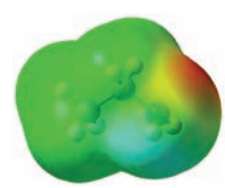

However, a more important factor accounting for amides being weaker bases than amines is the powerful electron-withdrawing effect of the carbonyl group of the amide. This effect is illustrated by the electrostatic potential maps for ethylamine and acetamide shown in Fig. 20.1. Significant negative charge is localized at the position of the nonbonding electron pair in ethylamine (as indicated by the red color). In acetamide, however, less negative charge resides near the nitrogen than in ethylamine.

Comparing the following equilibria, the reaction with the amide lies more to the left than the corresponding reaction with an amine. This is consistent with the amine being a stronger base than an amide.

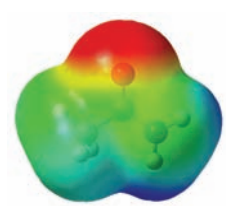


The nitrogen atoms of amides are so weakly basic that when an amide accepts a proton, it does so on its oxygen atom instead (see the mechanism for hydrolysis of an amide, Section 17.8F). Protonation on the oxygen atom occurs even though oxygen atoms (because of their greater electronegativity) are typically less basic than nitrogen atoms. Notice, however, that if an amide accepts a proton on its oxygen atom, resonance stabilization involving the nonbonding electron pair of the nitrogen atom is possible:





Ethylamine

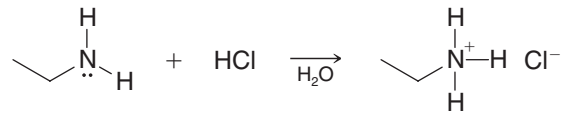


Acetamide

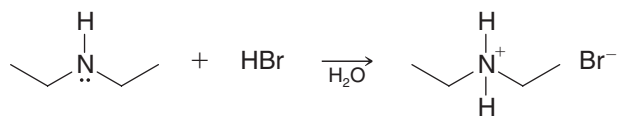
**FIGURE 20.1** Calculated electrostatic potential maps (calibrated to the same charge scale) for ethylamine and acetamide. The map for ethylamine shows localization of negative charge at the unshared electron pair of nitrogen. The map for acetamide shows most of the negative charge at its oxygen atom instead of at nitrogen, due to the electron-withdrawing effect of the carbonyl group.

## 20.3D Aminium Salts and Quaternary Ammonium Salts

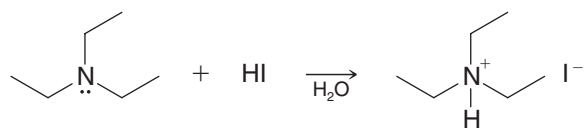
When primary, secondary, and tertiary amines act as bases and react with acids, they form compounds called **aminium salts**. In an aminium salt the positively charged nitrogen atom is attached to at least one hydrogen atom:




**Ethylaminium chloride (an aminium salt)**

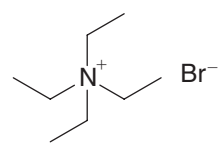



**Diethylaminium bromide**




**Triethylaminium iodide**

When the central nitrogen atom of a compound is positively charged *but is not attached to a hydrogen atom*, the compound is called a **quaternary ammonium salt**. For example,




**Tetraethylammonium bromide (a quaternary ammonium salt)**

Quaternary ammonium halides—because they do not have an unshared electron pair on the nitrogen atom—cannot act as bases. Quaternary ammonium *hydroxides*, however, are strong bases. As solids, or in solution, they consist *entirely* of quaternary ammonium cations ($R_4N^+$) and hydroxide ions ($HO^-$); they are, therefore, strong bases—as strong as sodium or potassium hydroxide. Quaternary ammonium hydroxides react with acids to form quaternary ammonium salts:

$$(CH_3)_4\overset{+}{N}OH^- + HCl \longrightarrow (CH_3)_4\overset{+}{N}Cl^- + H_2O$$

In Section 20.12A we shall see how quaternary ammonium salts can be used to form alkenes by a reaction called the *Hofmann elimination*.

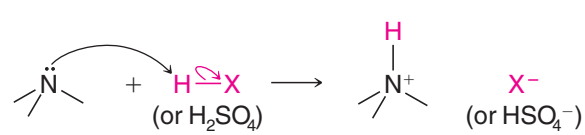
## 20.3E Solubility of Amines in Aqueous Acids

- Almost all alkylaminium chloride, bromide, iodide, and sulfate salts are soluble in water. Thus, primary, secondary, or tertiary amines that are not soluble in water will dissolve in dilute aqueous HCl, HBr, HI, and $H_2SO_4$.

**Helpful Hint**

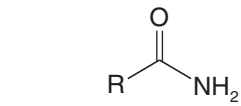
You may make use of the basicity of amines in your organic chemistry laboratory work for the separation of compounds or for the characterization of unknowns.

Solubility in dilute acid provides a convenient chemical method for distinguishing amines from nonbasic compounds that are insoluble in water. Solubility in dilute acid also gives us a useful method for separating amines from nonbasic compounds that are insoluble in water. The amine can be extracted into aqueous acid (dilute HCl) and then recovered by making the aqueous solution basic and extracting the amine into ether or $CH_2Cl_2$.




**Water-insoluble amine** **Water-soluble aminium salt**

*Because amides are far less basic than amines*, water-insoluble amides *do not dissolve* in dilute aqueous HCl, HBr, HI, or $H_2SO_4$:




**Water-insoluble amide**
**(not soluble in aqueous acids)**

**PRACTICE PROBLEM 20.1**

Outline a procedure for separating hexylamine from cyclohexane using dilute HCl, aqueous NaOH, and diethyl ether.

**PRACTICE PROBLEM 20.2**

Outline a procedure for separating a mixture of benzoic acid, 4-methylphenol, aniline, and benzene using acids, bases, and organic solvents.

## 20.3F Amines as Resolving Agents

- Enantiomerically pure amines are often used to resolve racemic forms of acidic compounds by the formation of diastereomeric salts.

We can illustrate the principles involved in **resolution** by showing how a racemic form of an organic acid might be resolved (separated) into its enantiomers with the single enantiomer of an **amine as a resolving agent** (Fig. 20.2).

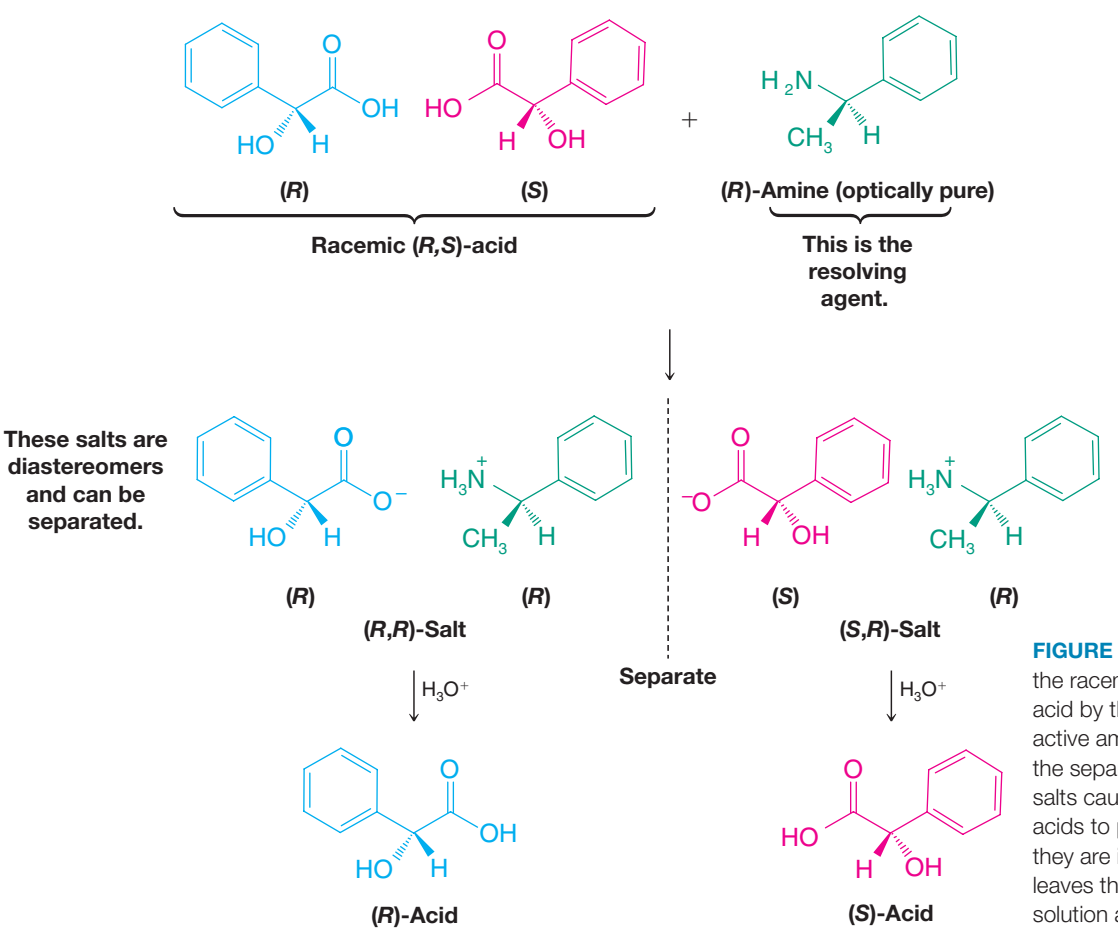


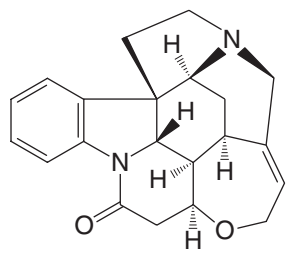

**FIGURE 20.2** Resolution of the racemic form of an organic acid by the use of an optically active amine. Acidification of the separated diastereomeric salts causes the enantiomeric acids to precipitate (assuming they are insoluble in water) and leaves the resolving agent in solution as its conjugate acid.

**Helpful Hint**

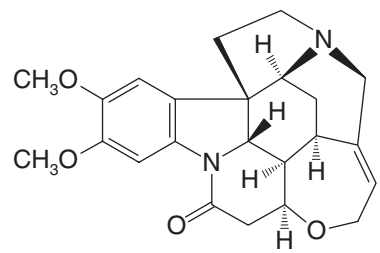
See "The Chemistry of…HPLC Resolution of Enantiomers" in *WileyPLUS* for information about another technique for resolving enantiomers.

In this procedure the single enantiomer of an amine, (*R*)-1-phenylethylamine, is added to a solution of the racemic form of an acid. The salts that form are *diastereomers*. The chirality centers of the acid portion of the salts are enantiomerically related to each other, but the chirality centers of the amine portion are not. The diastereomers have different solubilities and can be separated by careful crystallization. The separated salts are then acidified with hydrochloric acid and the enantiomeric acids are obtained from the separate solutions. The amine remains in solution as its hydrochloride salt.

Single enantiomers that are employed as resolving agents are often readily available from natural sources. Because most of the chiral organic molecules that occur in living organisms are synthesized by enzymatically catalyzed reactions, most of them occur as single enantiomers. Naturally occurring optically active amines such as (−)-quinine (see "The Chemistry of…Biologically Important Amines" in this section), (−)-strychnine, and (−)-brucine are often employed as resolving agents for racemic acids. Acids such as (+)- or (−)-tartaric acid (Section 5.15A) are often used for resolving racemic bases.



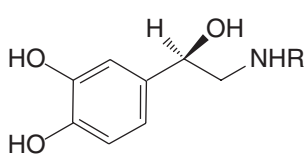
**(−)-Strychnine**



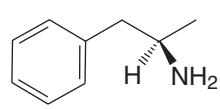
**(−)-Brucine**

## THE CHEMISTRY OF... Biologically Important Amines

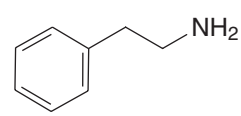
A large number of medically and biologically important compounds are amines. Listed here are some important examples:



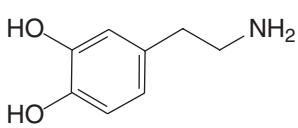
**R = $CH_3$, Adrenaline (epinephrine)**
**R = H, Noradrenaline (norepinephrine)**



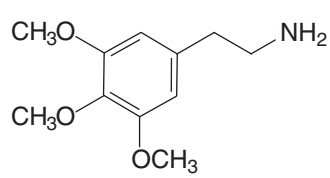
**Amphetamine (benzedrine)**



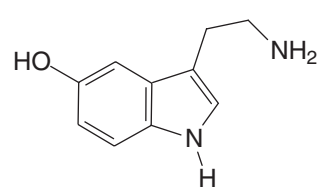
**2-Phenylethylamine**



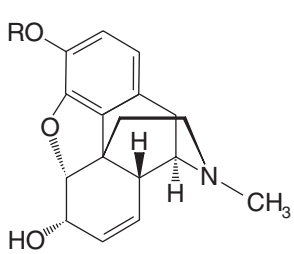
**Dopamine**



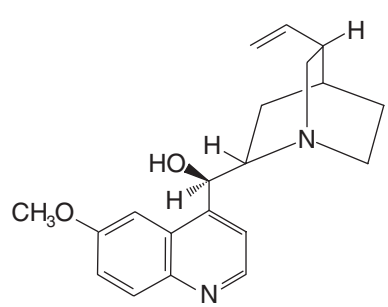
**Mescaline**



**Serotonin**



**Morphine (R = H)**
**Codeine (R = $CH_3$)**



**(−)-Quinine**

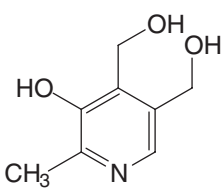
## 2-Phenylethylamines

Many phenylethylamine compounds have powerful physiological and psychological effects. Adrenaline and noradrenaline are two hormones secreted in the medulla of the adrenal gland. Released into the bloodstream when an animal senses danger, adrenaline causes an increase in blood pressure, a strengthening of the heart rate, and a widening of the passages of the lungs. All of these effects prepare the animal to fight or to flee. Noradrenaline also causes an increase in blood pressure, and it is involved in the transmission of impulses from the end of one nerve fiber to the next. Dopamine and serotonin are important neurotransmitters in the brain. Abnormalities in the level of dopamine in the brain are associated with many psychiatric disorders, including Parkinson's disease. Dopamine plays a pivotal role in the regulation and control of movement, motivation, and cognition. Serotonin is a compound of particular interest because it appears to be important in maintaining stable mental processes. It has been suggested that the mental disorder schizophrenia may be connected with abnormalities in the metabolism of serotonin.

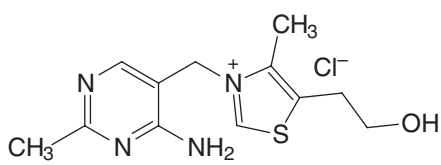
Amphetamine (a powerful stimulant) and mescaline (a hallucinogen) have structures similar to those of serotonin, adrenaline, and noradrenaline. They are all derivatives of 2-phenylethylamine. (In serotonin the nitrogen is connected to the benzene ring to create a five-membered ring.) The structural similarities of these compounds must be related to their physiological and psychological effects because many other compounds with similar properties are also derivatives of 2-phenylethylamine. Examples (not shown) are *N*-methylamphetamine and LSD (lysergic acid diethylamide). Even morphine and codeine, two powerful analgesics, have a 2-phenylethylamine system as a part of their structures. [Morphine and codeine are examples of compounds called alkaloids (Special Topic F in *WileyPLUS*). Try to locate the 2-phenylethylamine system in their structures.]

## Vitamins and Antihistamines

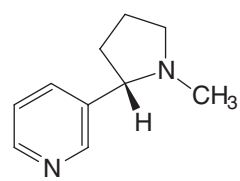
A number of amines are vitamins. These include nicotinic acid and nicotinamide, pyridoxine (vitamin $B_6$, see "The Chemistry of…Pyridoxal Phosphate" in *WileyPLUS* for Chapter 16), and thiamine chloride (vitamin $B_1$, see "The Chemistry of…Thiamine," in *WileyPLUS* for Chapter 17). Nicotine is a toxic alkaloid found in tobacco that makes smoking habit forming. Histamine, another toxic amine, is found bound to proteins in nearly all tissues of the body. Release of free histamine causes the symptoms associated with allergic reactions and the common cold. Chlorpheniramine, an "antihistamine," is an ingredient of many over-the-counter cold remedies.



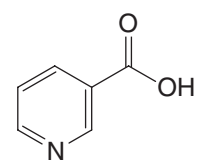
**Pyridoxine (vitamin $B_6$)**



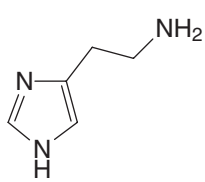
**Thiamine chloride (vitamin $B_1$)**



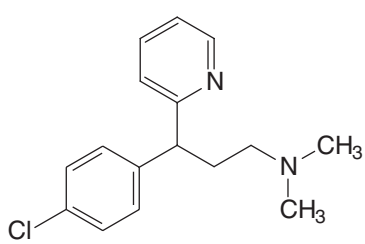
**Nicotine**



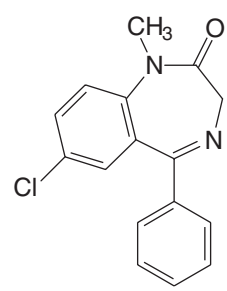
**Nicotinic acid (niacin)**



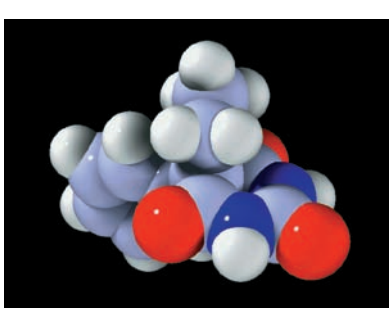
**Histamine**



**Chlorpheniramine**



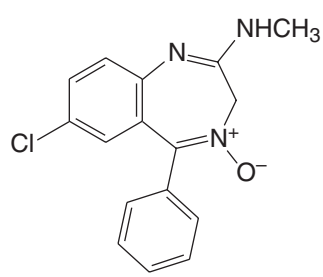
**Valium (diazepam)**



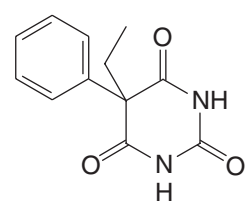
Phenobarbital.

## Tranquilizers

Valium (diazepam) is a widely prescribed tranquilizer. Chlordiazepoxide is a closely related compound. Phenobarbital (also see the model) is used to control epileptic seizures and as a sedative for insomnia and relief of anxiety.



**Chlordiazepoxide**

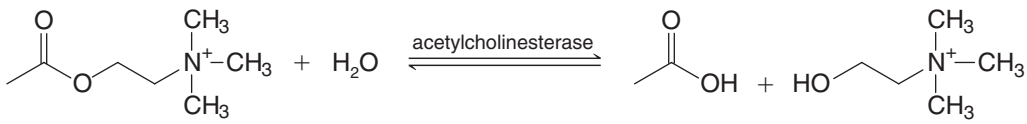


**Phenobarbital**

*(continued on next page)*

### Neurotransmitters

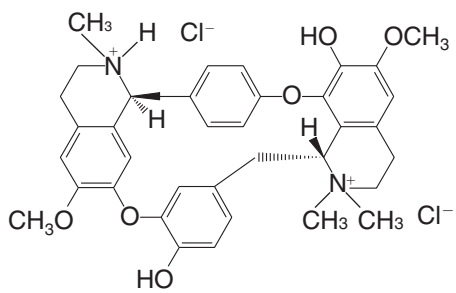
Nerve cells interact with other nerve cells or with muscles at junctions, or gaps, called synapses. Nerve impulses are carried across the synaptic gap by chemical compounds called *neurotransmitters*. Acetylcholine (see the following reaction) is an important neurotransmitter at neuromuscular synapses called *cholinergic synapses*. Acetylcholine contains a quaternary ammonium group. Being small and ionic, acetylcholine is highly soluble in water and highly diffusible, qualities that suit its role as a neurotransmitter. Acetylcholine molecules are released by the presynaptic membrane in the neuron in packets of about $10^4$ molecules. The packet of molecules then diffuses across the synaptic gap.



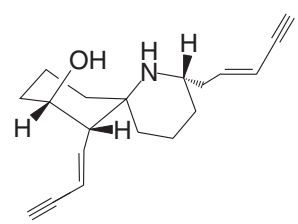

**Acetylcholine** **Choline**

Having carried a nerve impulse across the synapse to the muscle where it triggers an electrical response, the acetylcholine molecules must be hydrolyzed (to choline) within a few milliseconds to allow the arrival of the next impulse. This hydrolysis is catalyzed by an enzyme of almost perfect efficiency called *acetylcholinesterase*.

The acetylcholine receptor on the postsynaptic membrane of muscle is the target for some of the most deadly neurotoxins, including *d*-tubocurarine and histrionicotoxin, shown here.



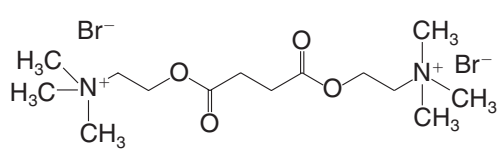
***d*-Tubocurarine chloride**



**Histrionicotoxin**

When *d*-tubocurarine binds at the acetylcholine receptor site, it prevents opening of the ion channels that depolarize the membrane. This prevents a nerve impulse, and results in paralysis.

Even though *d*-tubocurarine and histrionicotoxin are deadly poisons, both have been useful in research. For example, experiments in respiratory physiology that require absence of normal breathing patterns have involved curare-induced temporary (and voluntary!) respiratory paralysis of a researcher. While the experiment is underway and until the effects of the curare are reversed, the researcher is kept alive by a hospital respirator. In similar fashion, *d*-tubocurarine, as well as succinylcholine bromide, is used as a muscle relaxant during some surgeries.



**Succinylcholine bromide**

## 20.4 PREPARATION OF AMINES

In this section we discuss a variety of ways to synthesize amines. Some of these methods will be new to you, while others are methods you have studied earlier in the context of related functional groups and reactions. Later, in Chapter 24, you will see how some of the methods presented here, as well as some others for asymmetric synthesis, can be used to synthesize $\alpha$-amino acids, the building blocks of peptides and proteins.

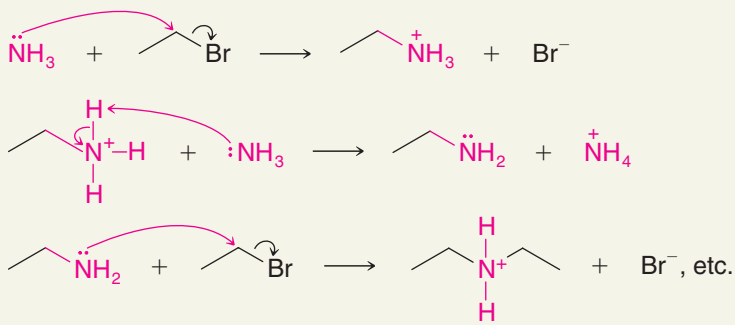
### 20.4A Through Nucleophilic Substitution Reactions

**Alkylation of Ammonia** Salts of primary amines can be prepared from ammonia and alkyl halides by nucleophilic substitution reactions. Subsequent treatment of the resulting aminium salts with a base gives primary amines:

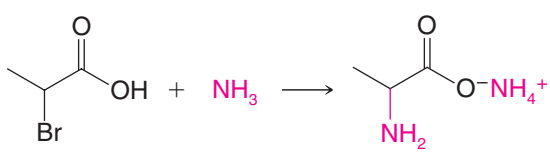
- This method is of very limited synthetic application because multiple alkylations occur.

When ethyl bromide reacts with ammonia, for example, the ethylaminium bromide that is produced initially can react with ammonia to liberate ethylamine. Ethylamine can then compete with ammonia and react with ethyl bromide to give diethylaminium bromide. Repetitions of alkylation and proton transfer reactions ultimately produce some tertiary amines and even some quaternary ammonium salts if the alkyl halide is present in excess.

## A MECHANISM FOR THE REACTION — Alkylation of $NH_3$

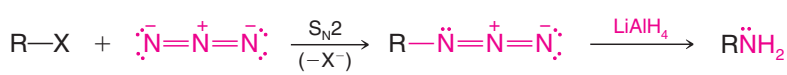


Multiple alkylations can be minimized by using a large excess of ammonia. (Why?) An example of this technique can be seen in the synthesis of alanine from 2-bromopropanoic acid:



**(1 mol)** **(70 mol)** **Alanine (65–70%)**

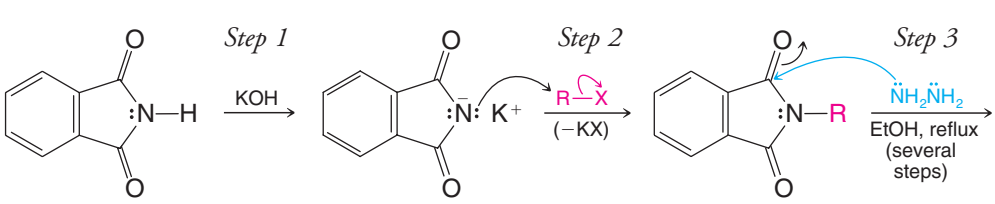
**Alkylation of Azide Ion and Reduction** A much better method for preparing a primary amine from an alkyl halide is first to convert the alkyl halide to an alkyl azide ($R—N_3$) by a nucleophilic substitution reaction, then reduce the azide to a primary amine with lithium aluminum hydride.



**Azide ion (a good nucleophile)** **Alkyl azide**

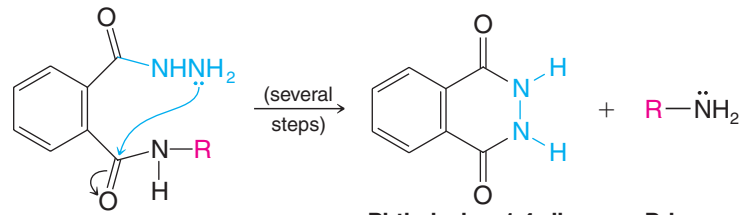
*A word of caution*: Alkyl azides are explosive, and low-molecular-weight alkyl azides should not be isolated but should be kept in solution. Sodium azide is used in automotive airbags.

**The Gabriel Synthesis** Potassium phthalimide (see the following reaction) can also be used to prepare primary amines by a method known as the *Gabriel synthesis*. This synthesis also avoids the complications of multiple alkylations that occur when alkyl halides are treated with ammonia:



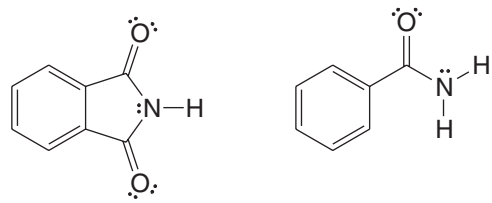
**Phthalimide** ***N*-Alkylphthalimide**

*(continued from previous page)*




Phthalimide is quite acidic ($pK_a = 9$); it can be converted to potassium phthalimide by potassium hydroxide (step 1). The phthalimide anion is a strong nucleophile and (in step 2) it reacts with an alkyl halide by an $S_N2$ mechanism to give an *N*-alkylphthalimide. At this point, the *N*-alkylphthalimide can be hydrolyzed with aqueous acid or base, but the hydrolysis is often difficult. It is often more convenient to treat the *N*-alkylphthalimide with hydrazine ($NH_2NH_2$) in refluxing ethanol (step 3) to give a primary amine and phthalazine-1,4-dione.

**PRACTICE PROBLEM 20.3** **(a)** Write resonance structures for the phthalimide anion that account for the acidity of phthalimide. **(b)** Would you expect phthalimide to be more or less acidic than benzamide? Why? **(c)** In step 3 of our reaction several steps have been omitted. Propose reasonable mechanisms for these steps.

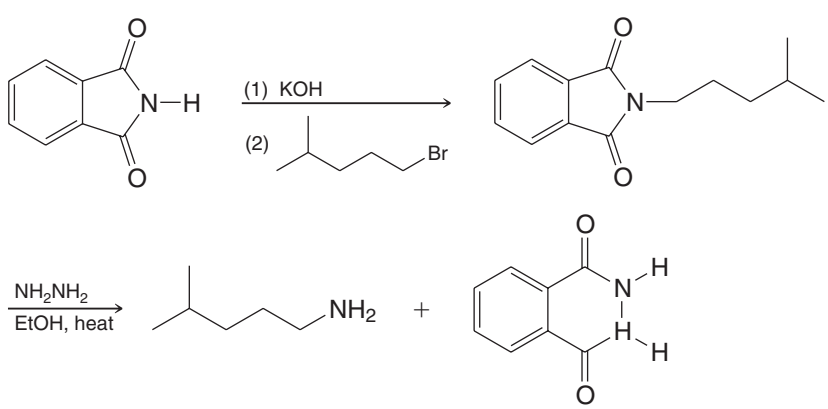



Syntheses of amines using the Gabriel synthesis are, as we might expect, restricted to the use of methyl, primary, and secondary alkyl halides. The use of tertiary halides leads almost exclusively to eliminations.

## SOLVED PROBLEM 20.1

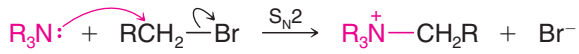
Outline a synthesis of 4-methylpentanamine using the Gabriel synthesis.

**ANSWER:**



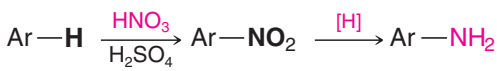

**PRACTICE PROBLEM 20.4** Outline a preparation of benzylamine using the Gabriel synthesis.

**Alkylation of Tertiary Amines** Multiple alkylations are not a problem when tertiary amines are alkylated with methyl or primary halides. Reactions such as the following take place in good yield:



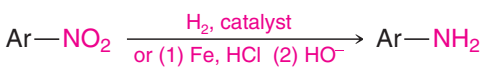

## 20.4B Preparation of Aromatic Amines through Reduction of Nitro Compounds

The most widely used method for preparing aromatic amines involves nitration of the ring and subsequent reduction of the nitro group to an amino group:

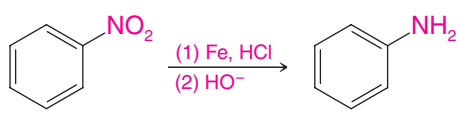



We studied ring nitration in Chapter 15 and saw there that it is applicable to a wide variety of aromatic compounds. Reduction of the nitro group can also be carried out in a number of ways. The most frequently used methods employ catalytic hydrogenation, or treatment of the nitro compound with acid and iron. Zinc, tin, or a metal salt such as $SnCl_2$ can also be used. Overall, this is a $6e^-$ reduction.

### *General Reaction*



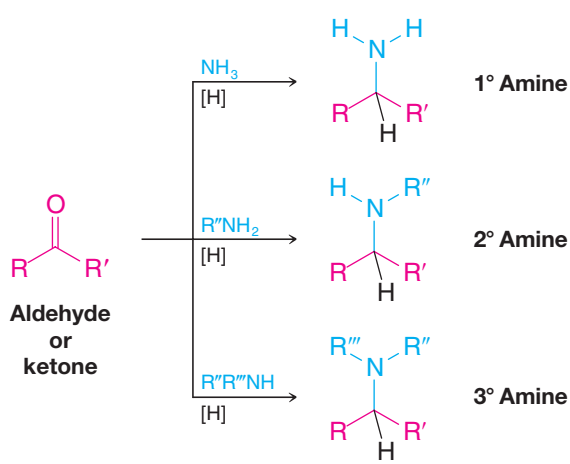

### *Specific Example*




97%

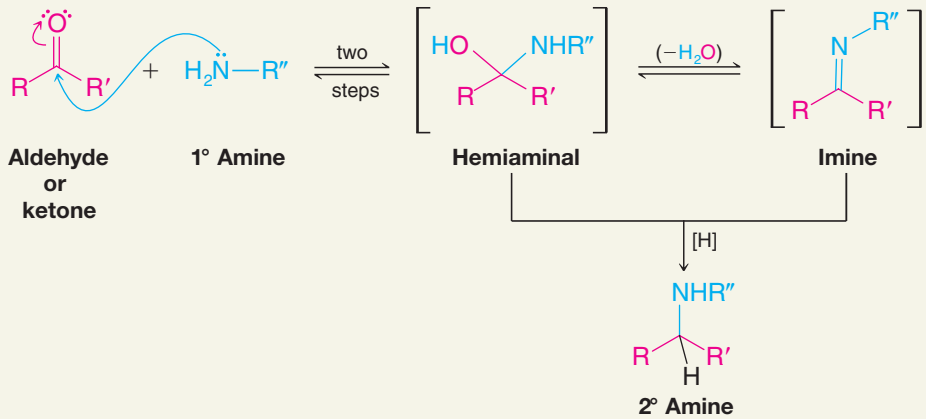
## 20.4C Preparation of Primary, Secondary, and Tertiary Amines through Reductive Amination

Aldehydes and ketones can be converted to amines through catalytic or chemical reduction in the presence of ammonia or an amine. Primary, secondary, and tertiary amines can be prepared this way:




This process, called **reductive amination** of the aldehyde or ketone (or *reductive alkylation* of the amine), appears to proceed through the following general mechanism (illustrated with a 1° amine).

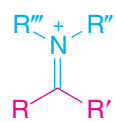
## A MECHANISM FOR THE REACTION — Reductive Amination




### Helpful Hint

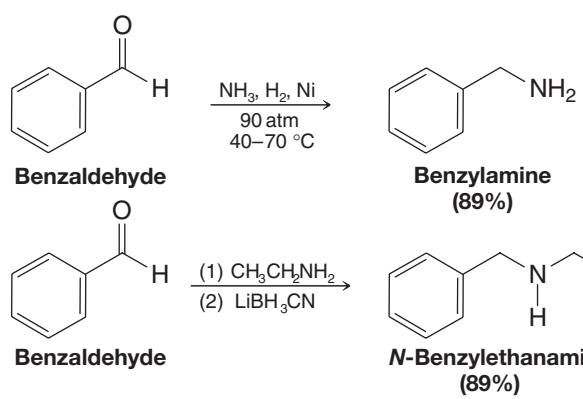
We saw the importance of imines in "The Chemistry of…Pyridoxal Phosphate" (vitamin $B_6$) in *WileyPLUS* for Chapter 16 (Section 16.8).

When ammonia or a primary amine is used, there are two possible pathways to the product: via an amino alcohol that is similar to a hemiacetal and is called a *hemiaminal* or via an imine (Section 16.8A). When secondary amines are used, an imine cannot form, and, therefore, the pathway is through the hemiaminal or through an iminium ion:



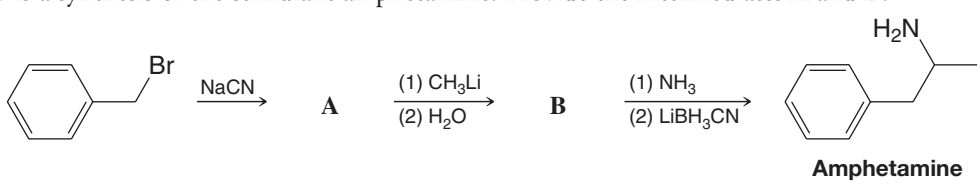
**Iminium ion**

The reducing agents employed include hydrogen and a catalyst (such as nickel) or $NaBH_3CN$ or $LiBH_3CN$ (sodium or lithium cyanoborohydride). The latter two reducing agents are similar to $NaBH_4$ and are especially effective in reductive aminations. Three specific examples of reductive amination follow:

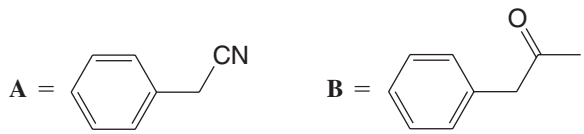



### SOLVED PROBLEM 20.2

Outlined below is a synthesis of the stimulant amphetamine. Provide the intermediates **A** and **B**.

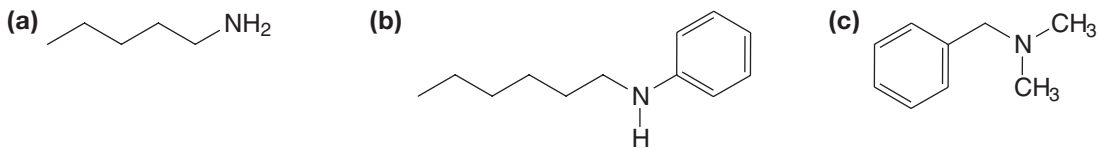


**ANSWER:**

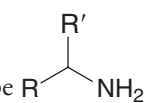



**PRACTICE PROBLEM 20.5**

Show how you might prepare each of the following amines through reductive amination:




**SOLVED PROBLEM 20.3**

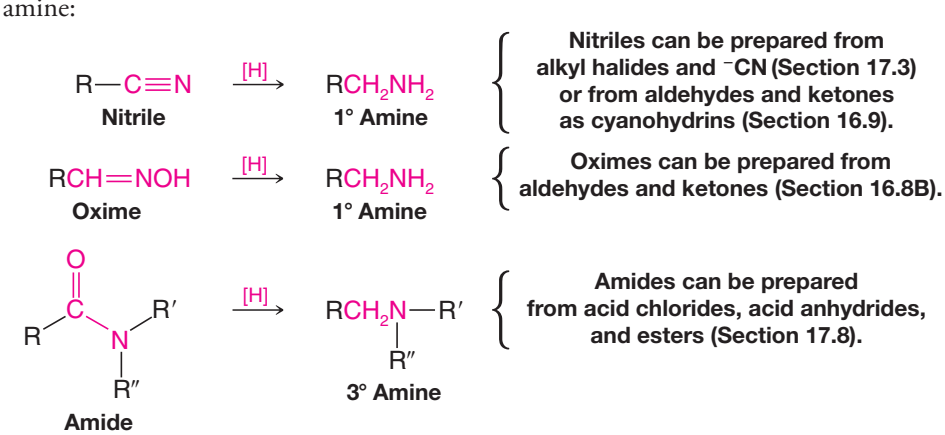
Reductive amination of a ketone is almost always a better method for the synthesis of an amine of the type 

than treatment of an alkyl halide with ammonia. Explain why this is true.

**STRATEGY AND ANSWER:** Consider the structure of the required alkyl halide. Reaction of a secondary halide with ammonia would inevitably be accompanied by considerable elimination, thereby decreasing the yield of the secondary amine. Multiple *N*-alkylations may also occur.

## 20.4D Preparation of Primary, Secondary, or Tertiary Amines through Reduction of Nitriles, Oximes, and Amides

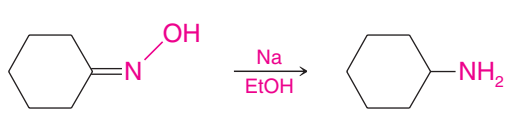
Nitriles, oximes, and amides can be reduced to amines. Reduction of a nitrile or an oxime yields a primary amine; reduction of an amide can yield a primary, secondary, or tertiary amine:

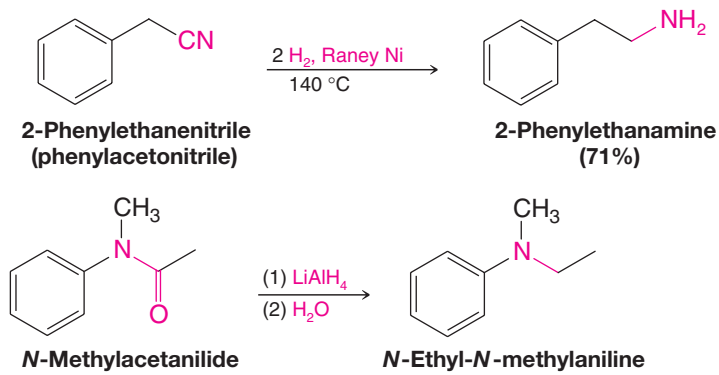



(In the last example, if R′ = H and R″ = H, the product is a 1° amine; if only R′ = H, the product is a 2° amine.)

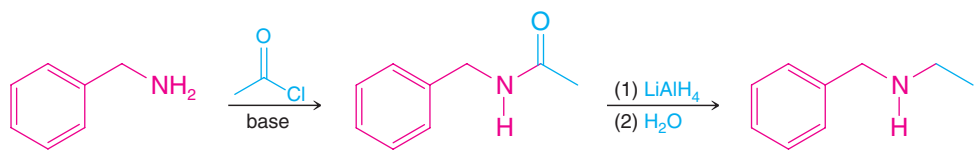
All of these reductions can be carried out with hydrogen and a catalyst or with $LiAlH_4$. Oximes are also conveniently reduced with sodium in ethanol.

Specific examples follow:






Reduction of an amide is the last step in a useful procedure for **monoalkylation of an amine**. The process begins with *acylation* of the amine using an acyl chloride or acid anhydride; then the amide is reduced with lithium aluminum hydride. For example,

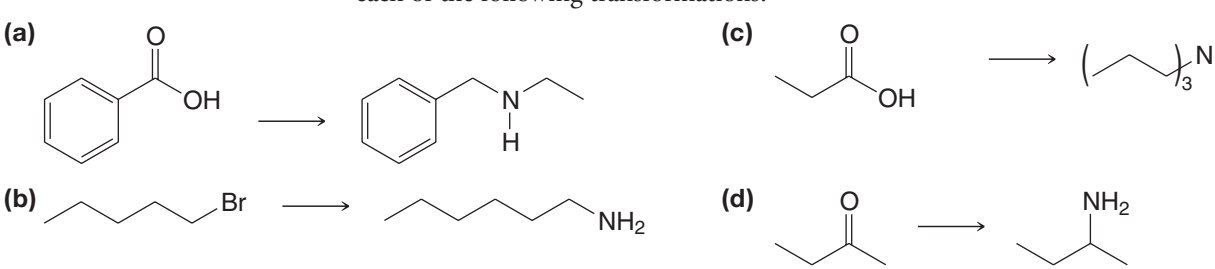



## SOLVED PROBLEM 20.4

Show how you might synthesize 2-propanamine from a three-carbon starting material that is a ketone, aldehyde, nitrile, or amide.

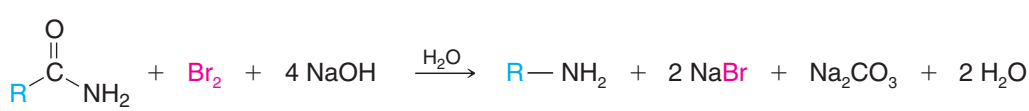
**STRATEGY AND ANSWER:** We begin by recognizing that 2-propanamine has a primary amine group bonded to a secondary carbon. Neither a three-carbon nitrile nor a three-carbon amide can lead to this structural unit from a $C_3$ starting material. An oxime can lead to the proper structure, but we must start with a three-carbon ketone rather than an aldehyde. Therefore, we choose propanone as our starting material, convert it to an oxime, and then reduce the oxime to an amine.

**PRACTICE PROBLEM 20.6** Show how you might utilize the reduction of an amide, oxime, or nitrile to carry out each of the following transformations:




## 20.4E Preparation of Primary Amines through the Hofmann and Curtius Rearrangements

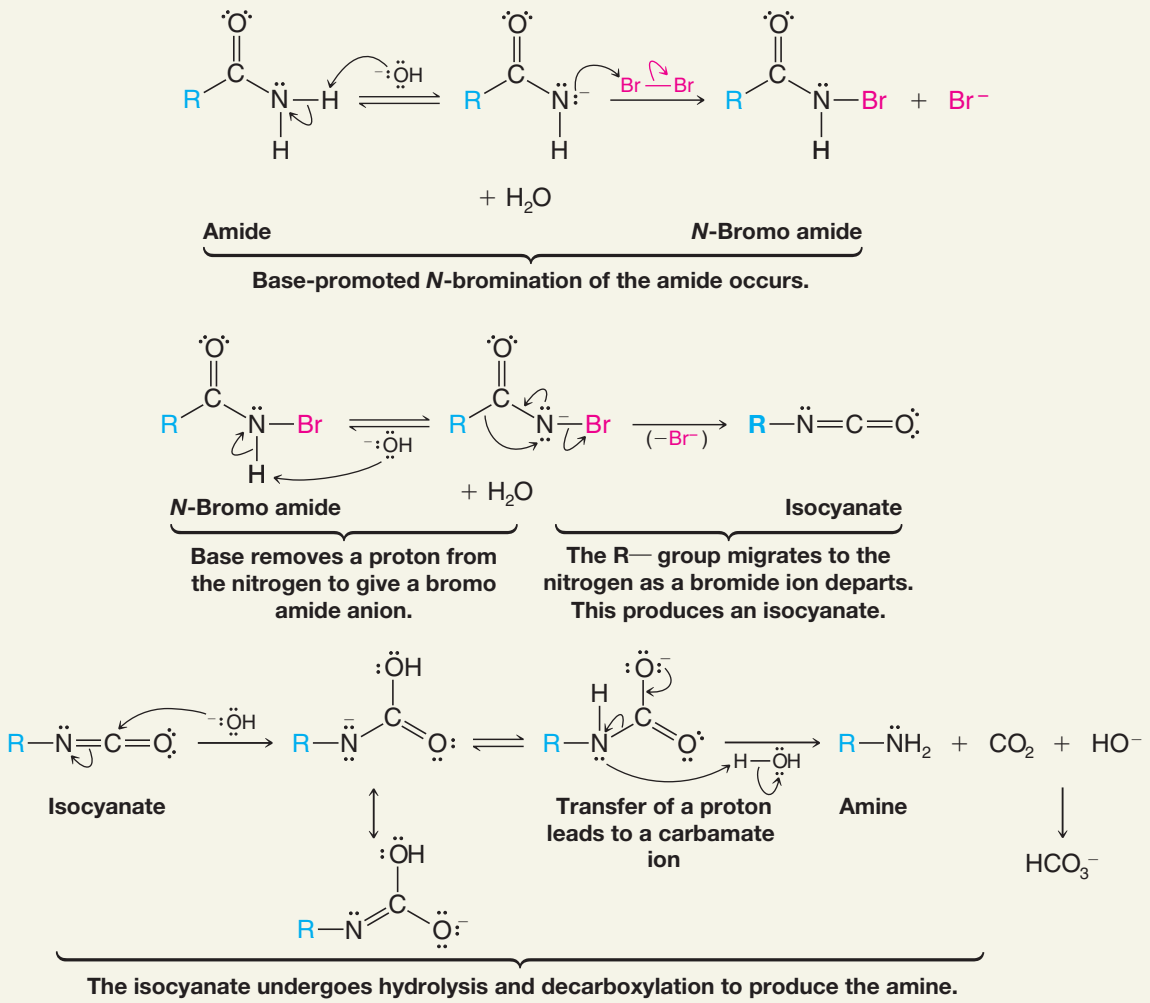
**Hofmann Rearrangement** Amides with no substituent on the nitrogen react with solutions of bromine or chlorine in sodium hydroxide to yield amines through loss of their carbonyl carbon by a reaction known as the *Hofmann rearrangement* or *Hofmann degradation*:



From this equation we can see that the carbonyl carbon atom of the amide is lost (as $CO_3^{2-}$) and that the R group of the amide becomes attached to the nitrogen of the amine. Primary amines made this way are not contaminated by 2° or 3° amines.

The mechanism for this interesting reaction is shown in the following scheme. In the first two steps the amide undergoes a base-promoted bromination, in a manner analogous to the base-promoted halogenation of a ketone that we studied in Section 18.3B. (The electron-withdrawing acyl group of the amide makes the amido hydrogens much more acidic than those of an amine.) The *N*-bromo amide then reacts with hydroxide ion to produce an anion, which spontaneously rearranges with the loss of a bromide ion to produce an isocyanate (Section 17.9A). In the rearrangement the R— group migrates with its electrons from the acyl carbon to the nitrogen atom at the same time the bromide ion departs. The isocyanate that forms in the mixture is quickly hydrolyzed by the aqueous base to a carbamate ion, which undergoes spontaneous decarboxylation resulting in the formation of the amine.

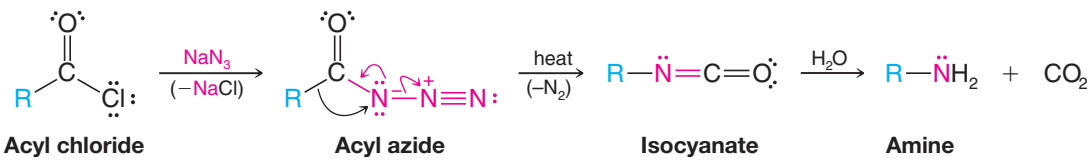
## A MECHANISM FOR THE REACTION — The Hofmann Rearrangement




An examination of the first two steps of this mechanism shows that, initially, two hydrogen atoms must be present on the nitrogen of the amide for the reaction to occur. Consequently, the Hofmann rearrangement is limited to amides of the type $RCONH_2$.

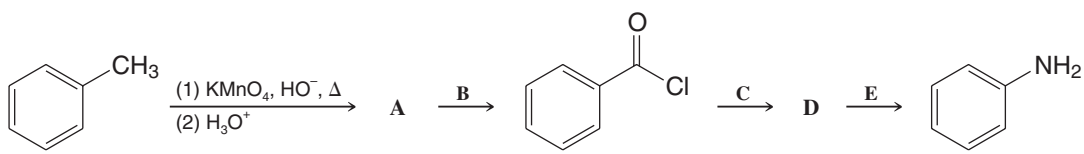
Studies of the Hofmann rearrangement of optically active amides in which the chirality center is directly attached to the carbonyl group have shown that these reactions occur with *retention of configuration*. Thus, the R group migrates to nitrogen with its electrons, *but without inversion*.

**Curtius Rearrangement** The *Curtius rearrangement* is a rearrangement that occurs with acyl azides and yields a primary amine with loss of the acyl carbon. It resembles the Hofmann rearrangement in that an R— group migrates from the acyl carbon to the nitrogen atom as the leaving group departs. In this instance the leaving group is $N_2$ (the best of all possible leaving groups since it is highly stable, is virtually nonbasic, and being a gas, removes itself from the medium). Acyl azides are easily prepared by allowing acyl chlorides to react with sodium azide. Heating the acyl azide brings about the rearrangement; afterward, adding water causes hydrolysis and decarboxylation of the isocyanate:

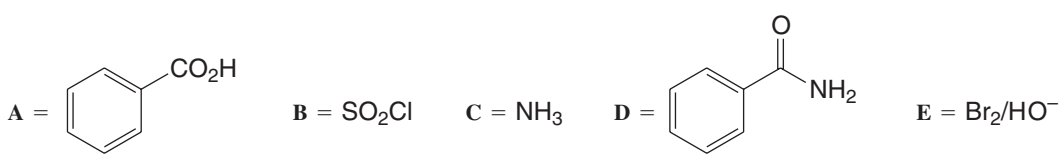



## SOLVED PROBLEM 20.5

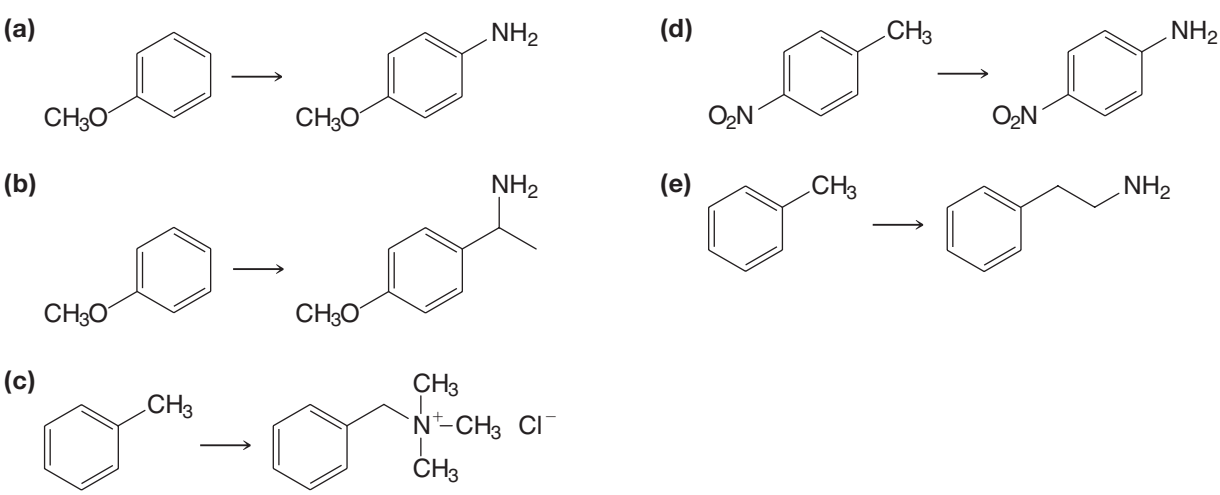
The reaction sequence below shows how a methyl group on a benzene ring can be replaced by an amino group. Supply the missing reagents and intermediates.




**STRATEGY AND ANSWER:** An acid chloride results from treatment of **A** with **B**. Therefore, **A** is likely to be a carboxylic acid, a conclusion that is consistent with the oxidizing conditions that led to formation of **A** from methylbenzene (toluene). **B** must be a reagent that can lead to an acid chloride. Thionyl chloride or $PCl_5$ would suffice. Overall, **C**, **D**, and **E** involve introduction of the nitrogen atom and loss of the carbonyl carbon. This sequence is consistent with preparation of an amide followed by a Hofmann rearrangement.




**PRACTICE PROBLEM 20.7** Using a different method for each part, but taking care in each case to select a *good* method, show how each of the following transformations might be accomplished:

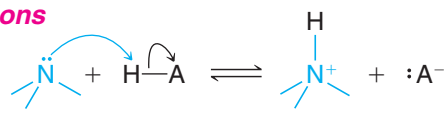


## 20.5 REACTIONS OF AMINES

We have encountered a number of important reactions of amines in earlier sections. In Section 20.3 we saw reactions in which primary, secondary, and tertiary amines act *as bases*. In Section 20.4 we saw their reactions as *nucleophiles* in *alkylation reactions*, and in Chapter 17 as *nucleophiles* in *acylation reactions*. In Chapter 15 we saw that an amino group on an aromatic ring acts as a powerful *activating group* and as an *ortho–para director*.

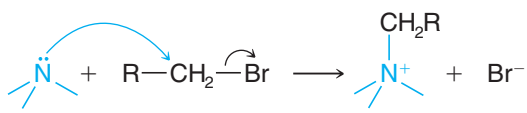
The feature of amines that underlies all of these reactions and that forms a basis for our understanding of most of the chemistry of amines is the ability of nitrogen to share an electron pair:

### Acid–Base Reactions



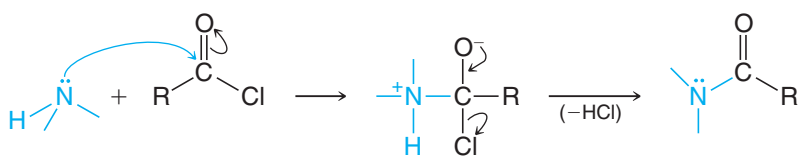
**An amine acting as a base**

### Alkylation



**An amine acting as a nucleophile in an alkylation reaction**

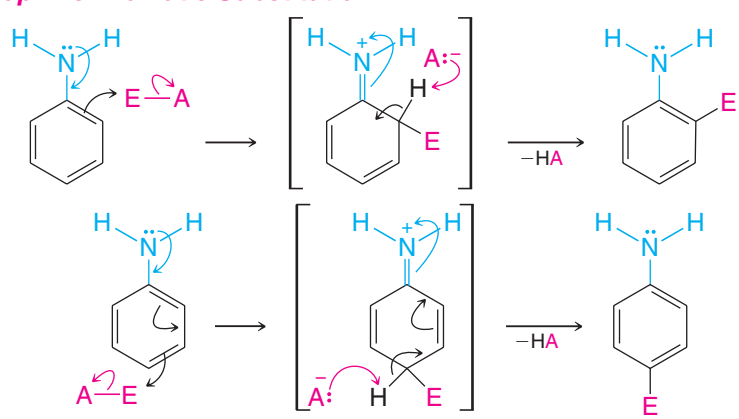
### Acylation



**A primary or secondary amine acting as a nucleophile in an acylation reaction**

In the preceding examples the amine acts as a nucleophile by donating its electron pair to an electrophilic reagent. In the following example, resonance contributions involving the nitrogen electron pair make *carbon* atoms nucleophilic:

### Electrophilic Aromatic Substitution



**The amino group acting as an activating group and as an ortho–para director in electrophilic aromatic substitution**

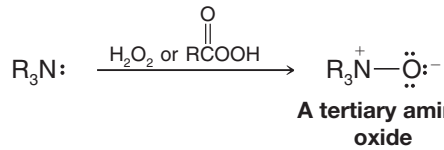
**PRACTICE PROBLEM 20.8**

Review the chemistry of amines given in earlier sections and provide a specific example for each of the previously illustrated reactions.

## 20.5A Oxidation of Amines

Primary and secondary aliphatic amines are subject to oxidation, although in most instances useful products are not obtained. Complicated side reactions often occur, causing the formation of complex mixtures.

Tertiary amines can be oxidized cleanly to tertiary amine oxides. This transformation can be brought about by using hydrogen peroxide or a peroxy acid:




Tertiary amine oxides undergo a useful elimination reaction to be discussed in Section 20.12B.

Arylamines are very easily oxidized by a variety of reagents, including the oxygen in air. Oxidation is not confined to the amino group but also occurs in the ring. (The amino group through its electron-donating ability makes the ring electron rich and hence especially susceptible to oxidation.) The oxidation of other functional groups on an aromatic ring cannot usually be accomplished when an amino group is present on the ring, because oxidation of the ring takes place first.

## 20.6 REACTIONS OF AMINES WITH NITROUS ACID

Nitrous acid (HO—N=O) is a weak, unstable acid. It is always prepared *in situ*, usually by treating sodium nitrite ($NaNO_2$) with an aqueous solution of a strong acid:

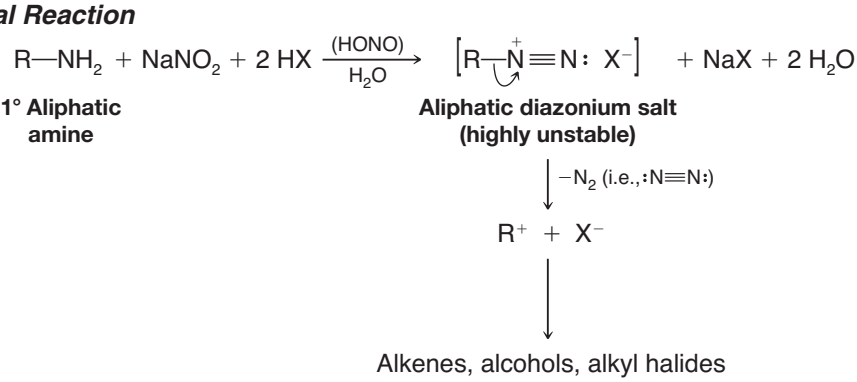
$$HCl_{(aq)} + NaNO_{2(aq)} \longrightarrow HONO_{(aq)} + NaCl_{(aq)}$$
$$H_2SO_4 + 2\ NaNO_{2(aq)} \longrightarrow 2\ HONO_{(aq)} + Na_2SO_{4(aq)}$$

Nitrous acid reacts with all classes of amines. The products that we obtain from these reactions depend on whether the amine is primary, secondary, or tertiary and whether the amine is aliphatic or aromatic.

### 20.6A Reactions of Primary Aliphatic Amines with Nitrous Acid

Primary aliphatic amines react with nitrous acid through a reaction called *diazotization* to yield highly unstable aliphatic **diazonium salts**. Even at low temperatures, *aliphatic* diazonium salts decompose spontaneously by losing nitrogen to form carbocations. The carbocations go on to produce mixtures of alkenes, alcohols, and alkyl halides by removal of a proton, reaction with $H_2O$, and reaction with $X^-$:

***General Reaction***




- Diazotizations of primary aliphatic amines are of little synthetic importance because they yield such a complex mixture of products.

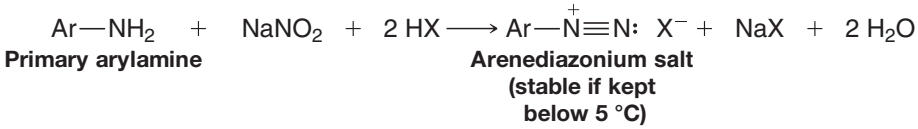
Diazotizations of primary aliphatic amines are used in some analytical procedures, however, because the evolution of nitrogen is quantitative. They can also be used to generate and thus study the behavior of carbocations in water, acetic acid, and other solvents.

### 20.6B Reactions of Primary Arylamines with Nitrous Acid

The most important reaction of amines with nitrous acid, by far, is the reaction of primary arylamines. We shall see why in Section 20.7.

- Primary arylamines react with nitrous acid to give arenediazonium salts.

Even though arenediazonium salts are unstable, they are still far more stable than aliphatic **diazonium salts**; they do not decompose at an appreciable rate in solution when the temperature of the reaction mixture is kept below 5 °C:

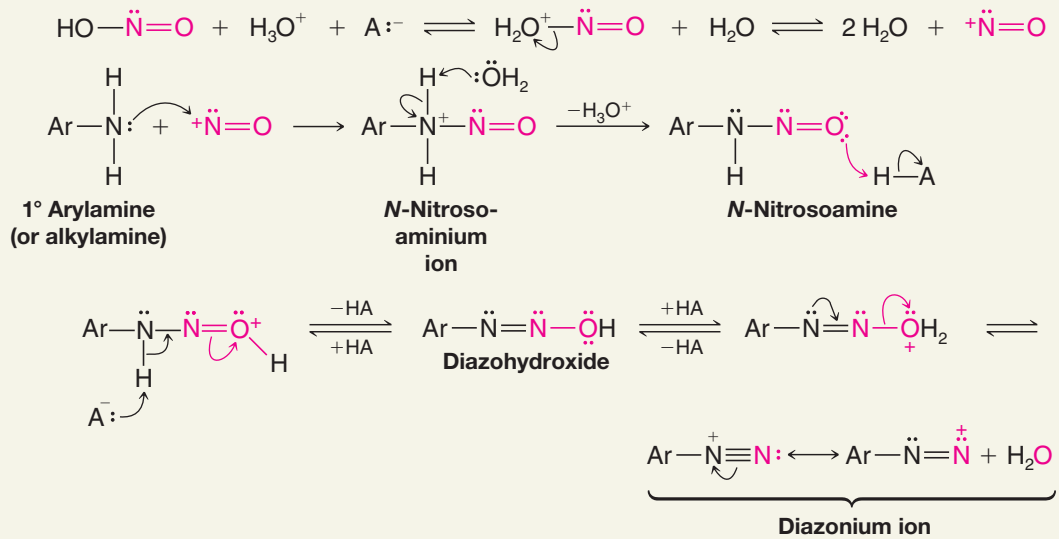



Diazotization of a primary amine takes place through a series of steps. In the presence of strong acid, nitrous acid dissociates to produce $^+NO$ ions. These ions then react with the nitrogen of the amine to form an unstable *N*-nitrosoaminium ion as an intermediate. This intermediate then loses a proton to form an *N*-nitrosoamine, which, in turn, tautomerizes to a diazohydroxide in a reaction that is similar to keto–enol tautomerization. Then, in the presence of acid, the diazohydroxide loses water to form the diazonium ion.

**Helpful Hint**

Primary arylamines can be converted to aryl halides, nitriles, and phenols via aryl diazonium ions (Section 20.7).

## A MECHANISM FOR THE REACTION — Diazotization




- Diazotization reactions of primary arylamines are of considerable synthetic importance because the diazonium group, $-\overset{+}{N}\equiv N:$ can be replaced by a variety of other functional groups.

We shall examine these reactions in Section 20.7.

## THE CHEMISTRY OF... *N*-Nitrosoamines

*N*-Nitrosoamines are very powerful carcinogens which scientists fear may be present in many foods, especially in cooked meats that have been cured with sodium nitrite.

Sodium nitrite is added to many meats (e.g., bacon, ham, frankfurters, sausages, and corned beef) to inhibit the growth of *Clostridium botulinum* (the bacterium that produces botulinus toxin) and to keep red meats from turning brown. (Food poisoning by botulinus toxin is often fatal.) In the presence of acid or under the influence of heat, sodium nitrite reacts with amines always present in the meat to produce *N*-nitrosoamines. Cooked bacon, for example, has been shown to contain *N*-nitrosodimethylamine and *N*-nitrosopyrrolidine.

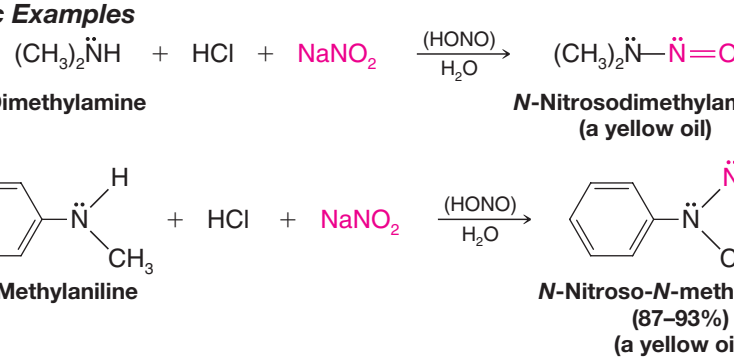
There is also concern that nitrites from food may produce nitrosoamines when they react with amines in the presence of the acid found in the stomach. In 1976, the FDA reduced the permissible amount of nitrite allowed in cured meats from 200 parts per million (ppm) to 50–125 ppm. Nitrites (and nitrates that can be converted to nitrites by bacteria) also occur naturally in many foods.

Cigarette smoke is known to contain *N*-nitrosodimethylamine. Someone smoking a pack of cigarettes a day inhales about 0.8 $\mu$g of *N*-nitrosodimethylamine, and even more has been shown to be present in the sidestream smoke.

## 20.6C Reactions of Secondary Amines with Nitrous Acid

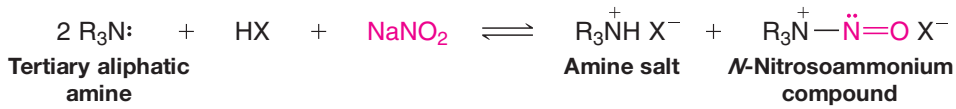
Secondary amines—both aryl and alkyl—react with nitrous acid to yield *N*-nitrosoamines. ***N*-Nitrosoamines** usually separate from the reaction mixture as oily yellow liquids:

***Specific Examples***




## 20.6D Reactions of Tertiary Amines with Nitrous Acid

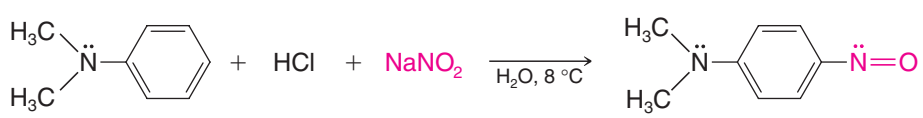
When a tertiary aliphatic amine is mixed with nitrous acid, an equilibrium is established among the tertiary amine, its salt, and an *N*-nitrosoammonium compound:




Although *N*-nitrosoammonium compounds are stable at low temperatures, at higher temperatures and in aqueous acid they decompose to produce aldehydes or ketones. These reactions are of little synthetic importance, however.

Tertiary arylamines react with nitrous acid to form *C*-nitroso aromatic compounds. Nitrosation takes place almost exclusively at the para position if it is open and, if not, at the ortho position. The reaction (see Practice Problem 20.9) is another example of electrophilic aromatic substitution.

***Specific Example***




**PRACTICE PROBLEM 20.9** Para-nitrosation of *N*,*N*-dimethylaniline (*C*-nitrosation) is believed to take place through an electrophilic attack by $\overset{+}{N}O$ ions. **(a)** Show how $\overset{+}{N}O$ ions might be formed in an aqueous solution of $NaNO_2$ and HCl. **(b)** Write a mechanism for *p*-nitrosation of *N*,*N*-dimethylaniline. **(c)** Tertiary aromatic amines and phenols undergo *C*-nitrosation reactions, whereas most other benzene derivatives do not. How can you account for this difference?

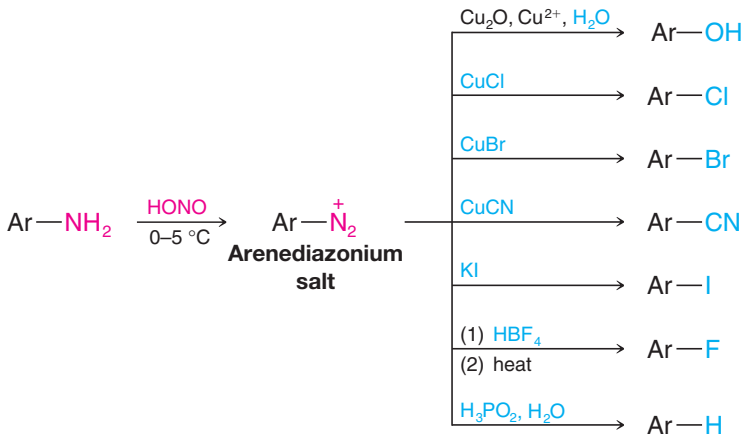
# 20.7 REPLACEMENT REACTIONS OF ARENEDIAZONIUM SALTS

- Arenediazonium salts are highly useful intermediates in the synthesis of aromatic compounds, because the diazonium group can be replaced by any one of a number of other atoms or groups, including —F, —Cl, —Br, —I, —CN, —OH, and —H.

**Diazonium salts** are almost always prepared by diazotizing primary aromatic amines. Primary arylamines can be synthesized through reduction of nitro compounds that are readily available through direct nitration reactions.

## 20.7A Syntheses Using Diazonium Salts

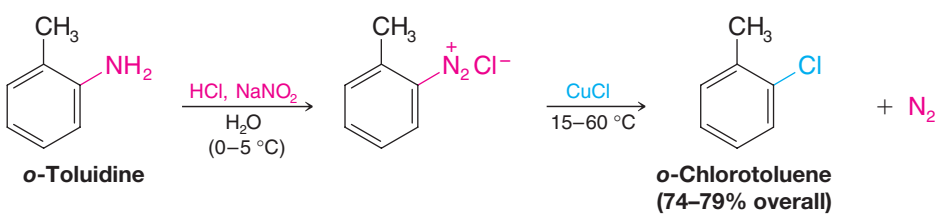
Most arenediazonium salts are unstable at temperatures above 5–10 °C, and many explode when dry. Fortunately, however, most of the replacement reactions of diazonium salts do not require their isolation. We simply add another reagent (CuCl, CuBr, KI, etc.) to the mixture, gently warm the solution, and the replacement (accompanied by the evolution of nitrogen) takes place:



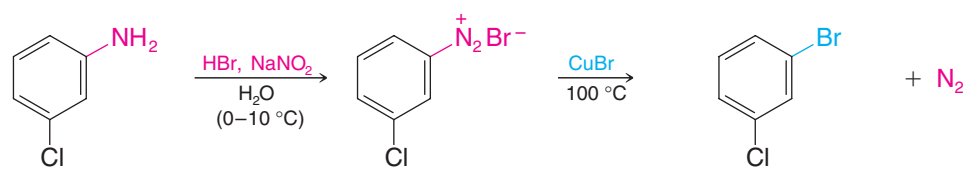

Only in the replacement of the diazonium group by —F need we isolate a diazonium salt. We do this by adding $HBF_4$ to the mixture, causing the sparingly soluble and reasonably stable arenediazonium fluoroborate, $ArN_2^+ BF_4^-$, to precipitate.

## 20.7B The Sandmeyer Reaction: Replacement of the Diazonium Group by —Cl, —Br, or —CN

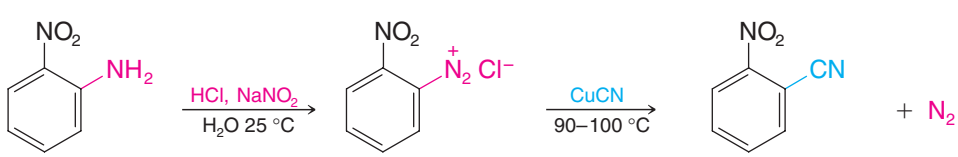
Arenediazonium salts react with cuprous chloride, cuprous bromide, and cuprous cyanide to give products in which the diazonium group has been replaced by —Cl, —Br, and —CN, respectively. These reactions are known generally as *Sandmeyer reactions*. Several specific examples follow. The mechanisms of these replacement reactions are not fully understood; the reactions appear to be radical in nature, not ionic.




***o*-Toluidine** — ***o*-Chlorotoluene (74–79% overall)**



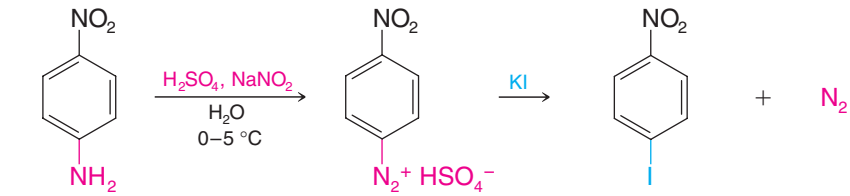

***m*-Chloroaniline** — ***m*-Bromochlorobenzene (70% overall)**




***o*-Nitroaniline** — ***o*-Nitrobenzonitrile (65% overall)**

## 20.7C Replacement by —I

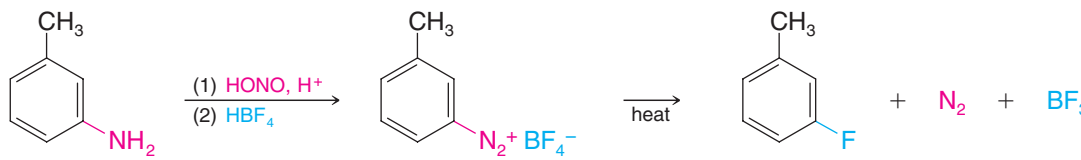
Arenediazonium salts react with potassium iodide to give products in which the diazonium group has been replaced by —I. An example is the synthesis of *p*-iodonitrobenzene:




***p*-Nitroaniline** — ***p*-Iodonitrobenzene (81% overall)**

## 20.7D Replacement by —F

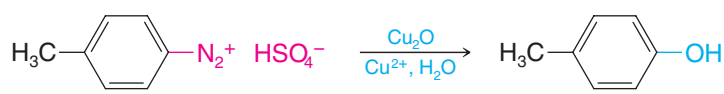
The diazonium group can be replaced by fluorine by treating the diazonium salt with fluoroboric acid ($HBF_4$). The diazonium fluoroborate that precipitates is isolated, dried, and heated until decomposition occurs. An aryl fluoride is produced:




***m*-Toluidine** — ***m*-Toluenediazonium fluoroborate (79%)** — ***m*-Fluorotoluene (69%)**

## 20.7E Replacement by —OH

The diazonium group can be replaced by a hydroxyl group by adding cuprous oxide to a dilute solution of the diazonium salt containing a large excess of cupric nitrate:




***p*-Toluenediazonium hydrogen sulfate** — ***p*-Cresol (93%)**

This variation of the Sandmeyer reaction (developed by T. Cohen, University of Pittsburgh) is a much simpler and safer procedure than an older method for phenol preparation, which required heating the diazonium salt with concentrated aqueous acid.

**PRACTICE PROBLEM 20.10** In the preceding examples of diazonium reactions, we have illustrated syntheses beginning with the compounds (a)–(d) here. Show how you might prepare each of the following compounds from benzene:

**(a)** *m*-Chloroaniline **(b)** *m*-Bromoaniline **(c)** *o*-Nitroaniline **(d)** *p*-Nitroaniline

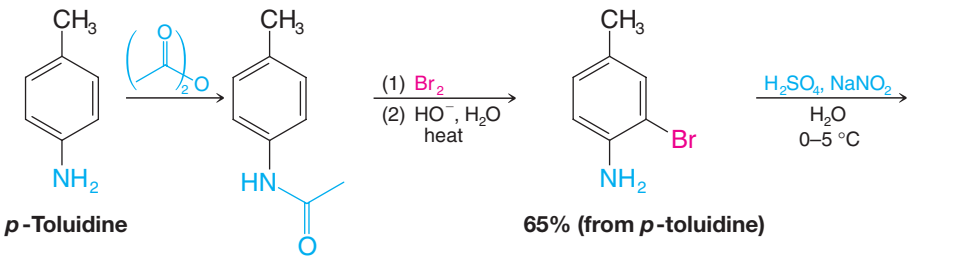
## 20.7F Replacement by Hydrogen: Deamination by Diazotization

Arenediazonium salts react with hypophosphorous acid ($H_3PO_2$) to yield products in which the diazonium group has been replaced by —H.

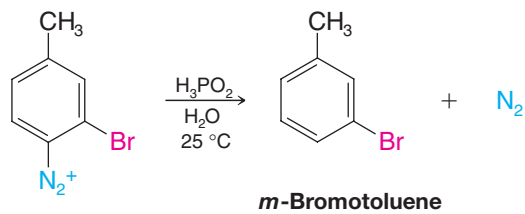
Since we usually begin a synthesis using diazonium salts by nitrating an aromatic compound, that is, replacing —H by $-NO_2$ and then by $-NH_2$, it may seem strange that we would ever want to replace a diazonium group by —H. However, replacement of the diazonium group by —H can be a useful reaction. We can introduce an amino group into an aromatic ring to influence the orientation of a subsequent reaction. Later we can

remove the amino group (i.e., carry out a *deamination*) by diazotizing it and treating the diazonium salt with $H_3PO_2$.

We can see an example of the usefulness of a deamination reaction in the following synthesis of *m*-bromotoluene.




***p*-Toluidine** **65% (from *p*-toluidine)**



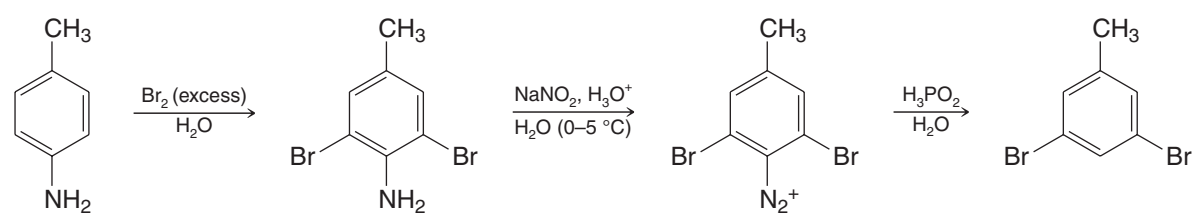

***m*-Bromotoluene (85% from 2-bromo-4-methylaniline)**

We cannot prepare *m*-bromotoluene by direct bromination of toluene or by a Friedel–Crafts alkylation of bromobenzene because both reactions give *o*- and *p*-bromotoluene. (Both $CH_3$— and Br— are ortho–para directors.) However, if we begin with *p*-toluidine (prepared by nitrating toluene, separating the para isomer, and reducing the nitro group), we can carry out the sequence of reactions shown and obtain *m*-bromotoluene in good yield. The first step, synthesis of the *N*-acetyl derivative of *p*-toluidine, is done to reduce the activating effect of the amino group. (Otherwise both ortho positions would be brominated.) Later, the acetyl group is removed by hydrolysis.

### SOLVED PROBLEM 20.6

Suggest how you might modify the preceding synthesis in order to prepare 3,5-dibromotoluene.

**STRATEGY AND ANSWER:** An amino group is a stronger activating group than an amido group. If we brominate directly with the amino group present, rather than after converting the amine to an amide, we can brominate both ortho positions. We must also be sure to provide sufficient bromine.




### PRACTICE PROBLEM 20.11

**(a)** In Section 20.7D we showed a synthesis of *m*-fluorotoluene starting with *m*-toluidine. How would you prepare *m*-toluidine from toluene? **(b)** How would you prepare *m*-chlorotoluene? **(c)** *m*-Bromotoluene? **(d)** *m*-Iodotoluene? **(e)** *m*-Tolunitrile (*m*-$CH_3C_6H_4CN$)? **(f)** *m*-Toluic acid?

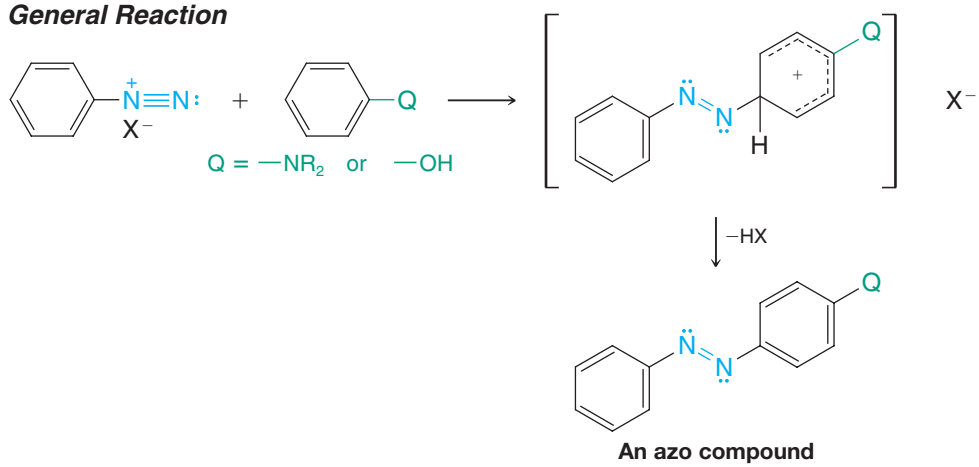
### PRACTICE PROBLEM 20.12

Starting with *p*-nitroaniline [Practice Problem 20.10(d)], show how you might synthesize 1,2,3-tribromobenzene.

## 20.8 COUPLING REACTIONS OF ARENEDIAZONIUM SALTS

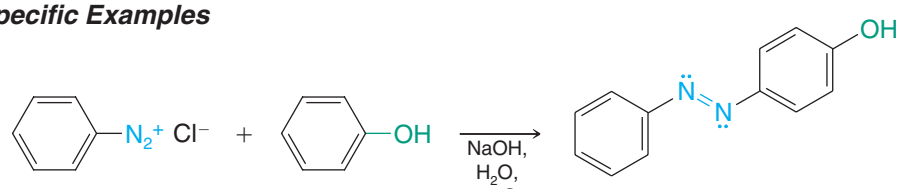
Arenediazonium ions are weak electrophiles; they react with highly reactive aromatic compounds—with phenols and tertiary arylamines—to yield *azo* compounds. This electrophilic aromatic substitution is often called a *diazo coupling reaction*.

***General Reaction***

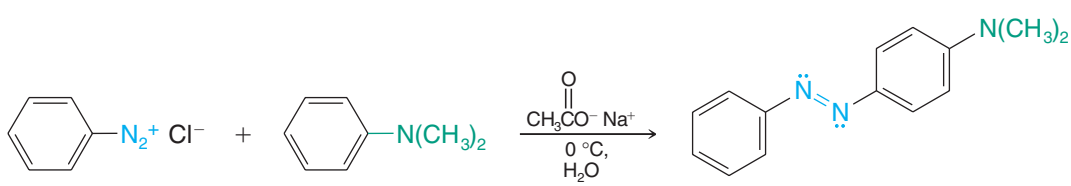



**An azo compound**

***Specific Examples***

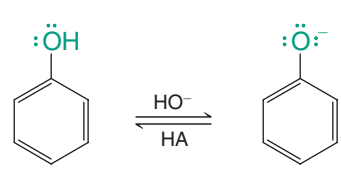



**Benzenediazonium chloride** + **Phenol** → ***p*-(Phenylazo)phenol (orange solid)**

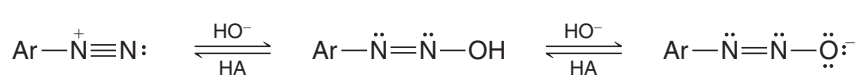



**Benzenediazonium chloride** + ***N,N*-Dimethylaniline** → ***N,N*-Dimethyl-*p*-(phenylazo)aniline (yellow solid)**

Couplings between arenediazonium cations and phenols take place most rapidly in *slightly* alkaline solution. Under these conditions an appreciable amount of the phenol is present as a phenoxide ion, $ArO^-$, and phenoxide ions are even more reactive toward electrophilic substitution than are phenols themselves. (Why?) If the solution is too alkaline (pH > 10), however, the arenediazonium salt itself reacts with hydroxide ion to form a relatively unreactive diazohydroxide or diazotate ion:

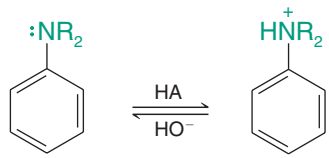



**Phenol (couples slowly)** ⇌ **Phenoxide ion (couples rapidly)**




**Arenediazonium ion (couples)** ⇌ **Diazohydroxide (does not couple)** ⇌ **Diazotate ion (does not couple)**

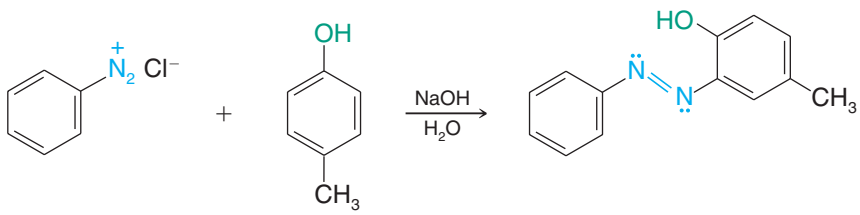
Couplings between arenediazonium cations and amines take place most rapidly in slightly acidic solutions (pH 5–7). Under these conditions the concentration of the arenediazonium cation is at a maximum; at the same time an excessive amount of the amine has not been converted to an unreactive aminium salt:




**Amine (couples)** **Aminium salt (does not couple)**

If the pH of the solution is lower than 5, the rate of amine coupling is low.

With phenols and aniline derivatives, coupling takes place almost exclusively at the para position if it is open. If it is not, coupling takes place at the ortho position.

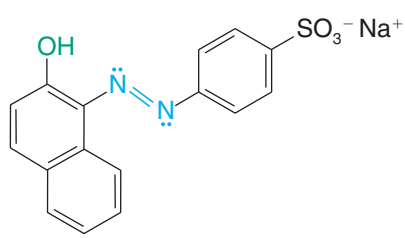



**4-Methylphenol (*p*-cresol)** **4-Methyl-2-(phenylazo)phenol**

Azo compounds are usually intensely colored because the azo (diazenediyl) linkage, —N═N—, brings the two aromatic rings into conjugation. This gives an extended system of delocalized $\pi$ electrons and allows absorption of light in the visible region. Azo compounds, because of their intense colors and because they can be synthesized from relatively inexpensive compounds, are used extensively as *dyes*.

*Azo dyes* almost always contain one or more $-SO_3^-Na^+$ groups to confer water solubility on the dye and assist in binding the dye to the surfaces of polar fibers (wool, cotton, or nylon). Many dyes are made by coupling reactions of naphthylamines and naphthols.

Orange II, a dye introduced in 1876, is made from 2-naphthol:



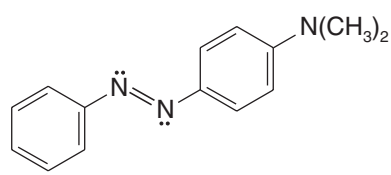

**Orange II**

**PRACTICE PROBLEM 20.13**

Outline a synthesis of orange II from 2-naphthol and *p*-aminobenzenesulfonic acid.

**PRACTICE PROBLEM 20.14**

Butter yellow is a dye once used to color margarine. It has since been shown to be carcinogenic, and its use in food is no longer permitted. Outline a synthesis of butter yellow from benzene and *N*,*N*-dimethylaniline.




**Butter yellow**

**PRACTICE PROBLEM 20.15** Azo compounds can be reduced to amines by a variety of reagents including stannous chloride ($SnCl_2$):

$$Ar{-}N{=}N{-}Ar' \xrightarrow{SnCl_2} ArNH_2 + Ar'NH_2$$

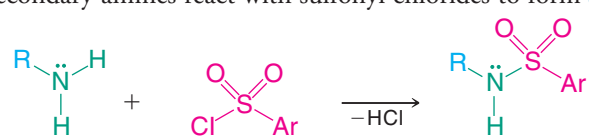
This reduction can be useful in synthesis as the following example shows:

$$\text{4-Ethoxyaniline} \xrightarrow[\text{(2) phenol, } HO^-]{\text{(1) HONO, } H_3O^+} \mathbf{A}\ (C_{14}H_{14}N_2O_2) \xrightarrow{NaOH,\ CH_3CH_2Br} \mathbf{B}\ (C_{16}H_{18}N_2O_2) \xrightarrow{SnCl_2} \text{two molar equivalents of } \mathbf{C}\ (C_8H_{11}NO) \xrightarrow{\text{acetic anhydride}} \text{phenacetin } (C_{10}H_{13}NO_2)$$

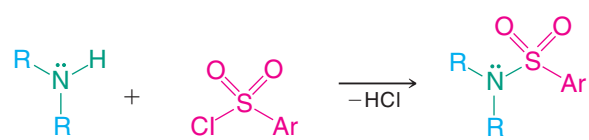
Give a structure for phenacetin and for the intermediates **A**, **B**, and **C**. (Phenacetin, formerly used as an analgesic, is also the subject of Problem 17.45.)

## 20.9 REACTIONS OF AMINES WITH SULFONYL CHLORIDES

Primary and secondary amines react with sulfonyl chlorides to form **sulfonamides**:

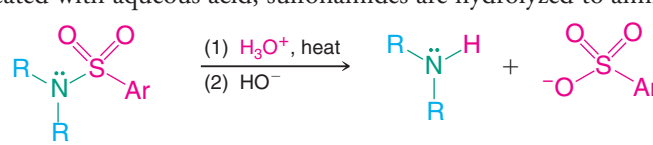



**1° Amine** | **Sulfonyl chloride** | ***N*-Substituted sulfonamide**




**2° Amine** | ***N,N*-Disubstituted sulfonamide**

When heated with aqueous acid, sulfonamides are hydrolyzed to amines:




This hydrolysis is much slower, however, than hydrolysis of carboxamides.

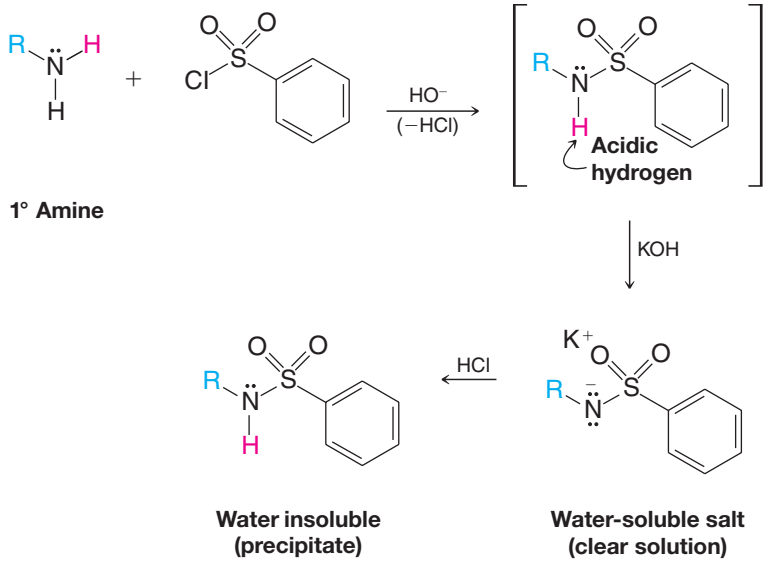
### 20.9A The Hinsberg Test

- Sulfonamide formation is the basis for a chemical test, called the Hinsberg test, that can be used to demonstrate whether an amine is primary, secondary, or tertiary.

A Hinsberg test involves two steps. First, a mixture containing a small amount of the amine and benzenesulfonyl chloride is shaken with *excess* potassium hydroxide. Next, after allowing time for a reaction to take place, the mixture is acidified. Each type of amine—primary, secondary, or tertiary—gives a different set of *visible* results after each of these two stages of the test.

Primary amines react with benzenesulfonyl chloride to form *N*-substituted benzenesulfonamides. These, in turn, undergo acid–base reactions with the excess potassium hydroxide to form water-soluble potassium salts. (These reactions take place because the hydrogen attached to nitrogen is made acidic by the strongly electron-withdrawing —$SO_2$— group.) At this stage our test tube contains a clear solution. Acidification of

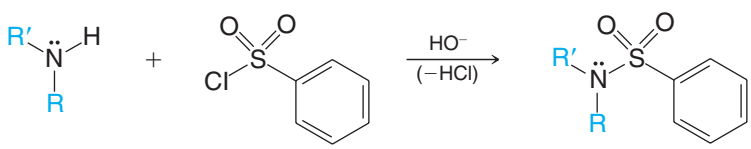
this solution will, in the next stage, cause the water-insoluble *N*-substituted sulfonamide to precipitate:




**1° Amine**

**Water insoluble (precipitate)** **Water-soluble salt (clear solution)**

Secondary amines react with benzenesulfonyl chloride in aqueous potassium hydroxide to form insoluble *N*,*N*-disubstituted sulfonamides that precipitate after the first stage. *N*,*N*-Disubstituted sulfonamides do not dissolve in aqueous potassium hydroxide because they do not have an acidic hydrogen. Acidification of the mixture obtained from a secondary amine produces no visible result; the nonbasic *N*,*N*-disubstituted sulfonamide remains as a precipitate and no new precipitate forms:




**Water insoluble (precipitate)**

If the amine is a tertiary amine and if it is water insoluble, no apparent change will take place in the mixture as we shake it with benzenesulfonyl chloride and aqueous KOH. When we acidify the mixture, the tertiary amine dissolves because it forms a water-soluble salt.

**PRACTICE PROBLEM 20.16**

An amine **A** has the molecular formula $C_7H_9N$. Compound **A** reacts with benzenesulfonyl chloride in aqueous potassium hydroxide to give a clear solution; acidification of the solution gives a precipitate. When **A** is treated with $NaNO_2$ and HCl at 0–5 °C, and then with 2-naphthol, an intensely colored compound is formed. Compound **A** gives a single strong IR absorption peak at 815 $cm^{-1}$. What is the structure of **A**?

**PRACTICE PROBLEM 20.17**

Sulfonamides of primary amines are often used to synthesize *pure* secondary amines. Suggest how this synthesis is carried out.

## THE CHEMISTRY OF... Essential Nutrients and Antimetabolites

All higher animals and many microorganisms lack the biochemical ability to synthesize certain essential organic compounds. These essential nutrients include many amine-containing compounds, such as vitamins, certain amino acids, unsaturated carboxylic acids, components of DNA bases such as purines and pyrimidines. The aromatic amine *p*-aminobenzoic acid, for example, is an essential nutrient for many bacteria (see Figure 20.3). These microorganisms rely on *p*-aminobenzoic acid as a key starting material, along with several other compounds, to synthesize folic acid in enzymatically-controlled processes.

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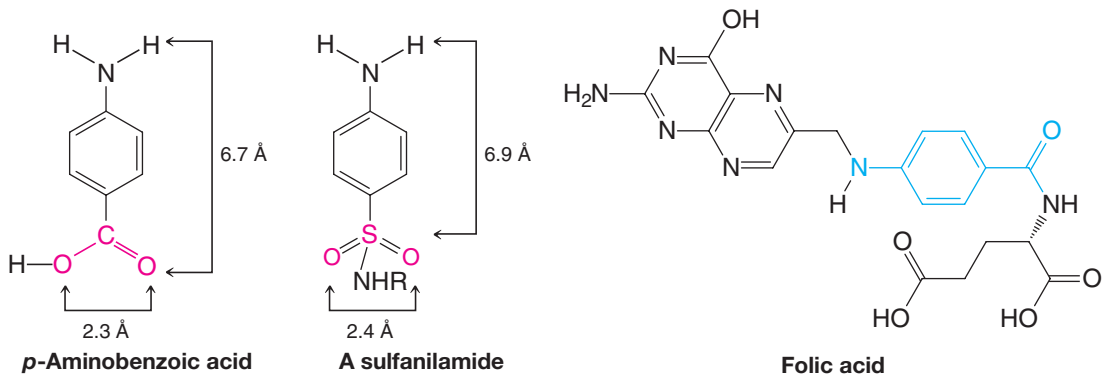
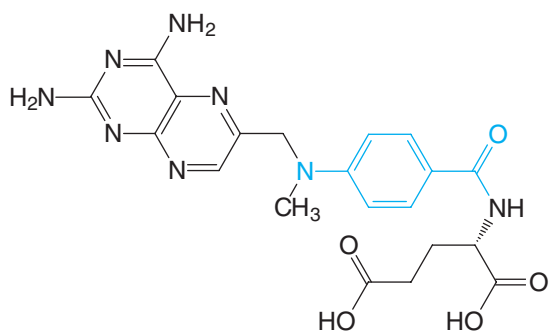



**FIGURE 20.3** The structural similarity of *p*-aminobenzoic acid and a sulfanilamide. (Reprinted with permission of John Wiley and Sons, Inc. from Korolkovas, *Essentials of Molecular Pharmacology*, Copyright 1970.)

Chemicals that inhibit the growth of microbes are known as antimetabolites. It turns out that certain amine-containing molecules known as sulfanilamides (which we will discuss in more detail shortly) are antimetabolites for those bacteria that rely on *p*-aminobenzoic acid. The reason: the homology of their overall shapes, key features of which are highlighted above. Indeed, the enzymes that these bacteria use to synthesize folic acid cannot distinguish between these two molecules. And, when a sulfanilamide is used as a substrate instead of *p*-aminobenzoic acid, folic acid does not result. This event ultimately leads to bacterial death since enough of that essential nutrient is not synthesized. Such treatments turn out to be especially useful for humans because we derive our folic acid from dietary sources (folic acid is a vitamin). Thus, we do not have any enzymes that synthesize it from *p*-aminobenzoic acid and are, as a result, unaffected in any negative ways by a sulfanilamide therapy.

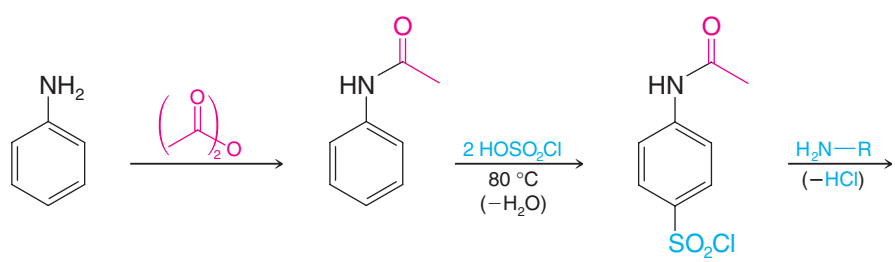


**Methotrexate**

Many other examples of this concept exist. A recent example is methotrexate, a derivative of folic acid that has been used successfully in treating certain carcinomas as well as rheumatoid arthritis. Just as in the case above, methotrexate, because of its resemblance to folic acid, can enter into some of the same chemical reactions as folic acid, but it cannot ultimately serve the same inherent biological function. Here that role is involvement in reactions critical to cellular division. Although methotrexate is toxic to all dividing cells, those cells that divide most rapidly—cancer cells—are most vulnerable to its effect.

## 20.10 SYNTHESIS OF SULFA DRUGS

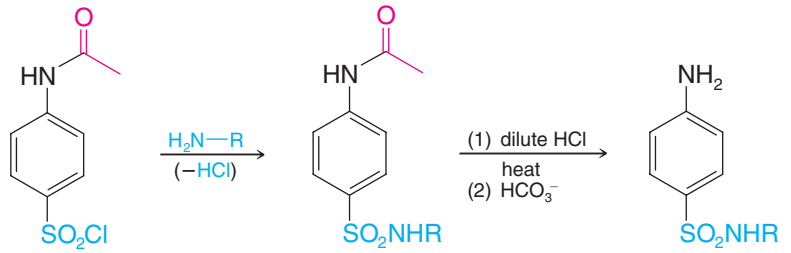
Sulfanilamides (**sulfa drugs**) can be synthesized from aniline through the following sequence of reactions:




**Aniline (1)** — **Acetanilide (2)** — ***p*-Acetamidobenzenesulfonyl chloride (3)**

*(continued on the next page)*

*(continued from previous page)*

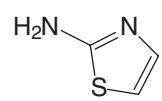



**p-Acetamidobenzene-sulfonyl chloride (3)** **(4)** **A sulfanilamide (5)**

Acetylation of aniline produces acetanilide **(2)** and protects the amino group from the reagent to be used next. Treatment of **2** with chlorosulfonic acid brings about an electrophilic aromatic substitution reaction and yields *p*-acetamidobenzene-sulfonyl chloride **(3)**. Addition of ammonia or a primary amine gives the diamide, **4** (an amide of both a carboxylic acid and a sulfonic acid). Finally, refluxing **4** with dilute hydrochloric acid selectively hydrolyzes the carboxamide linkage and produces a sulfanilamide. (Hydrolysis of carboxamides is much more rapid than that of sulfonamides.)

**PRACTICE PROBLEM 20.18**

**(a)** Starting with aniline and assuming that you have 2-aminothiazole available, show how you would synthesize sulfathiazole. **(b)** How would you convert sulfathiazole to succinylsulfathiazole?




**2-Aminothiazole**

## 20.11 ANALYSIS OF AMINES

### 20.11A Chemical Analysis

Amines are characterized by their basicity and, thus, by their ability to dissolve in dilute aqueous acid (Sections 20.3A, 20.3E). Moist pH paper can be used to test for the presence of an amine functional group in an unknown compound. If the compound is an amine, the pH paper shows the presence of a base. The unknown amine can then readily be classified as 1°, 2°, or 3° by IR spectroscopy (see below). Primary, secondary, and tertiary amines can also be distinguished from each other on the basis of the Hinsberg test (Section 20.9A). Primary aromatic amines are often detected through diazonium salt formation and subsequent coupling with 2-naphthol to form a brightly colored azo dye (Section 20.8).

### 20.11B Spectroscopic Analysis

**Infrared Spectra** Primary and secondary amines are characterized by IR absorption bands in the 3300–3555-$cm^{-1}$ region that arise from N—H stretching vibrations. Primary amines give two bands in this region (see Fig. 20.4); secondary amines generally give only one. Tertiary amines, because they have no N—H group, do not absorb in this region. Absorption bands arising from C—N stretching vibrations of aliphatic amines occur in the 1020–1220-$cm^{-1}$ region but are usually weak and difficult to identify. Aromatic amines generally give a strong C—N stretching band in the 1250–1360-$cm^{-1}$ region. Figure 20.4 shows an annotated IR spectrum of 4-methylaniline.

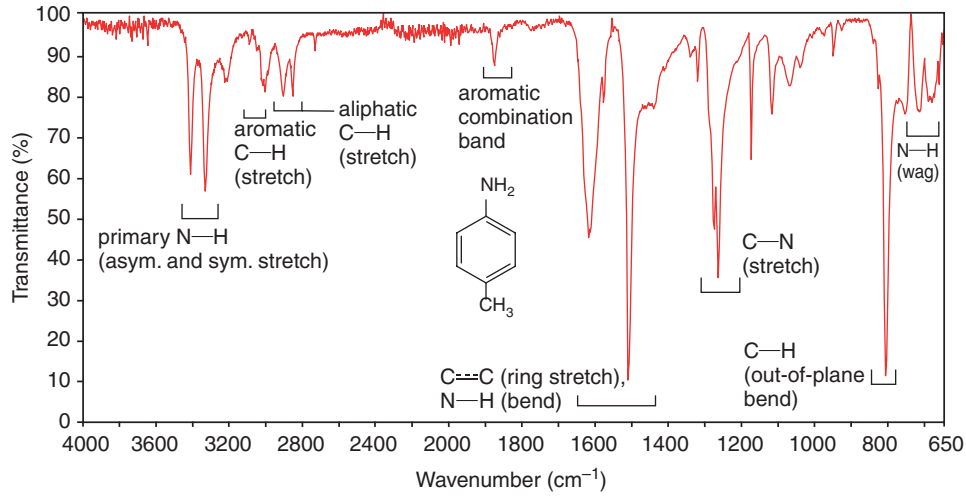



**FIGURE 20.4** Annotated IR spectrum of 4-methylaniline.

**$^1$H NMR Spectra** Primary and secondary amines show N—H proton signals in the region $\delta$ 0.5–5. These signals are usually broad, and their exact position depends on the nature of the solvent, the purity of the sample, the concentration, and the temperature. Because of proton exchange, N—H protons are not usually coupled to protons on adjacent carbons. As such, they are difficult to identify and are best detected by proton counting or by adding a small amount of $D_2O$ to the sample. Exchange of N—D deuterons for the N—H protons takes place, and the N—H signal disappears from the spectrum.

Protons on the $\alpha$ carbon of an aliphatic amine are deshielded by the electron-withdrawing effect of the nitrogen and absorb typically in the $\delta$ 2.2–2.9 region; protons on the $\beta$ carbon are not deshielded as much and absorb in the range $\delta$ 1.0–1.7.

Figure 20.5 shows an annotated $^1$H NMR spectrum of diisopropylamine.

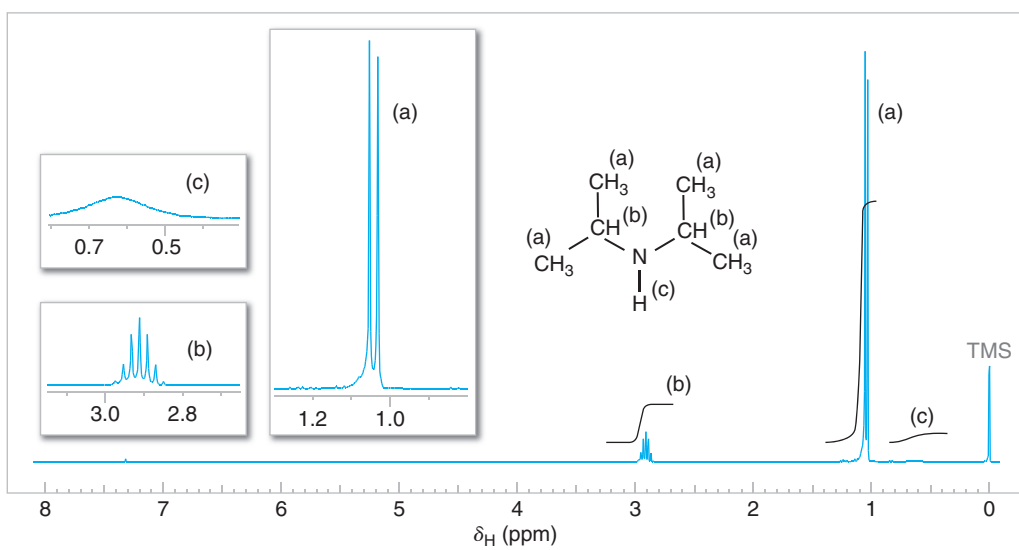
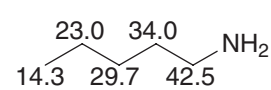



**FIGURE 20.5** The 300-MHz $^1$H NMR spectrum of diisopropylamine. Note the integral for the broad NH peak at approximately $\delta$ 0.7. Vertical expansions are not to scale.

**$^{13}$C NMR Spectra** The $\alpha$ carbon of an aliphatic amine experiences deshielding by the electronegative nitrogen, and its absorption is shifted downfield, typically appearing at $\delta$ 30–60. The shift is not as great as for the $\alpha$ carbon of an alcohol (typically $\delta$ 50–75), however, because nitrogen is less electronegative than oxygen. The downfield shift is even less for the $\beta$ carbon, and so on down the chain, as the chemical shifts of the carbons of pentyl amine show:



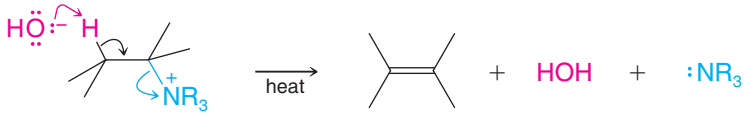

**$^{13}$C NMR chemical shifts ($\delta$)**

**Mass Spectra of Amines** The molecular ion in the mass spectrum of an amine has an odd number mass (unless there is an even number of nitrogen atoms in the molecule). The peak for the molecular ion is usually strong for aromatic and cyclic aliphatic amines but weak for acyclic aliphatic amines. Cleavage between the $\alpha$ and $\beta$ carbons of aliphatic amines is a common mode of fragmentation.

## 20.12 ELIMINATIONS INVOLVING AMMONIUM COMPOUNDS

### 20.12A The Hofmann Elimination

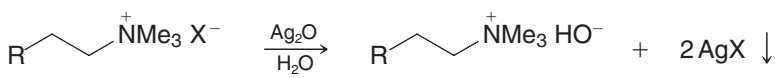
All of the eliminations that we have described so far have involved electrically neutral substrates. However, eliminations are known in which the substrate bears a positive charge. One of the most important of these is the E2-type elimination that takes place when a quaternary ammonium hydroxide is heated. The products are an alkene, water, and a tertiary amine:




**A quaternary ammonium hydroxide** — **An alkene** — **A tertiary amine**

This reaction was discovered in 1851 by August W. von Hofmann and has since come to bear his name.

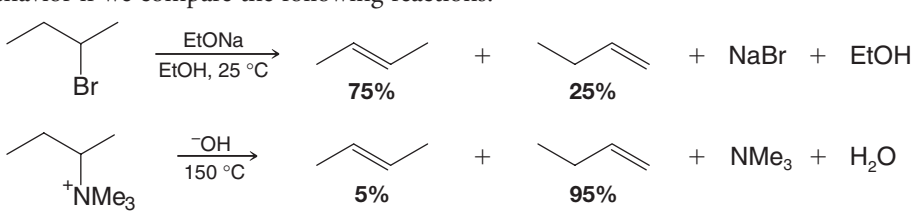
Quaternary ammonium hydroxides can be prepared from quaternary ammonium halides in aqueous solution through the use of silver oxide or an ion exchange resin:



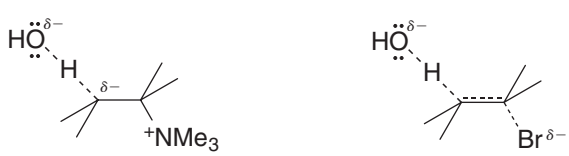

**A quaternary ammonium halide** — **A quaternary ammonium hydroxide**

Silver halide precipitates from the solution and can be removed by filtration. The quaternary ammonium hydroxide can then be obtained by evaporation of the water.

Although most eliminations involving neutral substrates tend to follow the *Zaitsev rule* (Section 7.6B), eliminations with charged substrates tend to follow what is called the **Hofmann rule** and *yield mainly the least substituted alkene*. We can see an example of this behavior if we compare the following reactions:




The precise mechanistic reasons for these differences are complex and are not yet fully understood. One possible explanation is that the transition states of elimination reactions with charged substrates have considerable carbanionic character. Therefore, these transition states show little resemblance to the final alkene product and are not stabilized appreciably by a developing double bond:

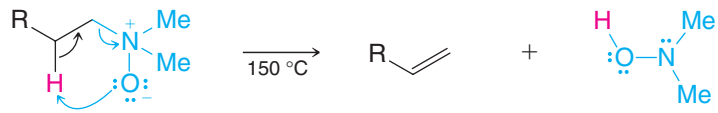



**Carbanion-like transition state (gives Hofmann orientation)** — **Alkene-like transition state (gives Zaitsev orientation)**

With a charged substrate, the base attacks the most acidic hydrogen instead. A primary hydrogen atom is more acidic because its carbon atom bears only one electron-releasing group.

### 20.12B The Cope Elimination

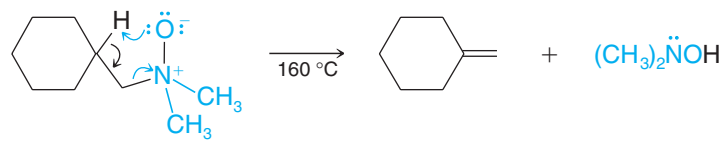
Tertiary amine oxides undergo the elimination of a dialkylhydroxylamine when they are heated. The reaction is called the Cope elimination, it is a syn elimination and proceeds through a cyclic transition state.




**A tertiary amine oxide** **An alkene** ***N,N*-Dimethylhydroxylamine**

Tertiary amine oxides are easily prepared by treating tertiary amines with hydrogen peroxide (Section 20.5A).

The Cope elimination is useful synthetically. Consider the following synthesis of methylenecyclohexane:

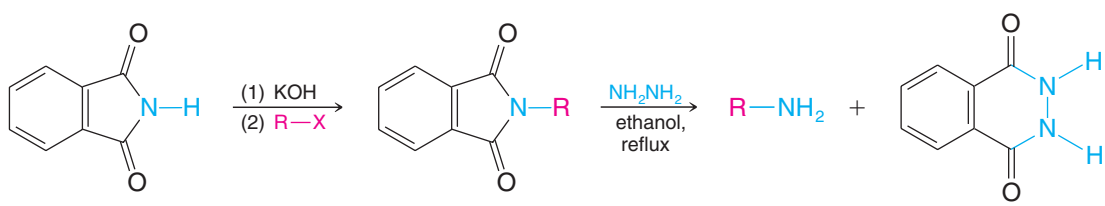



**98%**

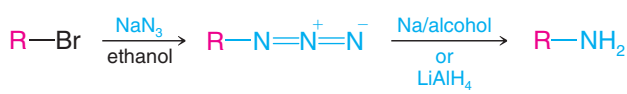
## 20.13 SUMMARY OF PREPARATIONS AND REACTIONS OF AMINES

### PREPARATION OF AMINES

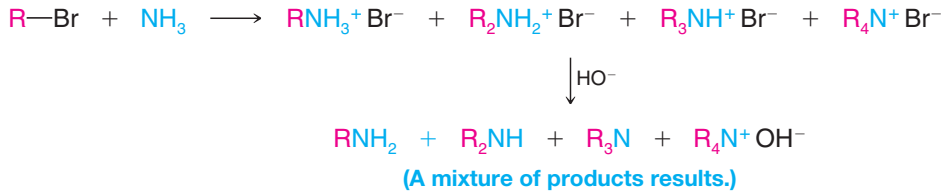
**1.** Gabriel synthesis (discussed in Section 20.4A):




**2.** By reduction of alkyl azides (discussed in Section 20.4A):



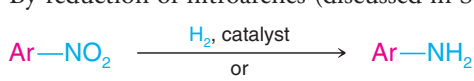

**3.** By amination of alkyl halides (discussed in Section 20.4A):



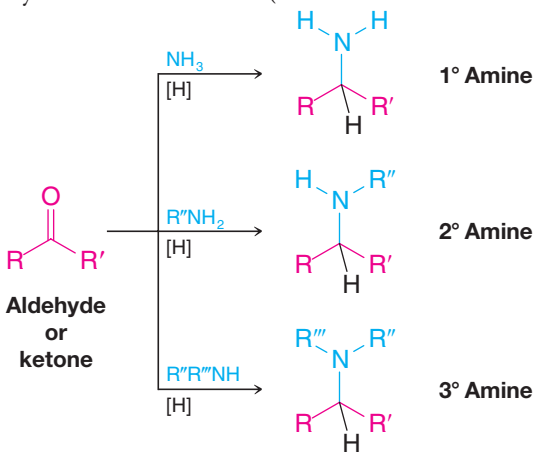

**(A mixture of products results.)**

**(R = a 1° alkyl group)**

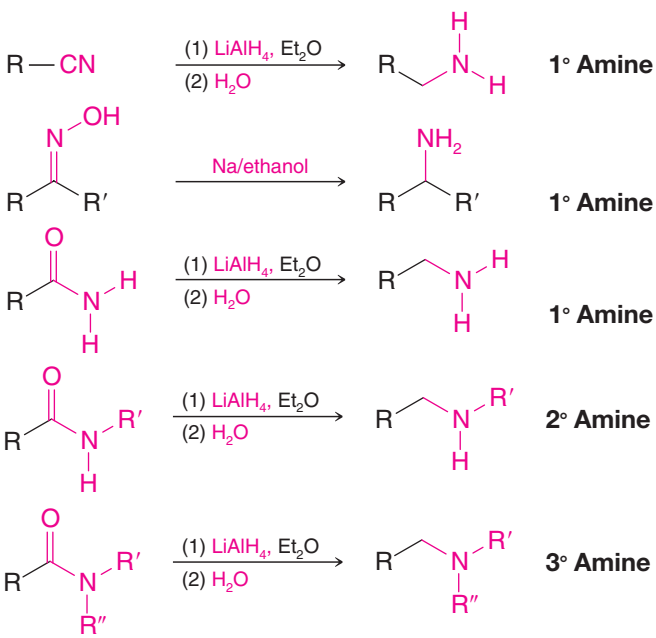
**4.** By reduction of nitroarenes (discussed in Section 20.4B):



**5.** By reductive amination (discussed in Section 20.4C):

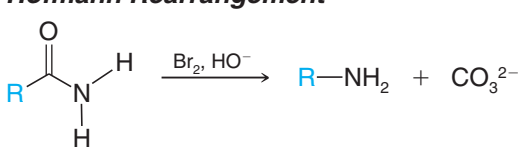



**6.** By reduction of nitriles, oximes, and amides (discussed in Section 20.4D):

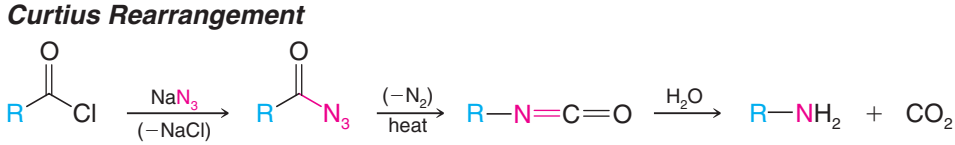



**7.** Through the Hofmann and Curtius rearrangements (discussed in Section 20.4E):

***Hofmann Rearrangement***

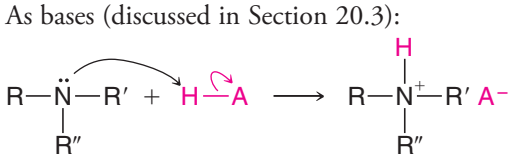



***Curtius Rearrangement***



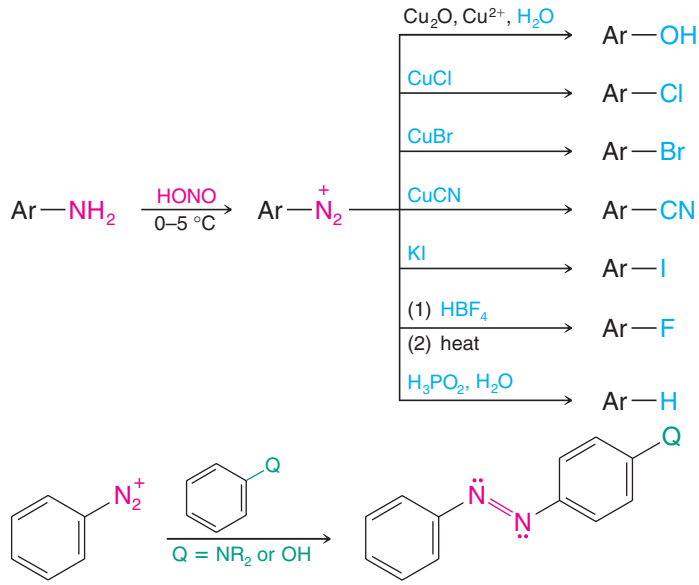

## REACTIONS OF AMINES

**1.** As bases (discussed in Section 20.3):

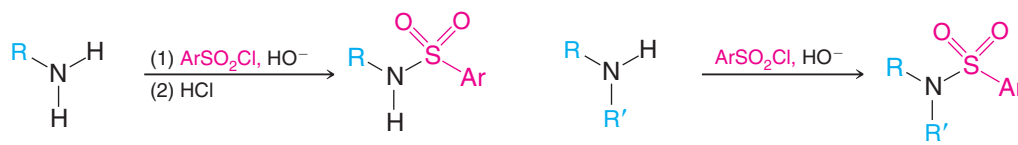


**(R, R′, and/or R″ may be alkyl, H, or Ar)**

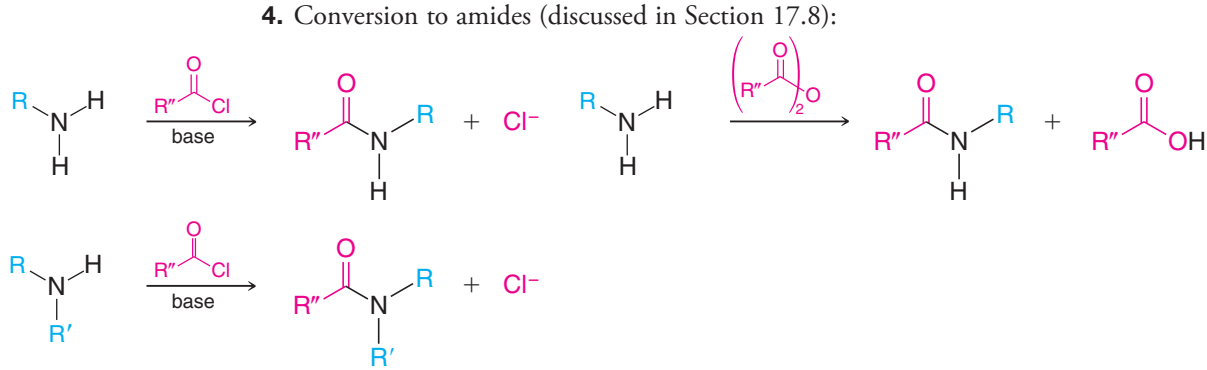
**2.** Diazotization of 1° arylamines and replacement of, or coupling with, the diazonium group (discussed in Sections 20.7 and 20.8):




**3.** Conversion to sulfonamides (discussed in Section 20.9):

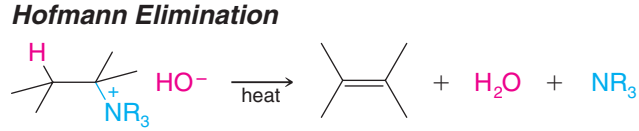



**4.** Conversion to amides (discussed in Section 17.8):

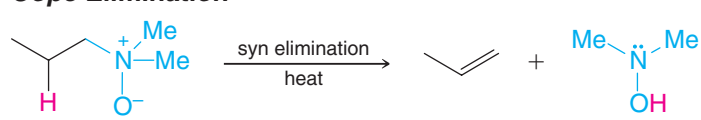



**5.** Hofmann and Cope eliminations (discussed in Section 20.12):

***Hofmann Elimination***




***Cope Elimination***



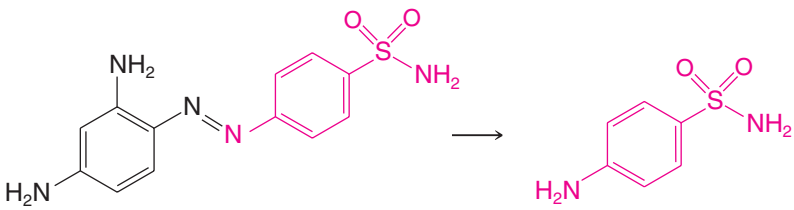

## WHY Do These Topics Matter? ]

### THE ORIGIN OF CHEMOTHERAPY AND SULFA DRUGS

Chemotherapy is defined as the use of chemical agents to destroy infectious or abnormal cells selectively without simultaneously destroying normal host cells. Although it may be difficult to believe in this age of wonder drugs, chemotherapy is a relatively modern phenomenon. Indeed, before 1900 there were only three specific remedies known for treating disease in any form: mercury (for syphilis, but with often disastrous results!), cinchona bark (i.e., quinine, for malaria), and ipecacuanha (for dysentery).

The term chemotherapy itself can be traced to a doctor named Paul Ehrlich. As a medical school student, Ehrlich had become impressed with the ability of certain dyes to stain tissues selectively. Believing that such staining was the result of a chemical reaction between the tissue and the dye, Ehrlich wondered whether it would be possible to identify dyes with selective affinities for microorganisms. He then hoped that he might be able to modify such dyes so that they could be specifically lethal to microorganisms but harmless to humans. He called such substances "magic bullets." In 1907, he discovered just such a substance in the form of a dye known as trypan red 1. This dye, which combated trypanosomiasis, led to his receipt of the 1908 Nobel Prize in Physiology or Medicine. In 1909, he followed up his initial discovery with a second magic bullet known as salvarsan, a remedy for syphilis, which contains aromatic amines in combination with arsenic atoms.

Paul Ehrlich's work in chemotherapy led to his sharing one-half of the 1908 Nobel Prize in Physiology or Medicine with Ilya Mechnikov.

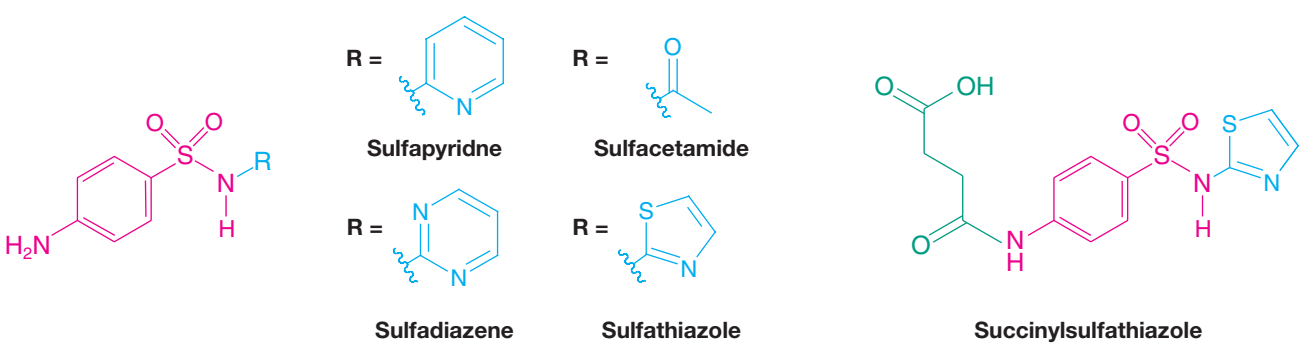


**Protosil** **Sulfanilamide**

With these powerful proofs of principle in hand, for the next several decades Ehrlich and many other scientists tested tens of thousands of chemicals (not just dyes) looking for additional magic bullets. Unfortunately, very few were found to have any promising effects. Then, in 1935, the daughter of Gerhard Domagk, a doctor employed by a German dye manufacturer (I. G. Farbenindustrie), contracted a streptococcal infection from a pinprick. As she neared death, Domagk decided to give her an oral dose of a dye called prontosil, a substance his firm had developed. In tests with mice prontosil had inhibited the growth of streptococci. Within a short time the little girl recovered. Domagk's gamble not only saved his daughter's life, but it also initiated a new and spectacularly modern phase in modem chemotherapy and ultimately led to his receipt of the Nobel Prize in Physiology or Medicine (1939).

Gerhard Domagk won the 1939 Nobel Prize in Physiology or Medicine for discovering the antibacterial effects of prontosil.

In 1936, Ernest Fourneau of the Pasteur Institute in Paris demonstrated that (1) prontosil breaks down in the human body to produce sulfanilamide, and (2) sulfanilamide is the actual active agent against streptococci. Prontosil, therefore, is a prodrug because it is converted into the active compound in vivo. Fourneau's announcement of these results set in motion a search for other chemicals related to sulfanilamide that might have even better chemotherapeutic effects. Literally thousands of chemical variations were played on the sulfanilamide theme; its structure was varied in almost every imaginable way. At the end, the best therapeutic agents were obtained from compounds in which one hydrogen of the $-SO_2NH_2$ group was replaced by some other group, usually a heterocyclic ring (shown in blue in the following structures). Among the most successful variations were the compounds shown below; sulfanilamide itself, ultimately, proved too toxic for general use.



**Sulfapyridne** **Sulfacetamide**

**Sulfadiazene** **Sulfathiazole** **Succinylsulfathiazole**

Sulfapyradine was shown to be effective against pneumonia in 1938; before that time, pneumonia epidemics had brought death to tens of thousands. Sulfacetamide was first used successfully in treating urinary tract infections in 1941. Succinylsulfathiazole and the related compound phthalylsulfathiazole were used as chemotherapeutics against infections of the gastrointestinal tract. Both compounds are hydrolyzed to sulfathiazole, a molecule that on its own saved the lives of countless soldiers in World War II.

# SUMMARY AND REVIEW TOOLS

The study aids for this chapter include key terms and concepts (which are highlighted in bold, blue text within the chapter and defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying *WileyPLUS* course (www.wileyplus.com), and the list of reaction types in Section 20.13.

# PROBLEMS

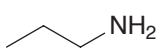
*Note to Instructors:* Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

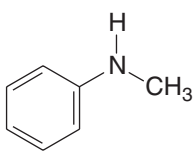
## NOMENCLATURE

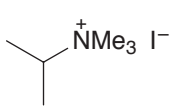
**20.19** Write structural formulas for each of the following compounds:

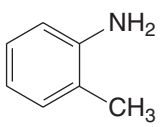
**(a)** Benzylmethylamine
**(b)** Triisopropylamine
**(c)** *N*-Ethyl-*N*-methylaniline
**(d)** *m*-Toluidine
**(e)** 2-Methylpyrrole
**(f)** *N*-Ethylpiperidine
**(g)** *N*-Ethylpyridinium bromide
**(h)** 3-Pyridinecarboxylic acid
**(i)** Indole
**(j)** Acetanilide
**(k)** Dimethylaminium chloride
**(l)** 2-Methylimidazole
**(m)** 3-Aminopropan-1-ol
**(n)** Tetrapropylammonium chloride
**(o)** Pyrrolidine
**(p)** *N*,*N*-Dimethyl-*p*-toluidine
**(q)** 4-Methoxyaniline
**(r)** Tetramethylammonium hydroxide
**(s)** *p*-Aminobenzoic acid
**(t)** *N*-Methylaniline

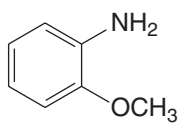
**20.20** Give common or systematic names for each of the following compounds:

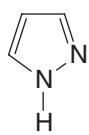
**(a)** 

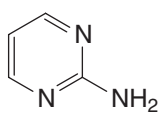

**(b)** 

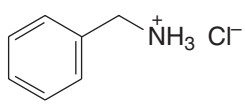

**(c)** 

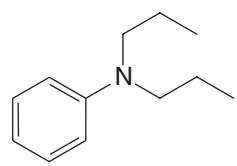

**(d)** 

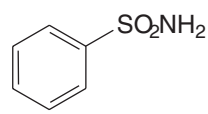

**(e)** 

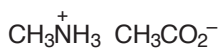

**(f)** 

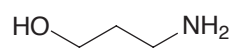

**(g)** 

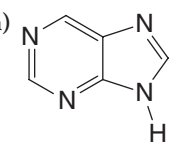

**(h)** 

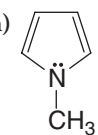

**(i)** 


**(j)** 


**(k)** 

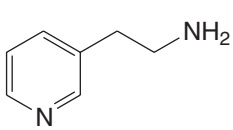

**(l)** 

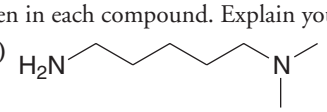

**(m)** 

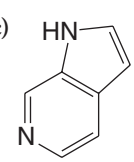

**(n)** 


## AMINE SYNTHESIS AND REACTIVITY

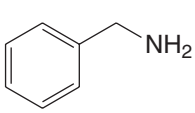
**20.21** Which is the most basic nitrogen in each compound. Explain your choices.

**(a)** 

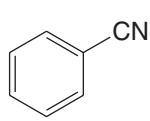

**(b)** 


**(c)** 

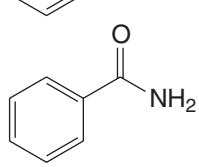

**20.22** Show how you might prepare benzylamine from each of the following compounds:



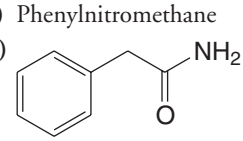

**Benzylamine**

**(a)** 


**Benzonitrile**

**(b)** 


**Benzamide**

**(c)** Benzyl bromide (two ways)
**(d)** Benzyl tosylate
**(e)** Benzaldehyde
**(f)** Phenylnitromethane
**(g)** 


**Phenylacetamide**

**20.23** Show how you might prepare aniline from each of the following compounds:

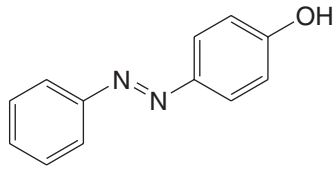
**(a)** Benzene **(b)** Bromobenzene **(c)** Benzamide

**20.24** Show how you might synthesize each of the following compounds from 1-butanol:

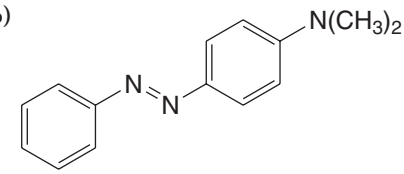
**(a)** Butylamine (free of 2° and 3° amines) **(b)** Pentylamine **(c)** Propylamine **(d)** Butylmethylamine

**20.25** Show how you might convert aniline into each of the following compounds. (You need not repeat steps carried out in earlier parts of this problem.)

**(a)** Acetanilide
**(b)** *N*-Phenylphthalimide
**(c)** *p*-Nitroaniline
**(d)** Sulfanilamide
**(e)** *N*,*N*-Dimethylaniline
**(f)** Fluorobenzene
**(g)** Chlorobenzene
**(h)** Bromobenzene
**(i)** Iodobenzene
**(j)** Benzonitrile
**(k)** Benzoic acid
**(l)** Phenol
**(m)** Benzene
**(n)**

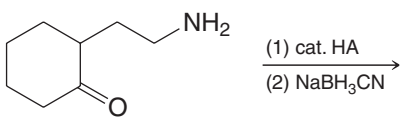



**(o)**

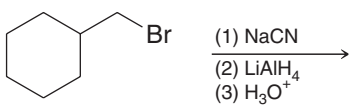



**20.26** Provide the major organic product from each of the following reactions.

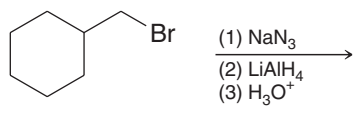
**(a)**



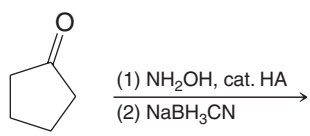

**(b)**



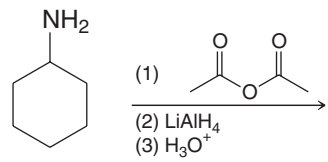

**(c)**




**(d)**




**(e)**



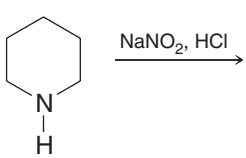

**20.27** What products would you expect to be formed when each of the following amines reacts with aqueous sodium nitrite and hydrochloric acid?

**(a)** Propylamine **(b)** Dipropylamine **(c)** *N*-Propylaniline **(d)** *N*,*N*-Dipropylaniline **(e)** *p*-Propylaniline

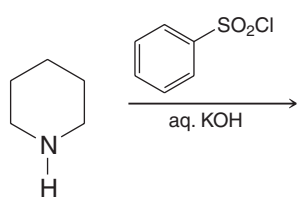
**20.28** **(a)** What products would you expect to be formed when each of the amines in the preceding problem reacts with benzenesulfonyl chloride and excess aqueous potassium hydroxide? **(b)** What would you observe in each reaction? **(c)** What would you observe when the resulting solution or mixture is acidified?

**20.29** What product would you expect to obtain from each of the following reactions?

**(a)**

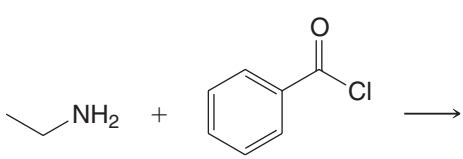



**(b)**

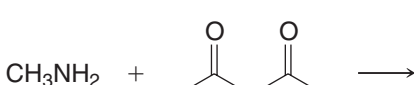



**20.30** Give structures for the products of each of the following reactions:

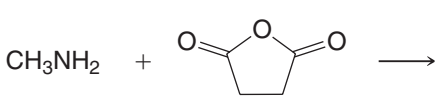
**(a)**




**(b)**

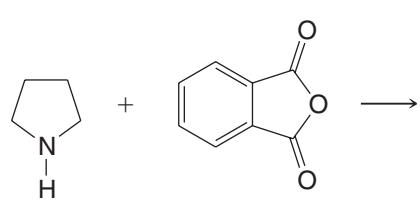



**(c)**

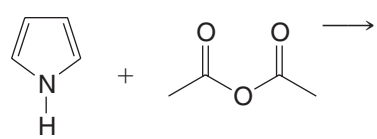



**(d)** Product of (c) $\xrightarrow{\text{heat}}$

**(e)**




**(f)**




**(g)** Aniline + propanoyl chloride $\longrightarrow$

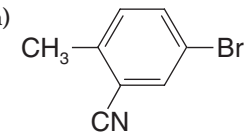
**(h)** Tetraethylammonium hydroxide $\xrightarrow{\text{heat}}$

**(i)** *p*-Toluidine + $Br_2$ (excess) $\xrightarrow{H_2O}$

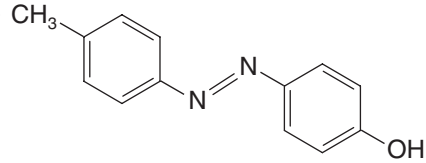
**20.31** Starting with benzene or toluene, outline a synthesis of each of the following compounds using diazonium salts as intermediates. (You need not repeat syntheses carried out in earlier parts of this problem.)

**(a)** *p*-Fluorotoluene
**(b)** *o*-Iodotoluene
**(c)** *p*-Cresol
**(d)** *m*-Dichlorobenzene
**(e)** *m*-$C_6H_4(CN)_2$
**(f)** *m*-Bromobenzonitrile
**(g)** 1,3-Dibromo-5-nitrobenzene
**(h)** 3,5-Dibromoaniline
**(i)** 3,4,5-Tribromophenol
**(j)** 3,4,5-Tribromobenzonitrile
**(k)** 2,6-Dibromobenzoic acid
**(l)** 1,3-Dibromo-2-iodobenzene

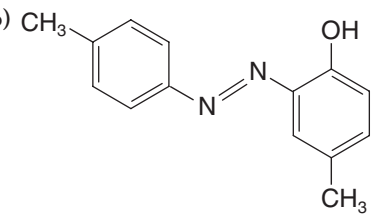
**(m)**




**(n)**




**(o)**



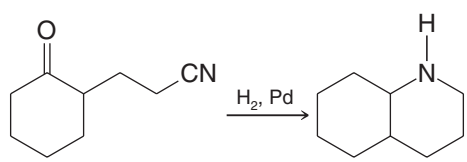

**20.32** Write equations for simple chemical tests that would distinguish between

**(a)** Benzylamine and benzamide
**(b)** Allylamine and propylamine
**(c)** *p*-Toluidine and *N*-methylaniline
**(d)** Cyclohexylamine and piperidine
**(e)** Pyridine and benzene
**(f)** Cyclohexylamine and aniline
**(g)** Triethylamine and diethylamine
**(h)** Tripropylaminium chloride and tetrapropylammonium chloride
**(i)** Tetrapropylammonium chloride and tetrapropylammonium hydroxide

**20.33** Describe with equations how you might separate a mixture of aniline, *p*-cresol, benzoic acid, and toluene using ordinary laboratory reagents.

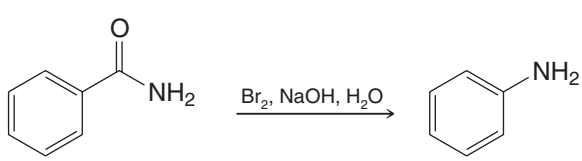
## MECHANISMS

**20.34** Using reactions that we have studied in this chapter, propose a mechanism that accounts for the following reaction:

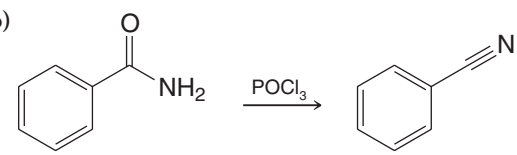



**20.35** Provide a detailed mechanism for each of the following reactions.

**(a)**



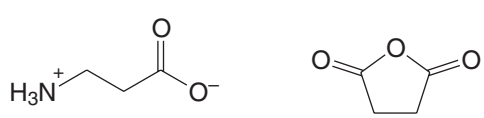

**(b)**




**20.36** Suggest an experiment to test the proposition that the Hofmann reaction is an intramolecular rearrangement—that is, one in which the migrating R group never fully separates from the amide molecule.

## GENERAL SYNTHESIS

**20.37** Show how you might synthesize β-aminopropionic acid from succinic anhydride. (β-Aminopropionic acid is used in the synthesis of pantothenic acid, a precursor of coenzyme A.)



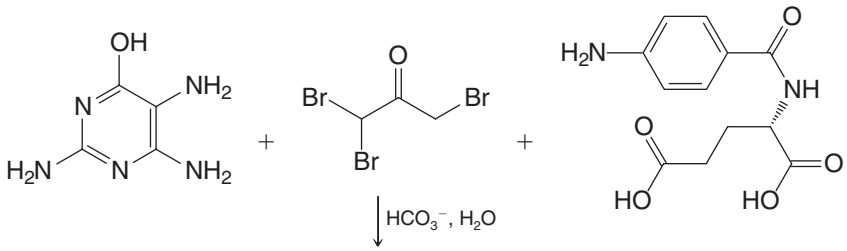

**β-Aminopropanoic acid** **Succinic anhydride**

**20.38** Show how you might synthesize each of the following from the compounds indicated and any other needed reagents:

**(a)** $Me_3N^+$ $(CH_2)_{10}$ $N^+Me_3$ $2Br^-$ from 1,10-decanediol

**(b)** Succinylcholine bromide (see "The Chemistry of…Biologically Important Amines" in Section 20.3) from succinic acid, 2-bromoethanol, and trimethylamine

**20.39** A commercial synthesis of folic acid consists of heating the following three compounds with aqueous sodium bicarbonate. Propose reasonable mechanisms for the reactions that lead to folic acid. *Hint:* The first step involves formation of an imine between the lower right $NH_2$ group of the heterocyclic amine and the ketone.



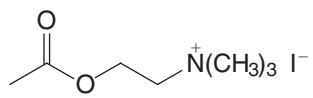

**Folic acid (~10%)**

**20.40** Give structures for compounds **R**–**W**:

*N*-Methylpiperidine $\xrightarrow{CH_3I}$ **R** ($C_7H_{16}NI$) $\xrightarrow[H_2O]{Ag_2O}$ **S** ($C_7H_{17}NO$) $\xrightarrow[\text{heat}]{(-H_2O)}$

**T** ($C_7H_{15}N$) $\xrightarrow{CH_3I}$ **U** ($C_5H_{18}NI$) $\xrightarrow[H_2O]{Ag_2O}$ **V** ($C_8H_{19}NO$) $\xrightarrow{\text{heat}}$ **W** ($C_5H_8$) + $H_2O$ + $(CH_3)_3N$

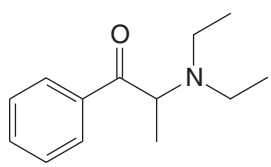
**20.41** Outline a synthesis of acetylcholine iodide using dimethylamine, oxirane, iodomethane, and acetyl chloride as starting materials.




**Acetylcholine iodide**

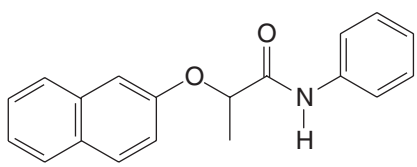
**20.42** Ethanolamine, $HOCH_2CH_2NH_2$, and diethanolamine, $(HOCH_2CH_2)_2NH$, are used commercially to form emulsifying agents and to absorb acidic gases. Propose syntheses of these two compounds.

**20.43** Diethylpropion (shown here) is a compound used in the treatment of anorexia. Propose a synthesis of diethylpropion starting with benzene and using any other needed reagents.




**Diethylpropion**

**20.44** Using as starting materials 2-chloropropanoic acid, aniline, and 2-naphthol, propose a synthesis of naproanilide, a herbicide used in rice paddies in Asia:




**Naproanilide**

## SPECTROSCOPY

**20.45** When compound **W** ($C_{15}H_{17}N$) is treated with benzenesulfonyl chloride and aqueous potassium hydroxide, no apparent change occurs. Acidification of this mixture gives a clear solution. The $^1H$ NMR spectrum of **W** is shown in Fig. 20.6. Propose a structure for **W**.

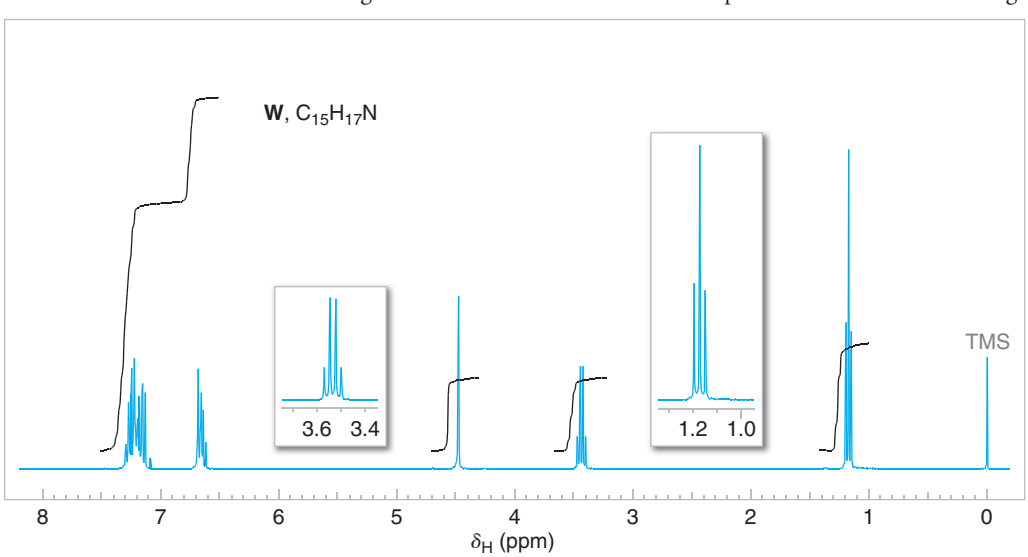



**FIGURE 20.6** The 300-MHz $^1H$ NMR spectrum of compound W, Problem 20.45. Expansions of the signals are shown in the offset plots.

**20.46** Propose structures for compounds **X**, **Y**, and **Z**:

$$\mathbf{X}\ (C_7H_7Br) \xrightarrow{NaCN} \mathbf{Y}\ (C_8H_7N) \xrightarrow{LiAlH_4} \mathbf{Z}\ (C_8H_{11}N)$$

The $^1$H NMR spectrum of **X** gives two signals, a multiplet at $\delta$ 7.3 (5H) and a singlet at $\delta$ 4.25 (2H); the 680–840-cm$^{-1}$ region of the IR spectrum of **X** shows peaks at 690 and 770 cm$^{-1}$. The $^1$H NMR spectrum of **Y** is similar to that of **X**: multiplet at $\delta$ 7.3 (5H), singlet at $\delta$ 3.7 (2H). The $^1$H NMR spectrum of **Z** is shown in Fig. 20.7.

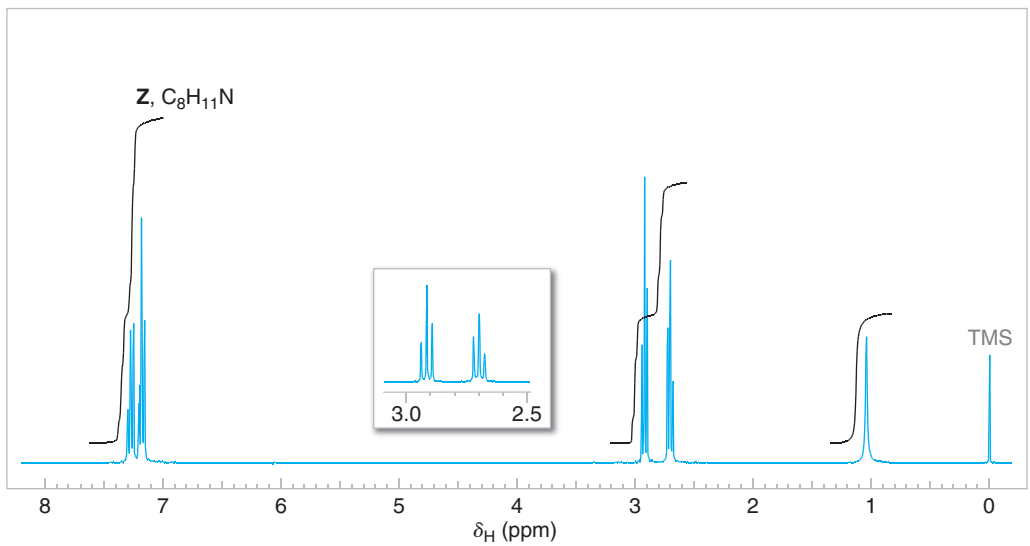



**FIGURE 20.7** The 300-MHz $^1$H NMR spectrum of compound Z, Problem 20.46. Expansion of the signals is shown in the offset plot.

**20.47** Compound **A** ($C_{10}H_{15}N$) is soluble in dilute HCl. The IR absorption spectrum shows two bands in the 3300–3500-cm$^{-1}$ region. The broadband proton-decoupled $^{13}$C spectrum of **A** is given in Fig. 20.8. Propose a structure for **A**.

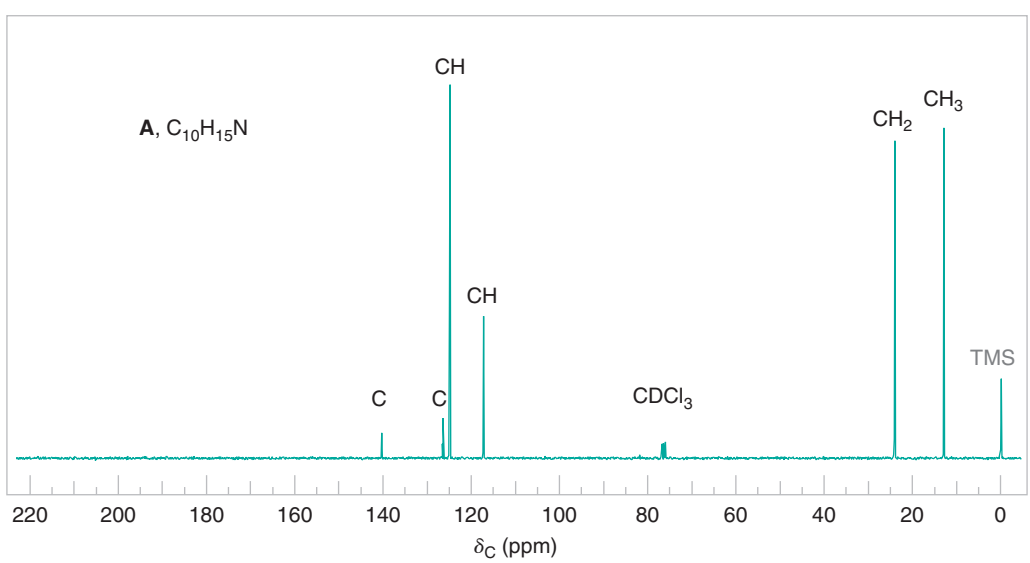
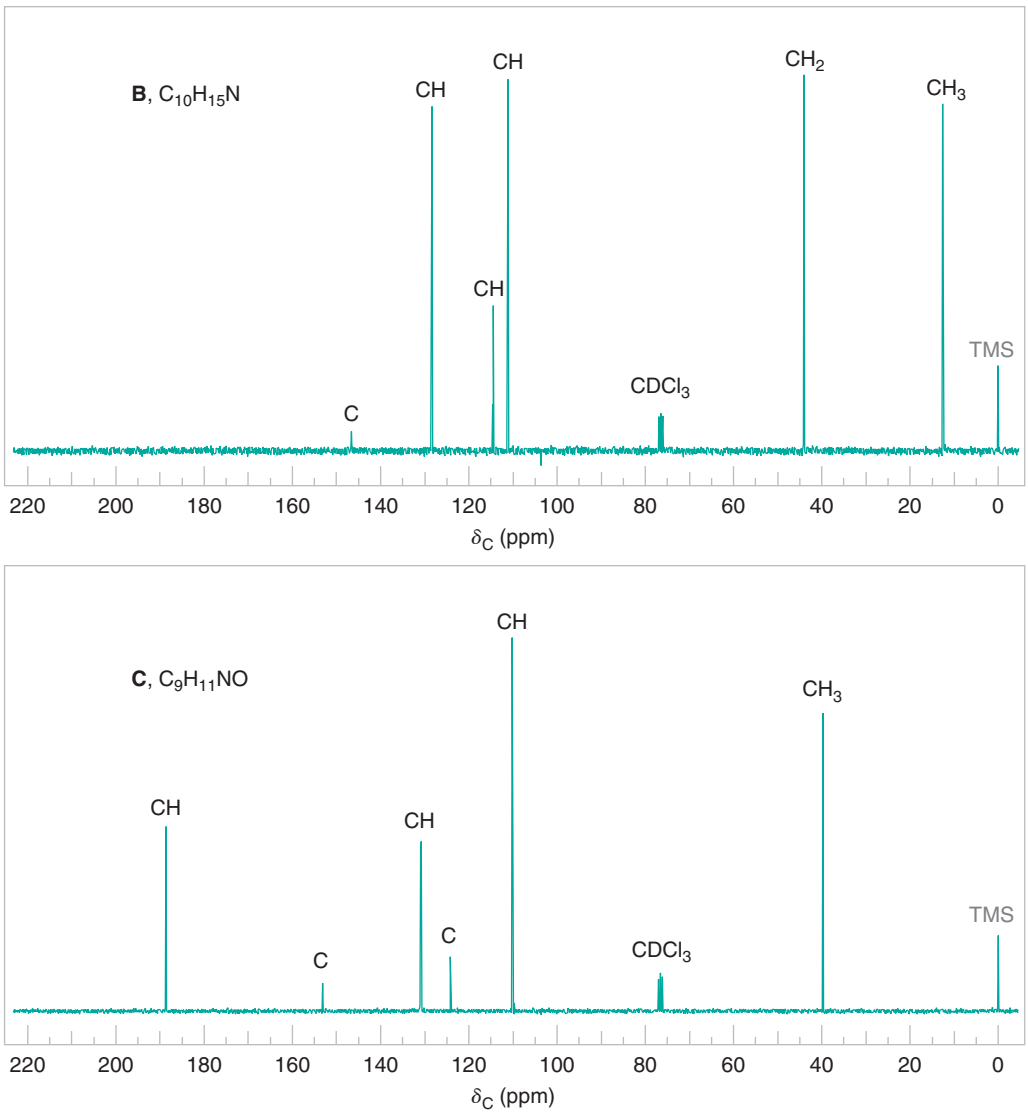



**FIGURE 20.8** The broadband proton-decoupled $^{13}$C NMR spectra of compounds A, B, and C, Problems 20.47–20.49. Information from the DEPT $^{13}$C NMR spectra is given above each peak.

**FIGURE 20.8** *(continued)*




**20.48** Compound **B,** an isomer of **A** (Problem 20.47), is also soluble in dilute HCl. The IR spectrum of **B** shows no bands in the 3300–3500-$cm^{-1}$ region. The broadband proton-decoupled $^{13}C$ spectrum of **B** is given in Fig. 20.8. Propose a structure for **B**.

**20.49** Compound **C** ($C_9H_{11}NO$) gives a positive Tollens' test (can be oxidized to a carboxylic acid) and is soluble in dilute HCl. The IR spectrum of **C** shows a strong band near 1695 $cm^{-1}$ but shows no bands in the 3300–3500-$cm^{-1}$ region. The broadband proton-decoupled $^{13}C$ NMR spectrum of **C** is shown in Fig. 20.8. Propose a structure for **C**.

## CHALLENGE PROBLEMS

**20.50** When phenyl isothiocyanate, $C_6H_5N{=}C{=}S$, is reduced with lithium aluminum hydride, the product formed has these spectral data:

**MS** (*m/z*): 107, 106

**IR** ($cm^{-1}$): 3330 (sharp), 3050, 2815, 760, 700

**$^1$H NMR** ($\delta$): 2.7 (s, 3H), 3.5 (broad, 1H), 6.6 ($\delta$, 2H), 6.7 (t, 1H) 7.2 (t, 2H)

**$^{13}$C NMR** ($\delta$): 30 ($CH_3$), 112 (CH), 117 (CH), 129 (CH), 150 (C)

**(a)** What is the structure of the product?

**(b)** What is the structure that accounts for the 106 *m/z* peak and how is it formed? (It is an iminium ion.)

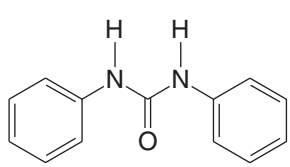
**20.51** When *N*,*N*′-diphenylurea **(A)** is reacted with tosyl chloride in pyridine, it yields product **B**. The spectral data for **B** include:

**MS** (*m/z*): 194 ($M^{+\cdot}$)

**IR** ($cm^{-1}$): 3060, 2130, 1590, 1490, 760, 700

**$^1$H NMR** ($\delta$): only 6.9–7.4 (m)

**$^{13}$C NMR** ($\delta$): 122 (CH), 127 (CH), 130 (CH), 149 (C), and 163 (C)

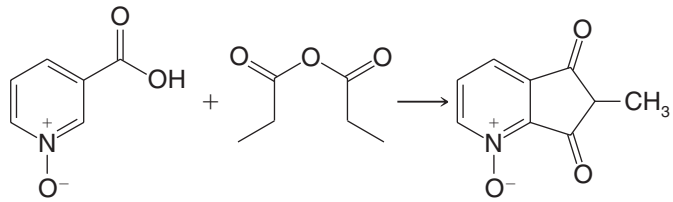



**A**

**(a)** What is the structure of **B**?

**(b)** Write a mechanism for the formation of **B**.

**20.52** Propose a mechanism that can explain the occurrence of this reaction:



**20.53** When acetone is treated with anhydrous ammonia in the presence of anhydrous calcium chloride (a common drying agent), crystalline product **C** is obtained on concentration of the organic liquid phase of the reaction mixture. These are spectral data for product **C**:

**MS** (*m/z*): 155 ($M^{+\cdot}$), 140

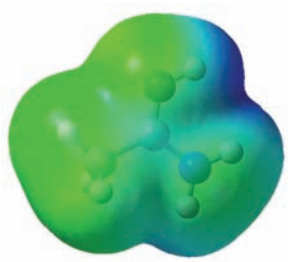
**IR** ($cm^{-1}$): 3350 (sharp), 2850–2960, 1705

**$^1$H NMR** ($\delta$): 2.3 (s, 4H), 1.7 (1H; disappears in $D_2O$), and 1.2 (s, 12H)

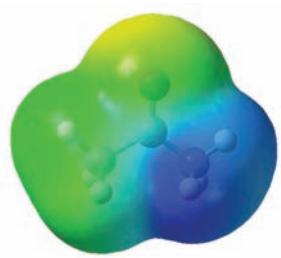
**(a)** What is the structure of **C**?

**(b)** Propose a mechanism for the formation of **C**.

**20.54** The difference in positive-charge distribution in an amide that accepts a proton on its oxygen or its nitrogen atom can be visualized with electrostatic potential maps. Consider the electrostatic potential maps for acetamide in its O—H and N—H protonated forms shown below. On the basis of the electrostatic potential maps, which protonated form appears to delocalize, and hence stabilize, the formal positive charge more effectively? Discuss your conclusion in terms of resonance contributors for the two possible protonated forms of acetamide.



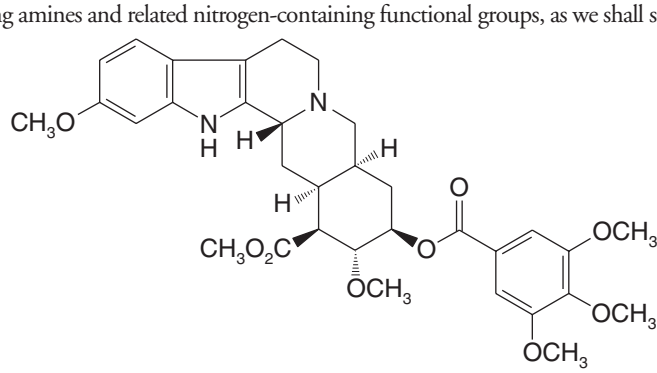
**Acetamide protonated on oxygen**



**Acetamide protonated on nitrogen**

## LEARNING GROUP PROBLEMS

**1.** Reserpine is a natural product belonging to the family of alkaloids (see Special Topic F in *WileyPLUS*). Reserpine was isolated from the Indian snakeroot *Rauwolfia serpentina*. Clinical applications of reserpine include treatment of hypertension and nervous and mental disorders. The synthesis of reserpine, which contains six chirality centers, was a landmark accomplishment reported by R. B. Woodward in 1955. Incorporated in the synthesis are several reactions involving amines and related nitrogen-containing functional groups, as we shall see on the following page.

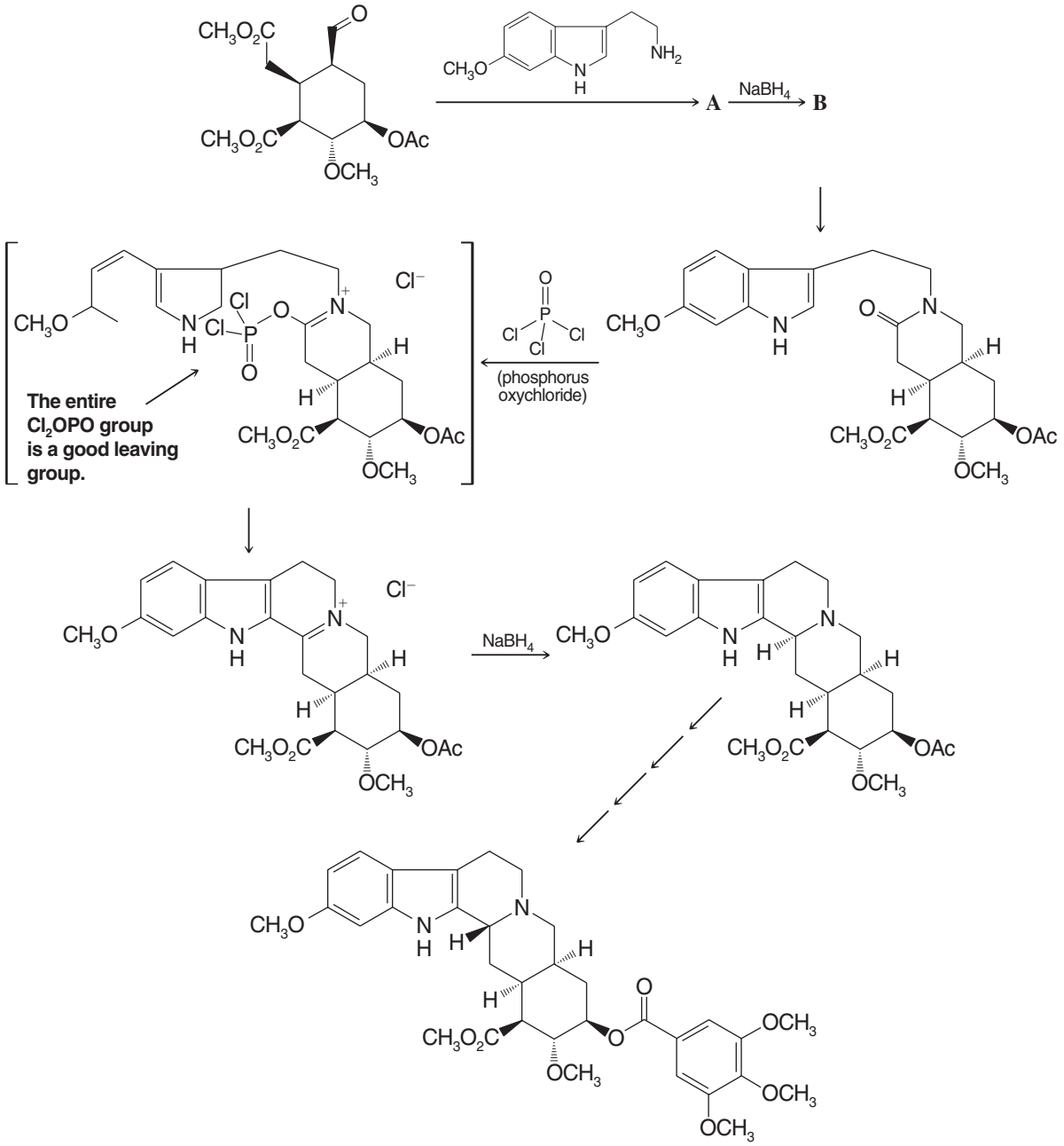


**Reserpine**

**(a)** The goal of the first two steps shown in the scheme on the following page, prior to formation of the amide, is preparation of a secondary amine. Draw the structure of the products labeled **A** and **B** from the first and second reactions, respectively. Write a mechanism for formation of **A**.

**(b)** The next sequence of reactions involves formation of a tertiary amine together with closure of a new ring. Write curved arrows to show how the amide functional group reacts with phosphorus oxychloride ($POCl_3$) to place the leaving group on the bracketed intermediate.

**(c)** The ring closure from the bracketed intermediate involves a type of electrophilic aromatic substitution reaction characteristic of indole rings. Identify the part of the structure that contains the indole ring. Write mechanism arrows to show how the nitrogen in the indole ring, via conjugation, can cause electrons from the adjacent carbon to attack an electrophile. In this case, the attack by the indole ring in the bracketed intermediate is an addition–elimination reaction, somewhat like reactions that occur at carbonyls bearing leaving groups.




**Reserpine**

**2.** **(a)** A student was given a mixture of two unknown compounds and asked to separate and identify them. One of the compounds was an amine and the other was a neutral compound (neither appreciably acidic nor basic). Describe how you would go about separating the unknown amine from the neutral compound using extraction techniques involving diethyl ether and solutions of aqueous 5% HCl and 5% $NaHCO_3$. The mixture as a whole was soluble in diethyl ether, but neither component was soluble in water at pH 7. Using R groups on a generic amine, write out the reactions for any acid–base steps you propose and explain why the compound of interest will be in the ether layer or aqueous layer at any given time during the process.

**(b)** Once the amine was successfully isolated and purified, it was reacted with benzenesulfonyl chloride in the presence of aqueous potassium hydroxide. The reaction led to a solution that on acidification produced a precipitate. The results just described constitute a test (Hinsberg's) for the class of an amine. What class of amine was the unknown compound: primary, secondary, or tertiary? Write the reactions involved for a generic amine of the class you believe this one to be.

**(c)** The unknown amine was then analyzed by IR, NMR, and MS. The following data were obtained. On the basis of this information, deduce the structure of the unknown amine. Assign the spectral data to specific aspects of the structure you propose for the amine.

**IR** ($cm^{-1}$): 3360, 3280, 3020, 2962, 1604, 1450, 1368, 1021, 855, 763, 700, 538
**$^1$H NMR** ($\delta$): 1.35 (d, 3H), 1.8 (bs, 2H), 4.1 (q, 1H), 7.3 (m, 5H)
**MS** (*m/z*): 121, 120, 118, 106 (base peak), 79, 77, 51, 44, 42, 28, 18, 15

See Special Topic F in *WileyPLUS*