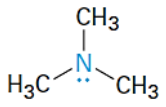
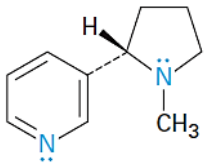
Amines and Heterocycles

Amines are organic derivatives of ammonia Like ammonia, amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic. in fact, that most of the chemistry of amines depends on the presence of this lone pair of electrons.

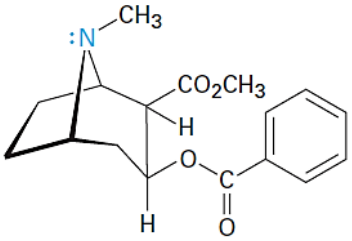
Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish; nicotine is found in tobacco; and cocaine is a stimulant found in the leaves of the South American coca bush. In addition, amino acids are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



Trimethylamine



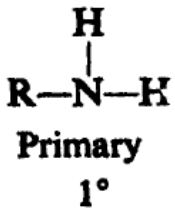
Nicotine



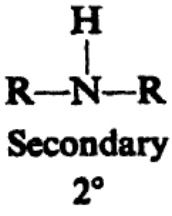
Cocaine

Classification

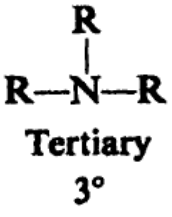
An amine has the general formula RNH_2 , R_2NH, or R_3N, where R is any alkyl or aryl group. Amines are classified as primary, secondary, or tertiary, according to the number of groups attached to the nitrogen atom.



Primary
1°



Secondary
2°



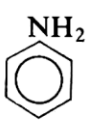
Tertiary
3°

CH_3NH_2
Methylamine
(1°)

$(CH_3)_2NH$
Dimethylamine
(2°)

$(CH_3)_3N$
Trimethylamine
(3°)

$H_2NCH_2CH_2NH_2$
Ethylenediamine
(1°)

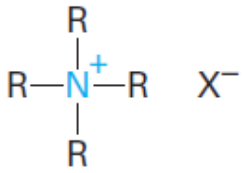


Aniline
(1°)

N-Methylaniline
(2°)

N,*N*-Dimethylaniline
(3°)

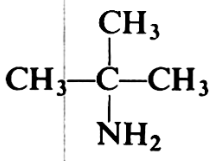
Compounds containing a nitrogen atom with four attached groups also exist, but nitrogen atom must carry a formal positive charge. Such compounds are the called quaternary ammonium salts.



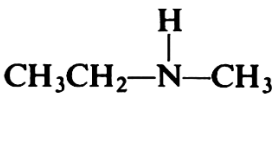
A quaternary ammonium salt

Nomenclature

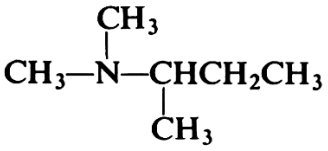
Aliphatic amines are named by naming the alkyl group or groups attached to nitrogen, and following these by the word *-amine*. More complicated ones are often named by prefixing *amino-* (or *N-methylamino-*, *N,N-diethylamino-*, etc.) to the name of the parent chain. For example:



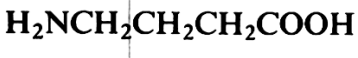
tert-Butylamine
(1°)



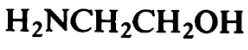
Ethylmethylamine
(2°)



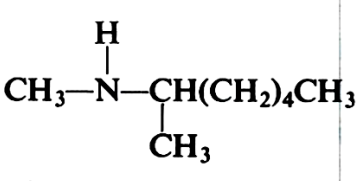
sec-Butyldimethylamine
(3°)



γ-Aminobutyric acid
(1°)

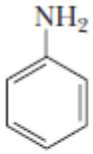


2-Aminoethanol
(Ethanolamine)
(1°)

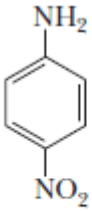


2-(*N*-Methylamino)heptane
(2°)

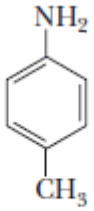
Aromatic amines—those in which nitrogen is attached directly to an aromatic ring—are generally named as derivatives of the simplest aromatic amine, **aniline**. An aminotoluene is given the special name of *toluidine*. For example:



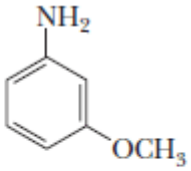
Aniline



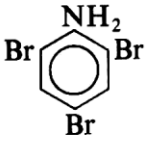
4-Nitroaniline
(*p*-Nitroaniline)



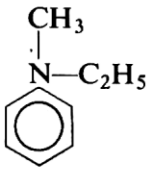
4-Methylaniline
(*p*-Toluidine)



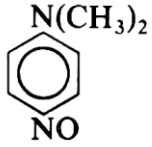
3-Methoxyaniline
(*m*-Anisidine)



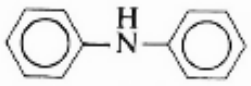
2,4,6-Tribromoaniline
(1°)



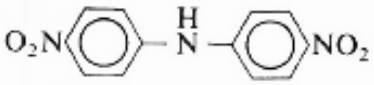
N-Ethyl-*N*-methylaniline
(3°)



p-Nitroso-*N*,*N*-dimethylaniline
(3°)

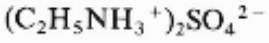


Diphenylamine
(2°)



4,4'-Dinitrodiphenylamine
(2°)

Salts of amines are generally named by replacing *-amine* by *-ammonium* (or *-aniline* by *-anilinium*), and adding the name of the anion (*chloride*, *nitrate*, *sulfate*, etc.). For example:

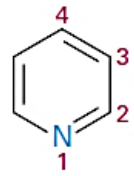


Ethylammonium sulfate

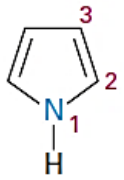
Trimethylammonium nitrate

Anilinium chloride

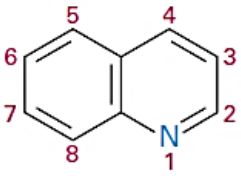
Heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.



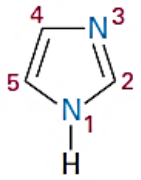
Pyridine



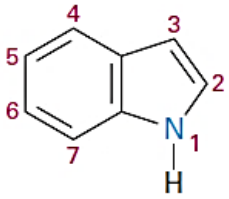
Pyrrole



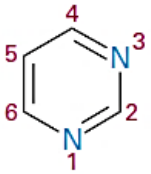
Quinoline



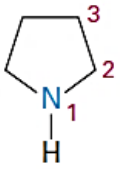
Imidazole



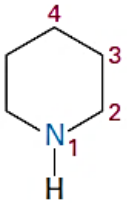
Indole



Pyrimidine



Pyrrolidine



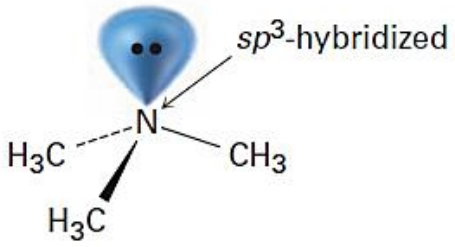
Piperidine

Saturated heterocyclic amines usually have the same chemistry as their open-chain analogs, but unsaturated heterocycles such as pyrrole, imidazole, pyridine, and pyrimidine are aromatic. All four are unusually stable, and all undergo aromatic substitution on reaction with electrophiles Fused-ring heterocycles such as quinoline, isoquinoline, indole, and purine are also commonly found in biological molecules.

Structure and Properties of Amines

The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp3-hybridized, with the three substituents occupying three corners of a regular tetrahedron and the lone pair of electrons occupying the fourth corner. As you might expect, the C - N -C bond angles are close to the 109° tetrahedral value.

For trimethylamine, the C - N - C bond angle is 108° and the C - N bond length is 147 pm

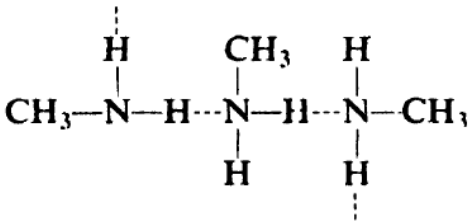


Trimethylamine

The chemistry of amines is dominated by the lone-pair electrons on nitrogen, which makes amines both basic and nucleophilic

Physical properties of amines

Like ammonia, amines are polar compounds and, except for tertiary amines, can form intermolecular hydrogen bonds. Amines have higher boiling points

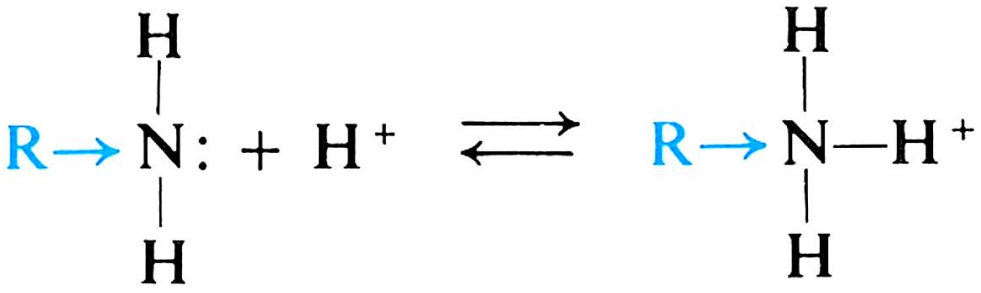


than non-polar compounds of the same molecular weight, but lower boiling points than alcohols or carboxylic acids. Amines of all three classes are capable of forming hydrogen bonds with water. As a result, smaller amines are quite soluble in water, with borderline solubility
being reached at about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene, etc. The methylamines and ethylamines smell very much like ammonia; the higher alkylamines have decidedly "fishy" odors.
being reached at about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene, etc. The methylamines and ethylamines smell very much like ammonia; the higher alkylamines have decidedly "fishy" odors.

Aromatic amines are generally very toxic; they are readily absorbed through the skin, often with fatal results.
Aromatic amines are very easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.

Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. They react with acids to form acid– base salts, and they react with electrophiles in many of the polar reactions.

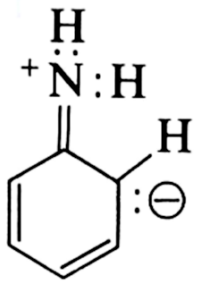


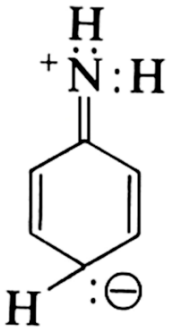
R releases electrons: makes unshared pair more available

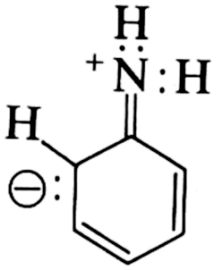
R releases electrons: stabilizes ion, increases basicity

Weaker base Smaller p*K*a for ammonium ion
Stronger base Larger p*K*a for ammonium ion

The basicity of arylamines is generally lower than that of alkylamines because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic ring π electron system and are less available for bonding to H^+

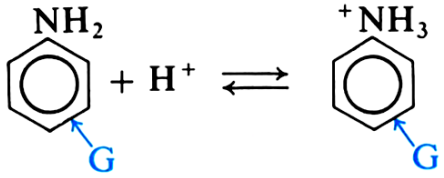






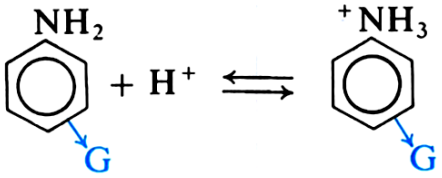
23.4 Effect of substituents on basicity of aromatic amines

Basicity of aromatic amines



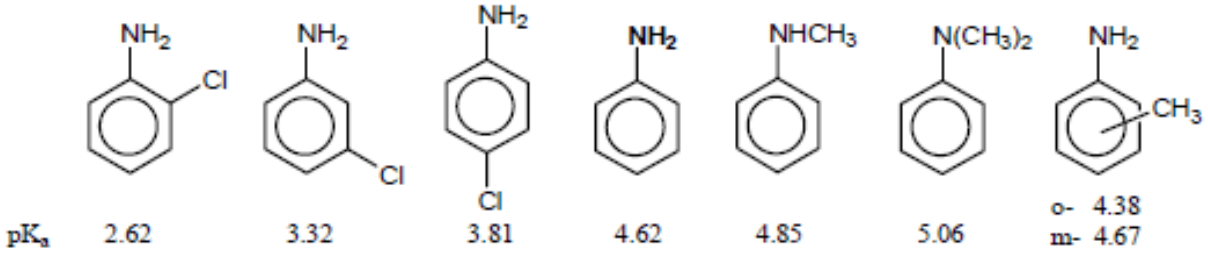
G *releases electrons:*
stabilizes cation,
increases basicity

G = —NH_2
—OCH_3
—CH_3



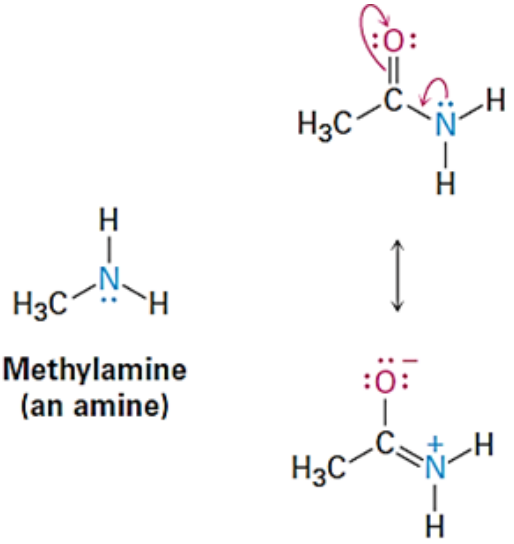
G *withdraws electrons:*
destabilizes cation,
decreases basicity

G = —NH_3^+
—NO_2
—SO_3^-
—COOH
—X

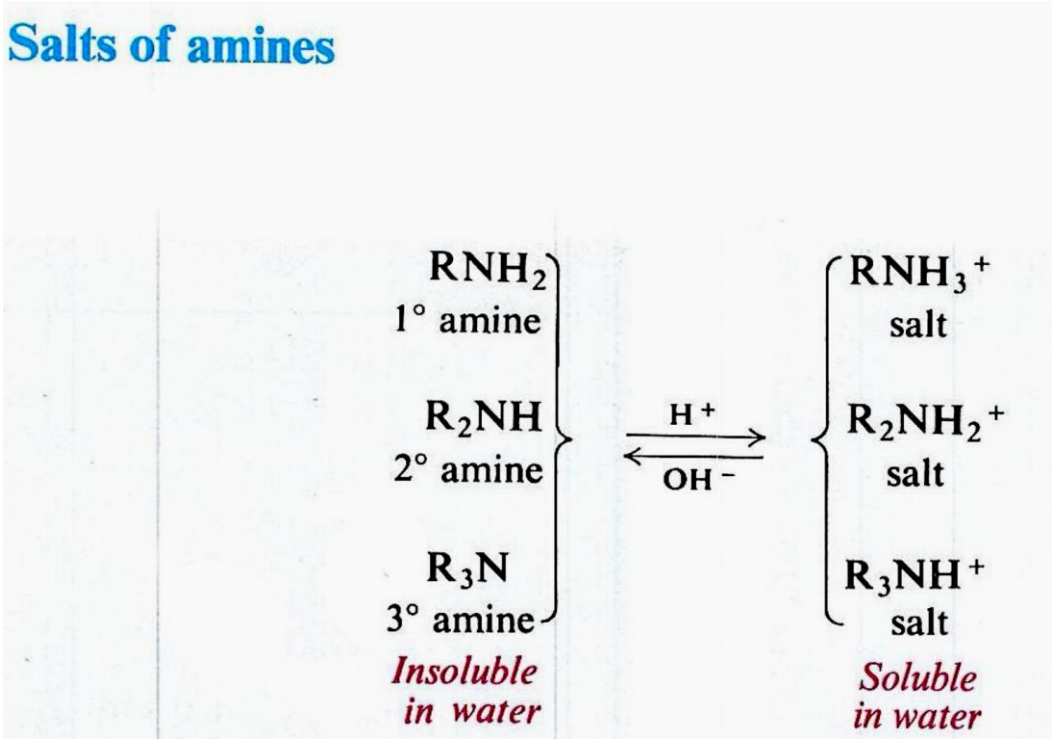


Conjugate-acid للحمض المرافق pK_a قيم

In contrast with amines, amides ($RCONH_2$) are nonbasic..



Salts of amines

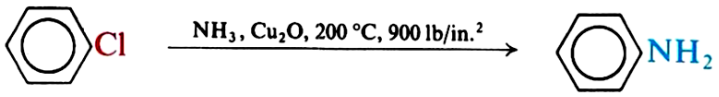


Industrial source

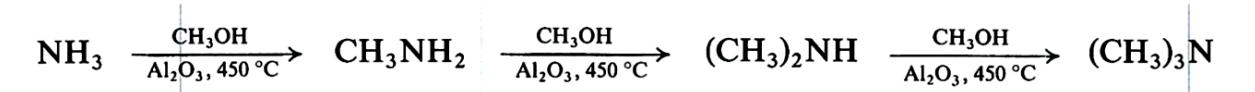
Some of the simplest and most important amines are prepared on an industrial scale by processes that are not practicable as laboratory methods.

The most important of all amines, **aniline**, is prepared in several ways: (a) reduction of nitrobenzene by the cheap reagents, iron and dilute hydrochloric acid (or by catalytic hydrogenation, Sec. 22.9); (b) treatment of chlorobenzene with

Nitrobenzene — Anilinium chloride — Aniline

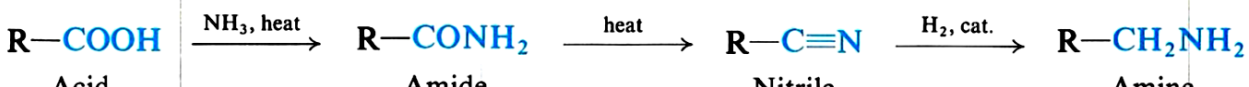


Chlorobenzene — Aniline



Ammonia — Methylamine — Dimethylamine — Trimethylamine

Alkyl halides are used to make some higher alkylamines, just as in the laboratory (Sec. 22.10). The acids obtained from fats (Sec. 33.5) can be converted into long-chain 1-aminoalkanes of even carbon number via reduction of nitriles (Sec. 22.8).



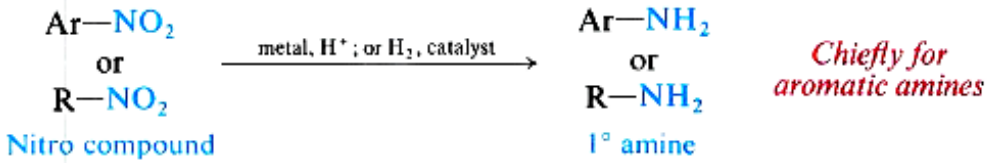
Acid — Amide — Nitrile — Amine

22.8 Preparation

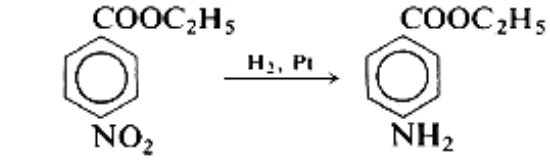
Some of the many methods that are used to prepare amines in the laboratory are outlined on the following pages.

PREPARATION OF AMINES

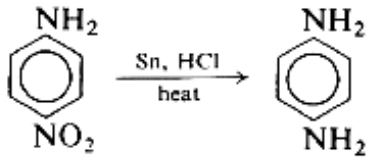
1. Reduction of nitro compounds. Discussed in Sec. 22.9.



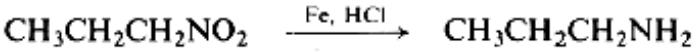
Examples:



Ethyl *p*-nitrobenzoate — Ethyl *p*-aminobenzoate

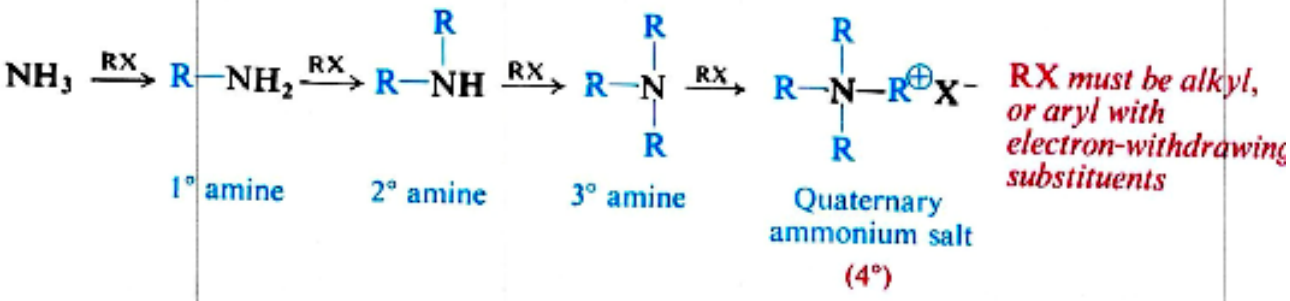


p-Nitroaniline — *p*-Phenylenediamine



1-Nitropropane — *n*-Propylamine

2. Reaction of halides with ammonia or amines. Discussed in Secs. 22.10 and 22.13.



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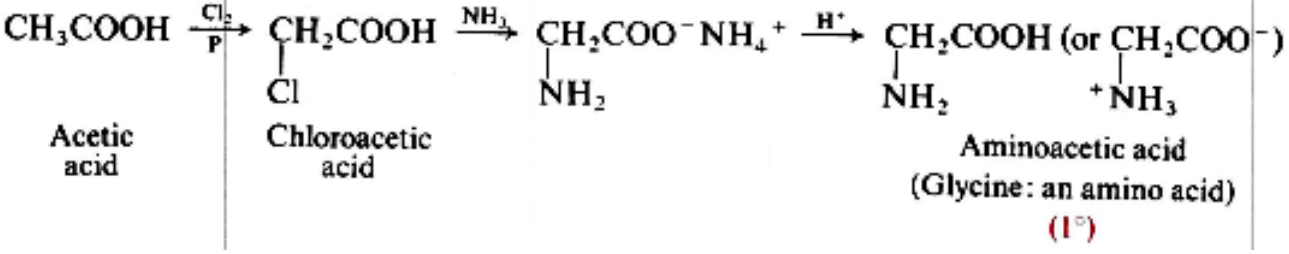
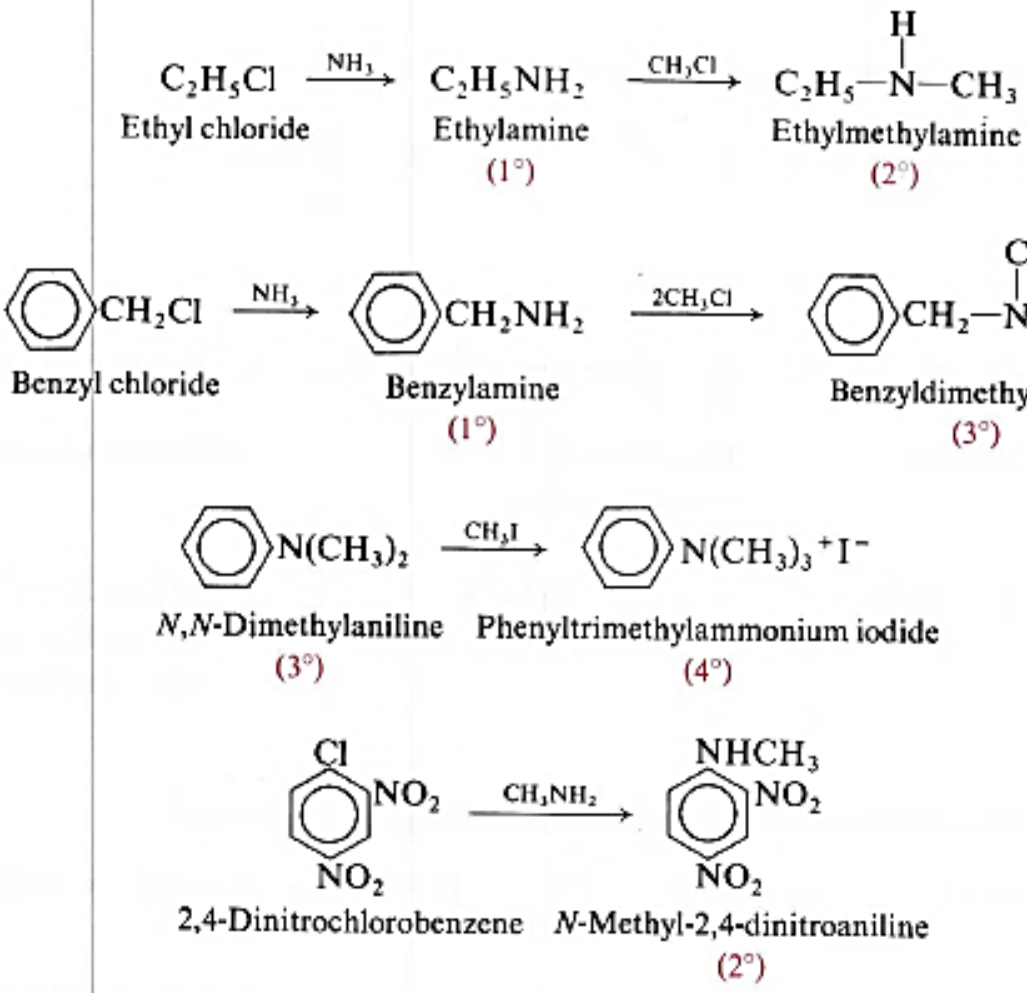
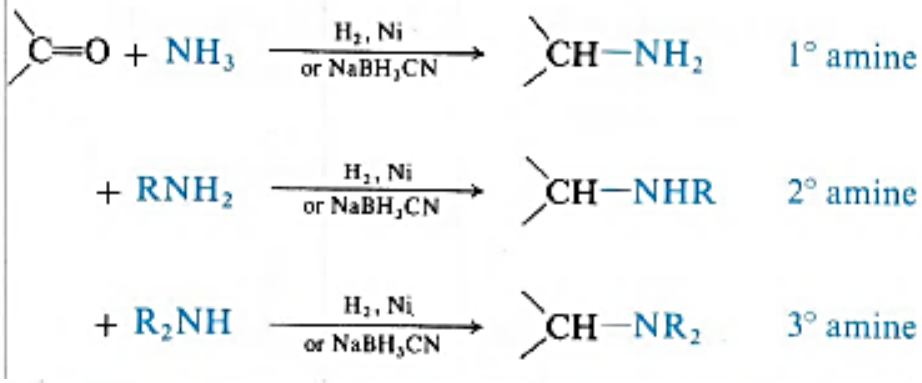
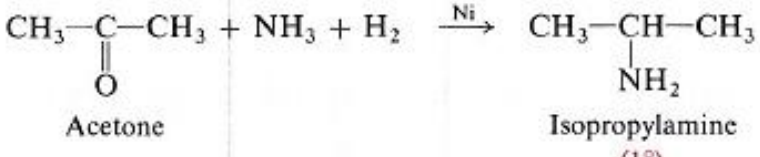


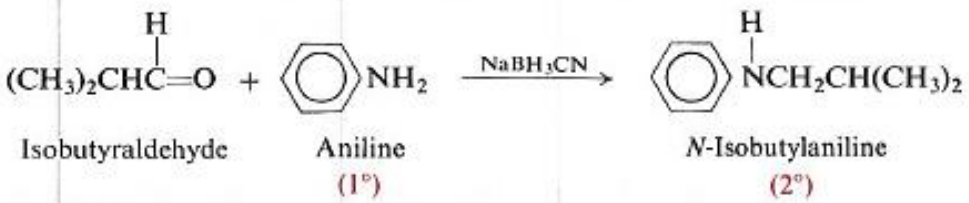


3. Reductive amination. Discussed in Sec. 22.11.



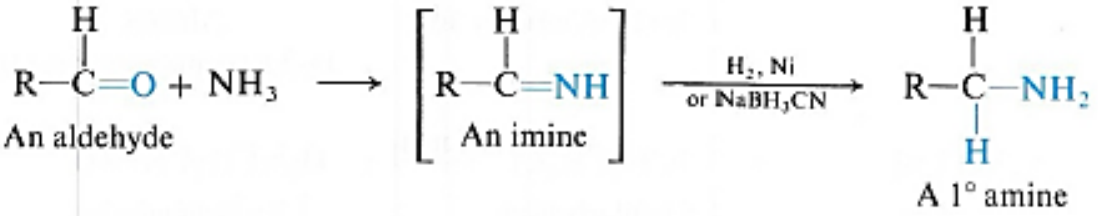
Examples:

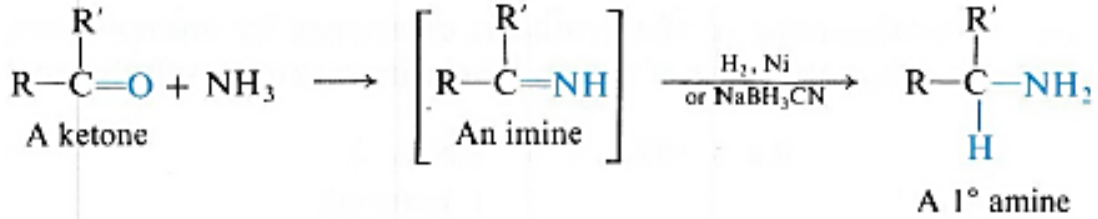




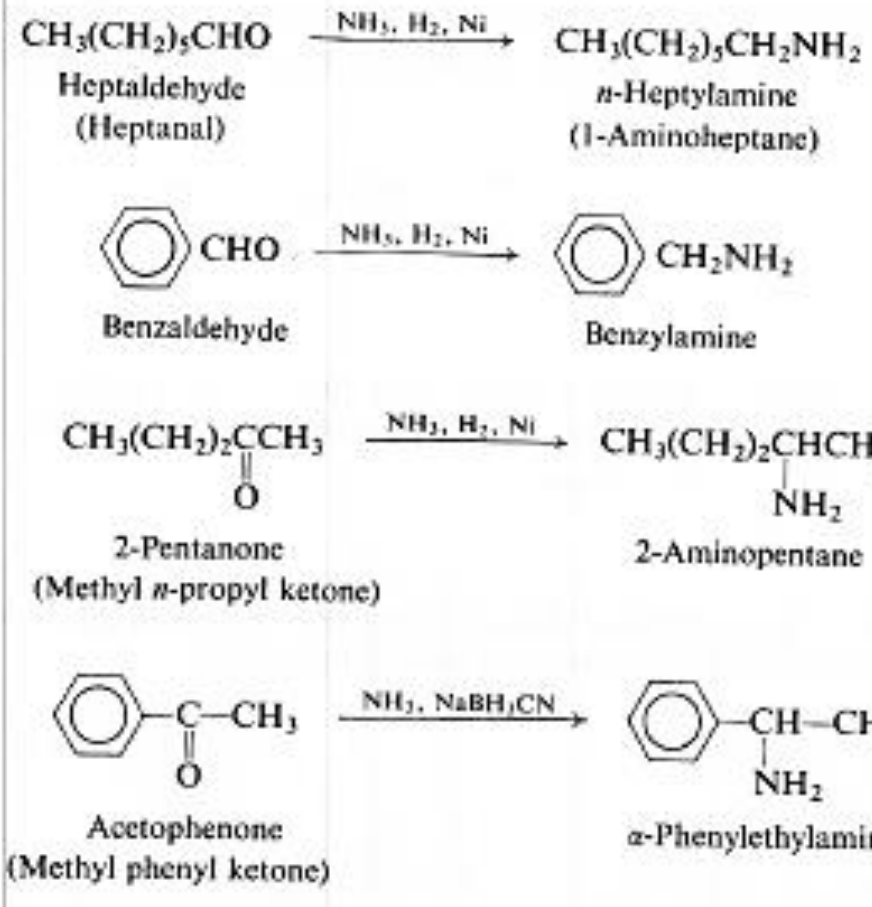
Reductive amination

Many aldehydes (RCHO) and ketones (R_2CO) are converted into amines by **reductive amination**: reduction in the presence of ammonia. Reduction can be accomplished catalytically or by use of sodium cyanohydridoborate, $NaBH_3CN$. Reaction involves reduction of an intermediate compound (an *imine*, RCH=NH or R_2C=NH) that contains a carbon–nitrogen double bond.

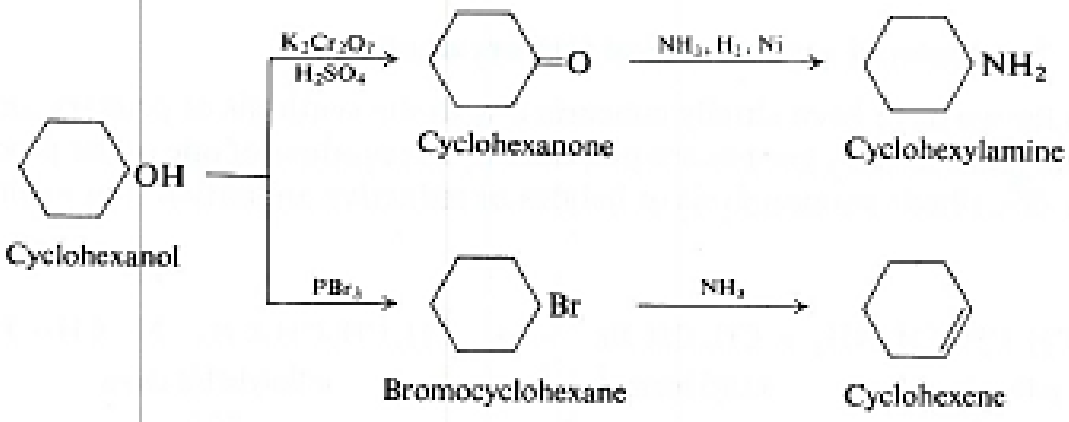




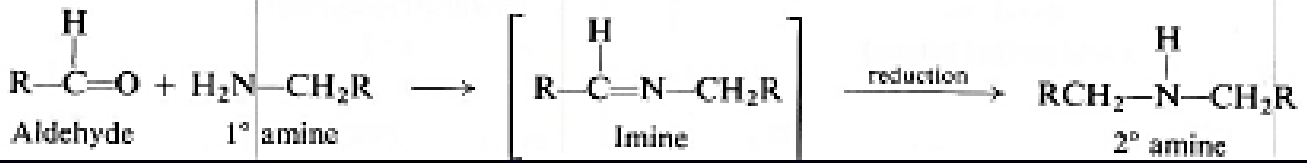
Reductive amination has been used successfully with a wide variety of aldehyde and ketones, both aliphatic and aromatic. For example:



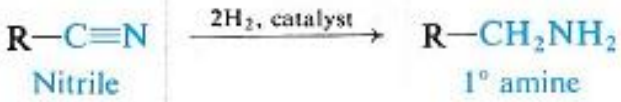
Reductive amination of ketones yields amines containing a *sec*-alkyl group; such amines are difficult to obtain by ammonolysis because of the tendency for *sec*-alkyl halides to undergo elimination. For example, cyclohexanone is converted into cyclohexylamine in good yield, whereas ammonolysis of bromocyclohexane yields only cyclohexene.



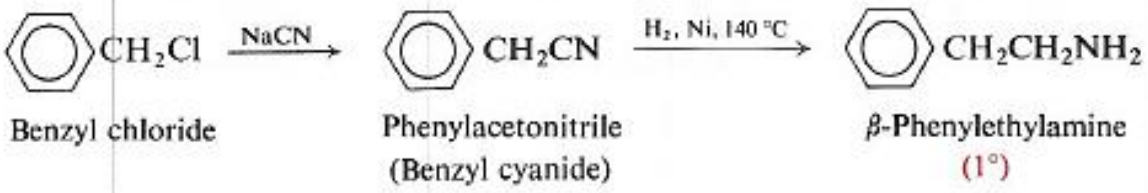
During reductive amination the aldehyde or ketone can react not only with ammonia but also with the primary amine that has already been formed, and thus yield a certain amount of secondary amine. The tendency for the reaction to go



4. Reduction of nitriles. Discussed in Sec. 22.8.



Examples:

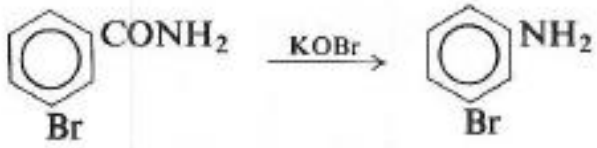


5. Hofmann degradation of amides. Discussed in Secs. 22.15–22.17.

$$\underset{\text{Amide}}{R{-}CONH_2} \text{ or } Ar{-}CONH_2 \xrightarrow{OBr^-} \underset{1^\circ \text{ amine}}{R{-}NH_2} \text{ or } Ar{-}NH_2 + CO_3^{2-}$$

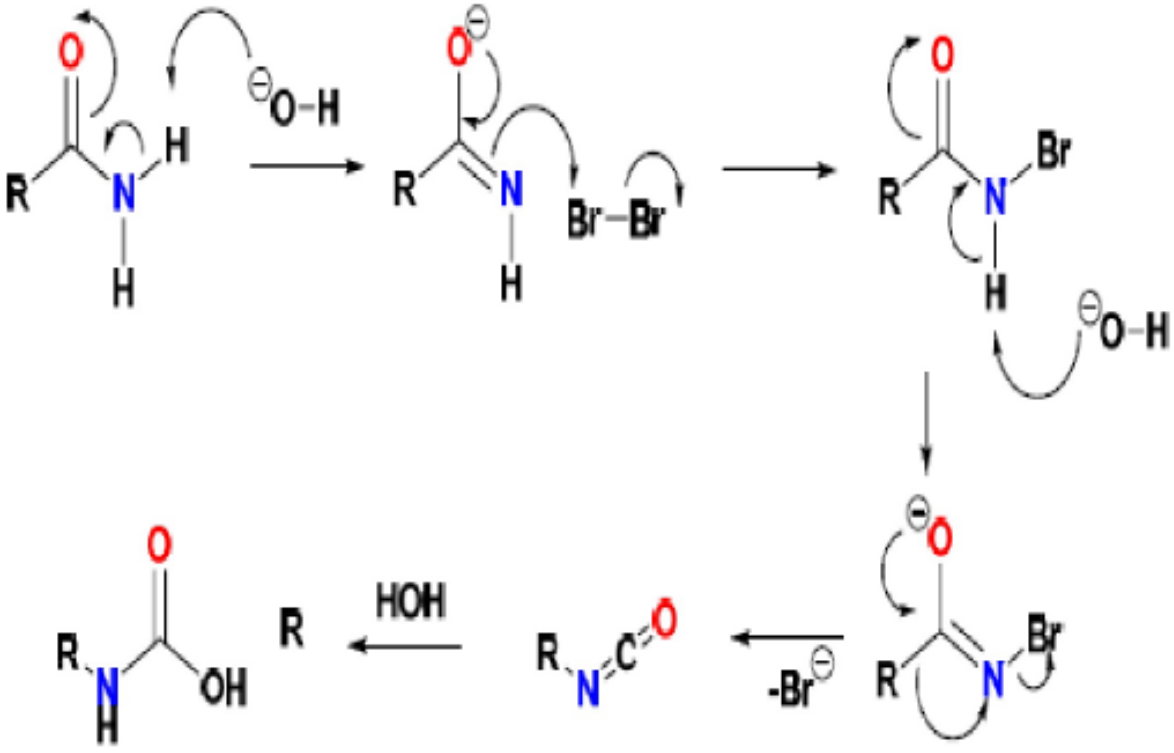
Examples:

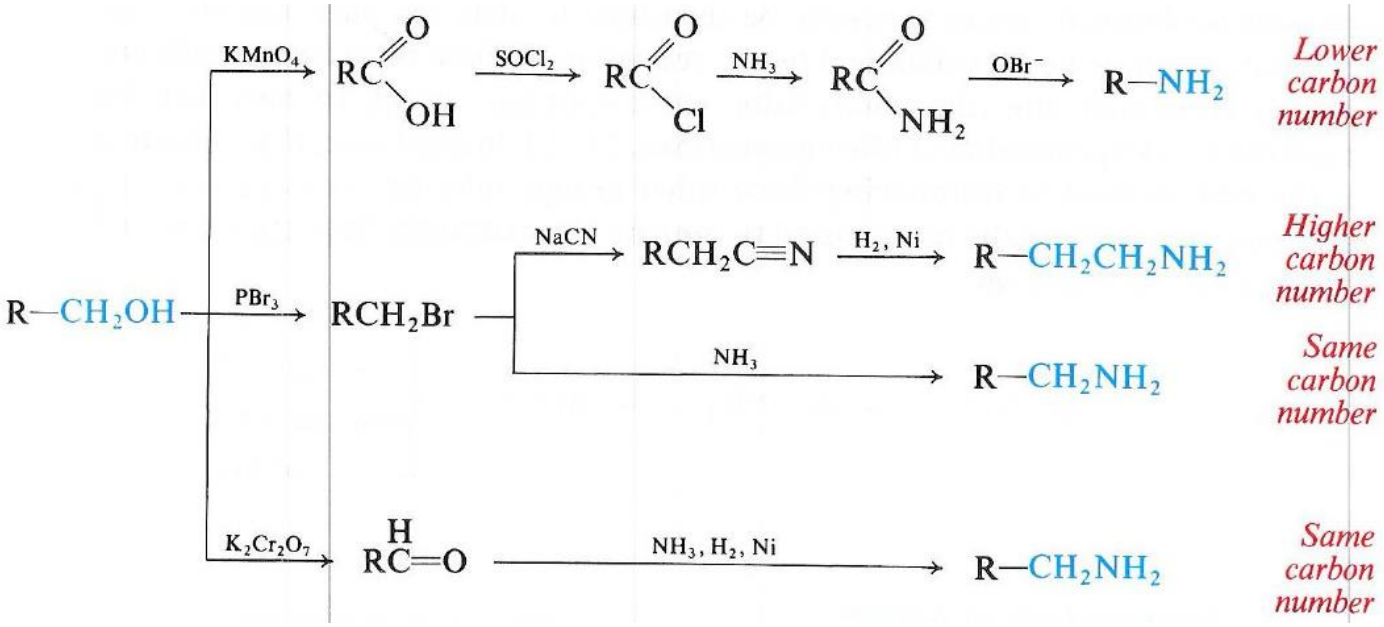
$$\underset{\substack{\text{Caproamide}\\(\text{Hexanamide})}}{CH_3(CH_2)_4CONH_2} \xrightarrow{KOBr} \underset{n\text{-Pentylamine}}{CH_3(CH_2)_4NH_2}$$



m-Bromobenzamide *m*-Bromoaniline

Mechanism of Hofmann Rearrangement





PROBLEMS

1. Draw structures, give names, and classify as primary, secondary, or tertiary:

(a) the eight isomeric amines of formula $C_4H_{11}N$
(b) the five isomeric amines of formula C_7H_9N that contain a benzene ring

2. Give the structural formulas of the following compounds:

(a) *sec*-butylamine
(b) *o*-toluidine
(c) anilinium chloride
(d) diethylamine
(e) *p*-aminobenzoic acid
(f) benzylamine
(g) isopropylammonium benzoate
(h) *N*,*N*-dimethylaniline
(i) 2-aminoethanol
(j) *β*-phenylethylamine
(k) *N*,*N*-dimethylaminocyclohexane
(l) diphenylamine
(m) 2,4-dimethylaniline
(n) tetra-*n*-butylammonium iodide

3. Show how *n*-propylamine could be prepared from each of the following:

(a) *n*-propyl bromide
(b) *n*-propyl alcohol
(c) propionaldehyde
(d) 1-nitropropane
(e) propionitrile
(f) *n*-butyramide
(g) *n*-butyl alcohol
(h) ethyl alcohol

Which of these methods can be applied to the preparation of aniline? Of benzylamine?

4. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer using any needed inorganic reagents.

(a) isopropylamine
(b) *n*-pentylamine
(c) *p*-toluidine
(d) ethylisopropylamine
(e) *α*-phenylethylamine
(f) *β*-phenylethylamine
(g) *m*-chloroaniline
(h) *p*-aminobenzoic acid
(i) 3-aminoheptane
(j) *N*-ethylaniline
(k) 2,4-dinitroaniline
(l) the drug *benzedrine* (2-amino-1-phenylpropane)
(m) *p*-nitrobenzylamine
(n) 2-amino-1-phenylethanol

5. Outline all steps in a possible laboratory synthesis from palmitic acid, n-$C_{15}H_{31}COOH$, of:

(a) n-$C_{16}H_{33}NH_2$
(b) n-$C_{17}H_{35}NH_2$
(c) n-$C_{15}H_{31}NH_2$
(d) n-$C_{15}H_{31}CH(NH_2)$-n-$C_{16}H_{33}$

6. On the basis of the following synthesis give the structures of *putrescine* and *cadaverine*, found in rotting flesh:

(a) ethylene bromide $\xrightarrow{KCN}$ $C_4H_4N_2$ $\xrightarrow{Na,\ C_2H_5OH}$ putrescine ($C_4H_{12}N_2$)

(b) $Br(CH_2)_5Br$ $\xrightarrow{NH_3}$ cadaverine ($C_5H_{14}N_2$)

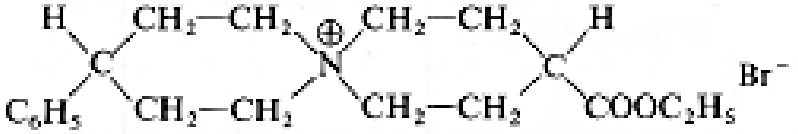
7. One of the raw materials for the manufacture of nylon-6,6 is *hexamethylenediamine*, $NH_2(CH_2)_6NH_2$. Much of this amine is made by a process that begins with the 1,4-addition of chlorine to 1,3-butadiene. What do you think might be the subsequent steps in this process?

8. Outline all steps in a possible synthesis of *β*-alanine (*β*-aminopropionic acid) from succinic anhydride.

9. Using models and then drawing formulas, show the stereoisomeric forms in which each of the following compounds can exist. Tell which stereoisomers when separated from all others would be optically active and which would be optically inactive.

(a) *α*-phenylethylamine
(b) *N*-ethyl-*N*-methylaniline
(c) ethylmethylphenyl-*n*-propylammonium bromide

(d)



(e) ethylmethylphenylamine oxide, $(CH_3)(C_2H_5)(C_6H_5)N{-}O$

10. Two geometric isomers of benzaldoxime, $C_6H_5CH{=}NOH$, are known. (a) Draw their structures, showing the geometry of the molecules. (b) Show how this geometry results from their electronic configurations. (c) Would you predict geometric isomerism for benzophenoneoxime, $(C_6H_5)_2C{=}NOH$? For acetophenoneoxime, $C_6H_5C(CH_3){=}NOH$? For azobenzene, $C_6H_5N{=}NC_6H_5$?

11. (a) Give structural formulas of compounds A through D.

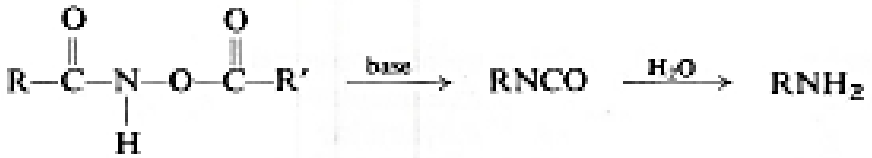
$$\text{phthalimide (Sec. 20.14)} + KOH(\text{alc.}) \longrightarrow A\ (C_8H_4O_2NK)$$

$$A + CH_3CH_2CH_2Br, \text{heat} \longrightarrow B\ (C_{11}H_{13}O_2N)$$

$$B + H_2O, OH^-, \text{heat} \longrightarrow C\ (C_3H_9N) + D$$

(b) This sequence illustrates the **Gabriel synthesis.** What class of compounds does it produce? What particular advantage does it have over alternative methods for the production of these compounds? On what special property of phthalimide does the synthesis depend?

12. In the presence of base, acyl derivatives of hydroxamic acids undergo the **Lossen rearrangement** to yield isocyanates or amines.



(a) Write a detailed mechanism for the rearrangement.

(b) Study of a series of compounds in which R and R′ were *m*- and *p*-substituted phenyl groups showed that reaction is speeded up by electron-releasing substituents in R and by electron-withdrawing substituents in R′. How do you account for these effects?