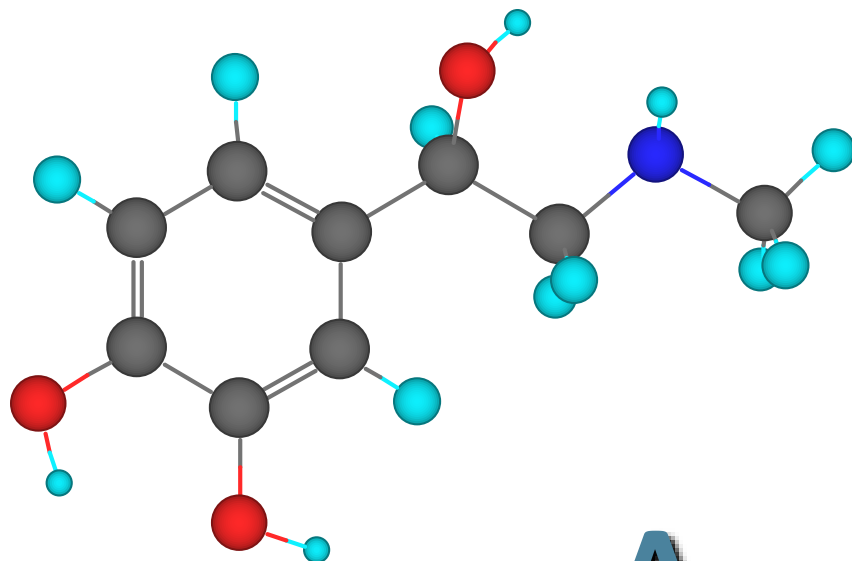




PHARMACEUTICAL ORGANIC CHEMISTRY

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COLLEGE OF PHARMACY, HAIL UNIVERSITY***

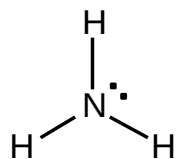


Amines

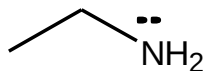


Structure and Classification of Amines

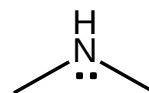
- Amines are derivatives of ammonia, the same way that alcohols are derivatives of water
- Amines have a nitrogen, with hydrogens and/or alkyl groups attached
- The shape around the nitrogen is pyramidal and there is a lone pair of electrons on the nitrogen
- Amines can be classified as 1^o, 2^o or 3^o, just like carbons, based on how many alkyl groups are attached to the nitrogen



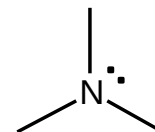
Ammonia



Primary Amine



Secondary Amine

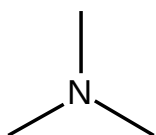


Tertiary Amine

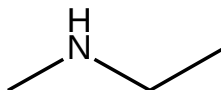


Naming Amines

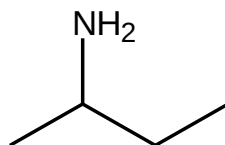
- Most simple amines are named by their common names (which are accepted by IUPAC)
- For common names, the alkyl groups attached to the N are named alphabetically, and amine is added to the end
- IUPAC rules are more often used for more complicated amines
 - find the longest chain bonded to N, and replace -e in alkane name with amine
 - number at end nearest N and give number for position of N
 - the prefixes di, tri etc. are used for multiple amines
 - when amines are with other functional groups they are called amino groups



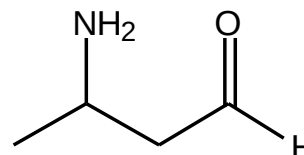
trimethylamine



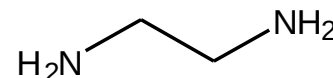
ethylmethanamine



2-butanamine



3-aminobutanal



1,2-ethanediamine

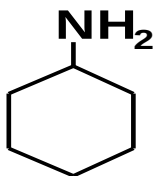


Naming Aromatic Amines

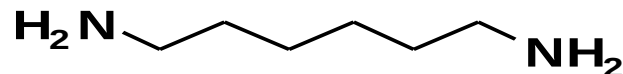
- Aromatic amines are named as anilines
- When alkyl groups are attached to the aromatic N, they are written as *N*-alkyl at the beginning of the name
- As substituents on the ring they are named as amino groups



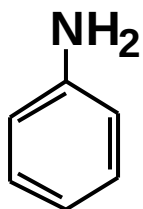
2-Propanamine



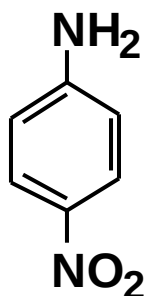
Cyclohexanamine



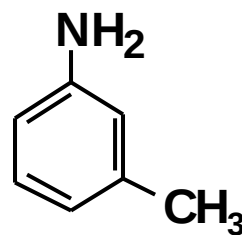
1,6-Hexanediamine



Aniline



4-Nitroaniline
(*p*-Nitroaniline)

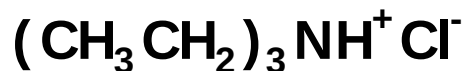


3-Methylaniline
(*m*-Toluidine)



Amine salts

- when four atoms or groups of atoms are bonded to a nitrogen atom, as for example CH_3NH_3^+ , nitrogen bears a positive charge and is associated with an anion as a salt
- name the compound as a salt of the corresponding amine
- replace the ending **-amine** or aniline by **-ammonium** or anilinium and add the name of the anion

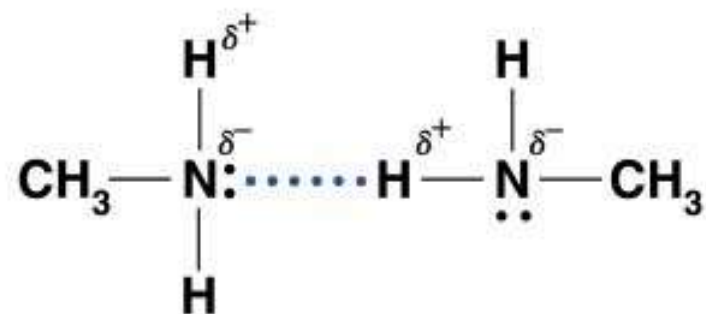
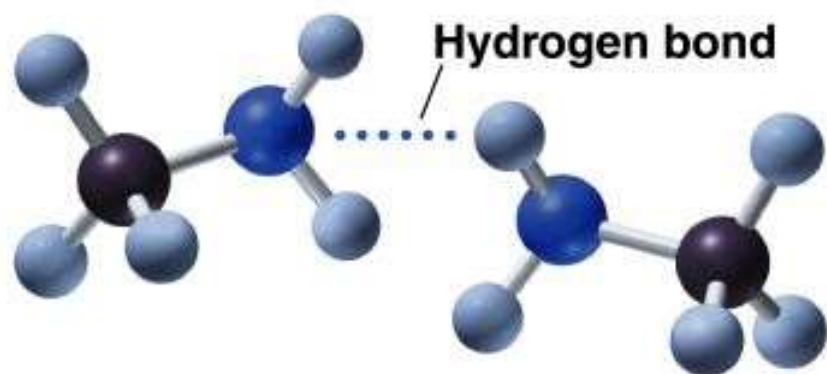


Triethylammonium chloride

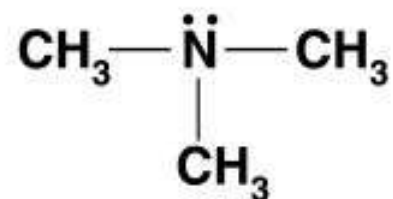
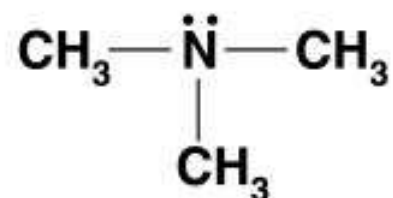


Physical Properties of Amines

- Primary and secondary amines can H-bond with themselves, so have relatively high boiling points
- However, because the N-H bond is less polar than the O-H bond, amines have lower boiling points than alcohols
- Primary and secondary amines have boiling points similar to aldehydes and ketones
- Tertiary amines can't H-bond with themselves, and so have boiling points near those of ethers and hydrocarbons
- Smaller amines (less than 5 carbons) are soluble in water
 - primary and secondary amines are more soluble than tertiary because they have more H-bonding with water



No hydrogen bonds in 3° amines





- an N-H---N hydrogen bond is weaker than an O-H---O hydrogen bond because the difference in electronegativity between N and H ($3.0 - 2.1 = 0.9$) is less than that between O and H ($3.5 - 2.1 = 1.4$)

Table 19.1 Comparison of Boiling Points (°C) of Amines, Alcohols, and Alkanes

NH ₃	-33		
1 Carbon Atom		3 Carbon Atoms	
CH ₄	-162	CH ₃ —CH ₂ —CH ₃	-42
CH ₃ —NH ₂	-7	CH ₃	
CH ₃ —OH	65		
		CH ₃ —N—CH ₃	3
2 Carbon Atoms		CH ₃ —CH ₂ —NH—CH ₃	36
CH ₃ —CH ₃	-89	CH ₃ —CH ₂ —CH ₂ —NH ₂	48
CH ₃ —NH—CH ₃	7	CH ₃ —CH ₂ —CH ₂ —OH	97
CH ₃ —CH ₂ —NH ₂	17		
CH ₃ —CH ₂ —OH	79		

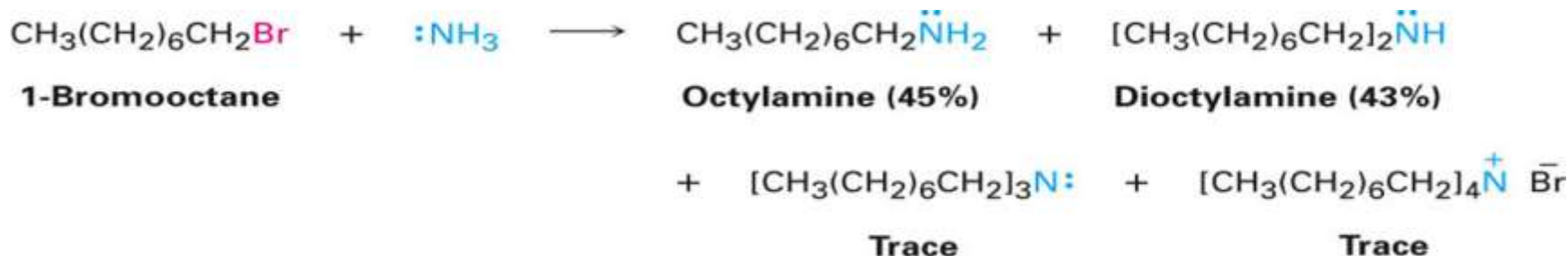


Preparation of Amines

1. S_N2 Reactions of Alkyl Halides

Ammonia and other alkylamines are good nucleophiles and react with 1° and 2° alkyl halides via an S_N2 reaction yielding alkyl amines.

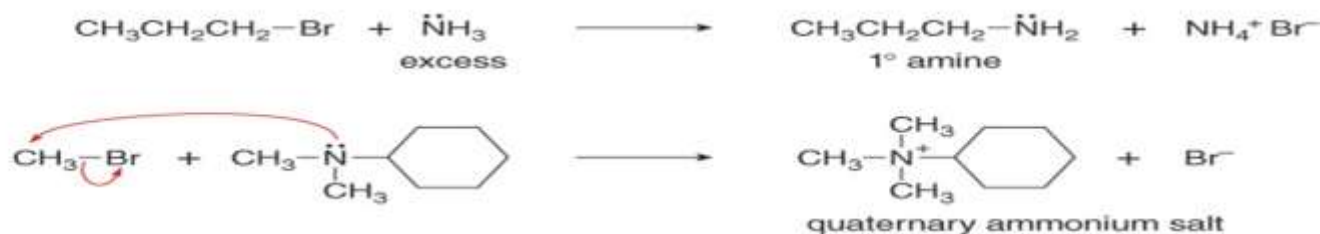
Any amine formed by nucleophilic substitution still has a nonbonded electron pair, making it a nucleophile as well. It will react with remaining alkyl halide to form a more substituted amine, resulting in a mixture of 1°, 2°, and 3° amine products.



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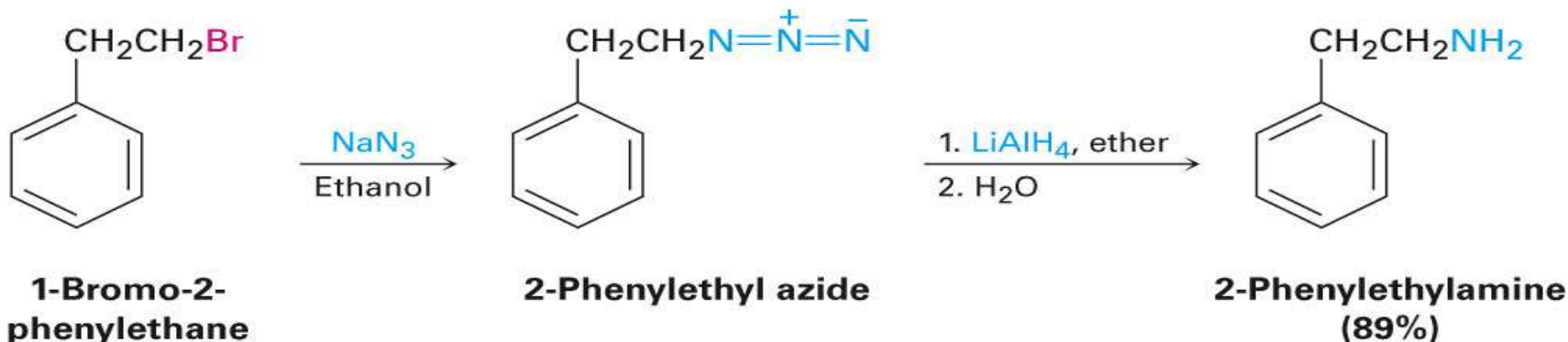
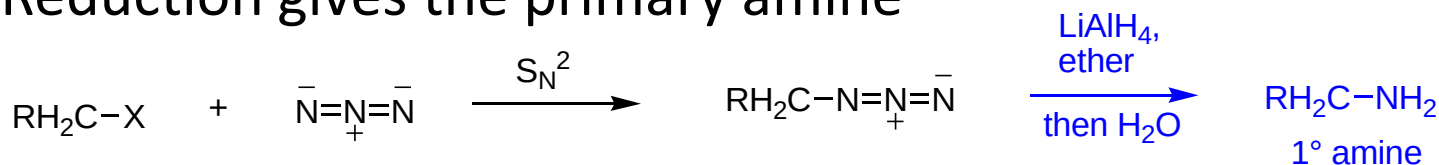
Consequently, the reaction is most useful in preparing 1° amines by using a large excess of NH₃, and for preparing quaternary ammonium salts by alkylating any nitrogen nucleophile with one or more equivalents of alkyl halide.

Useful S_N2 substitutions



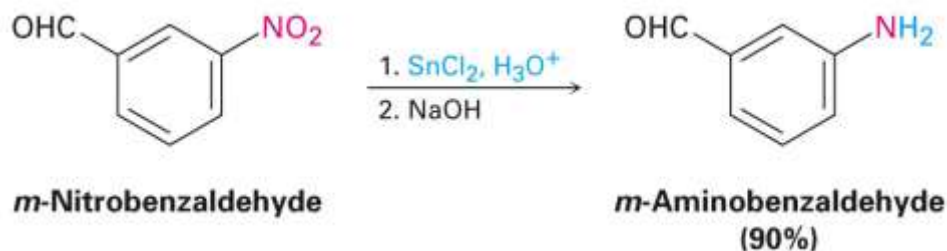
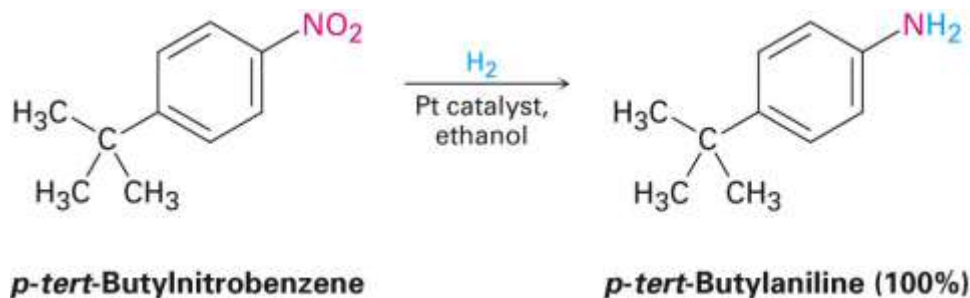
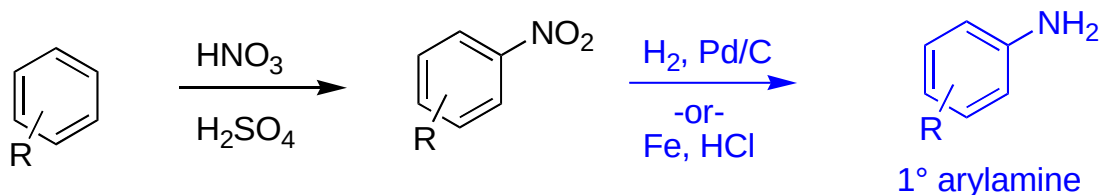
2. Selective Preparation of Primary Amines: the Azide Synthesis

- Azide ion, N_3^- displaces a halide ion from a primary or secondary alkyl halide to give an alkyl azide, RN_3
- Alkyl azides are not nucleophilic (but they are explosive)
- Reduction gives the primary amine



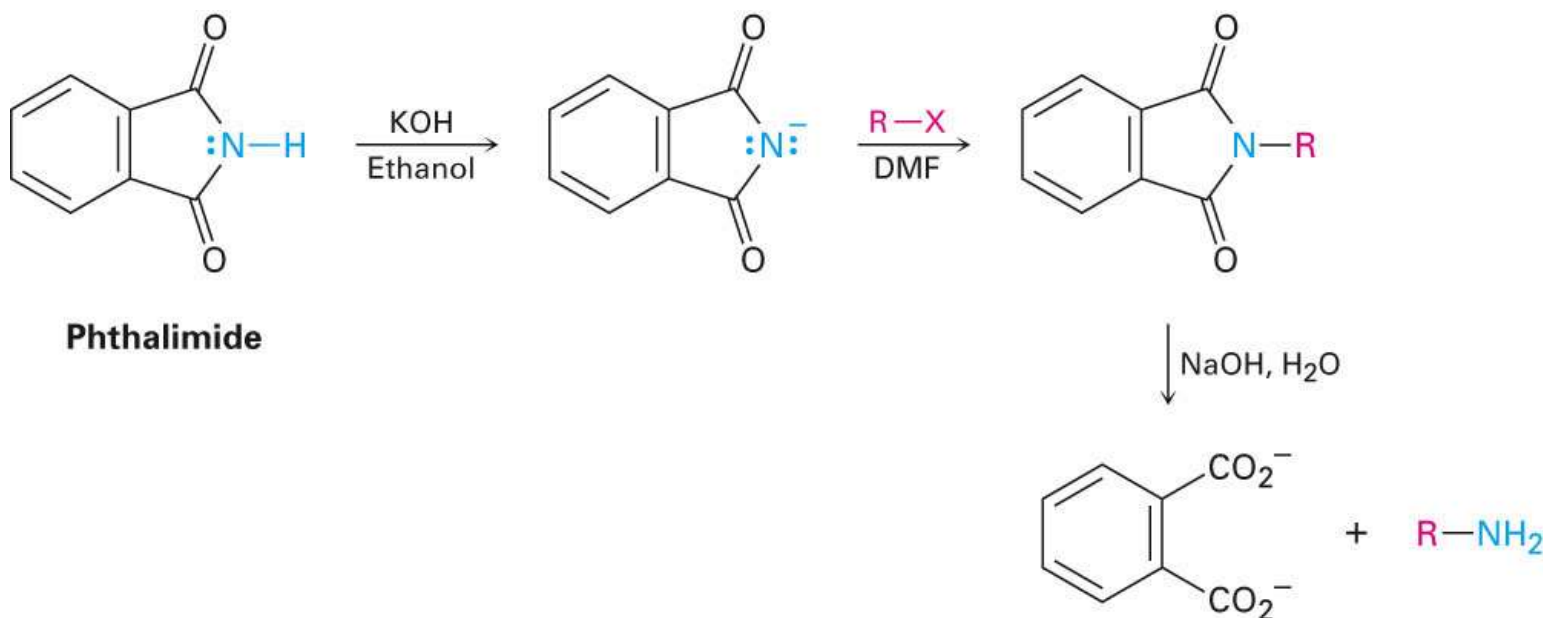
3. Reduction of Nitro compound

- Arylamines are prepared from nitration of an aromatic compound and reduction of the nitro group
- Reduction by catalytic hydrogenation over platinum is suitable if no other groups can be reduced



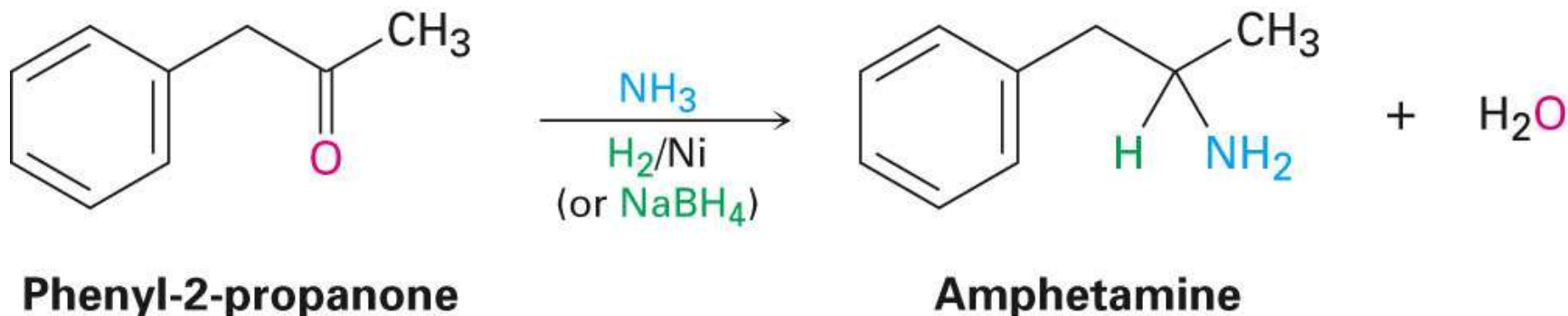
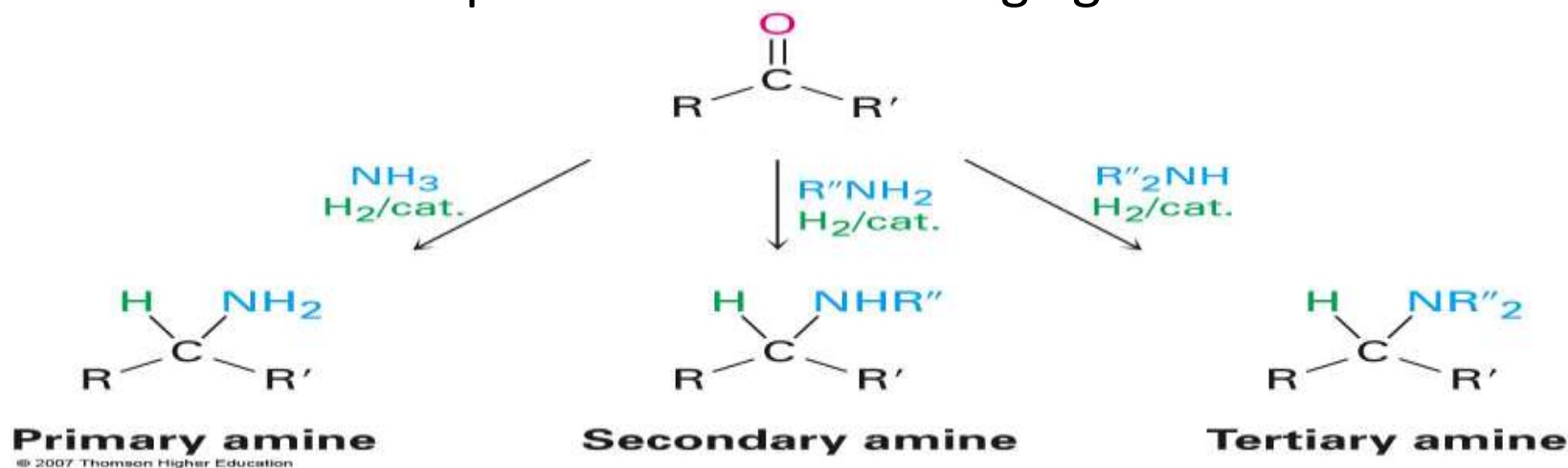
4. Gabriel Synthesis of Primary Amines

- A *phthalimide* alkylation for preparing a primary amine from an alkyl halide
- The N-H in imides (—CONHCO—) can be removed by KOH followed by alkylation and hydrolysis



5. Reductive Amination of Aldehydes and Ketones

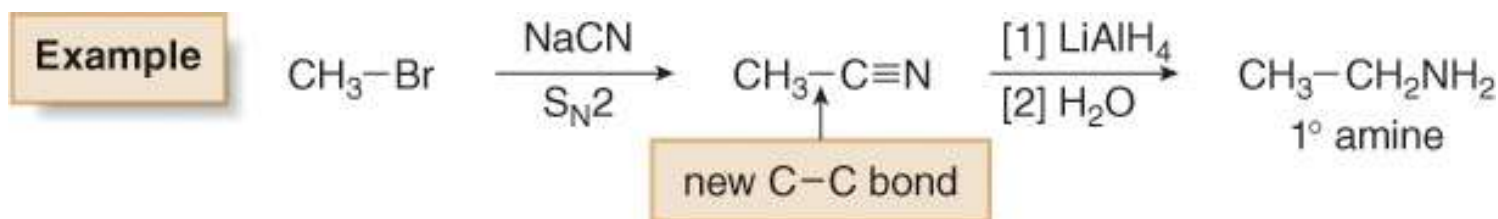
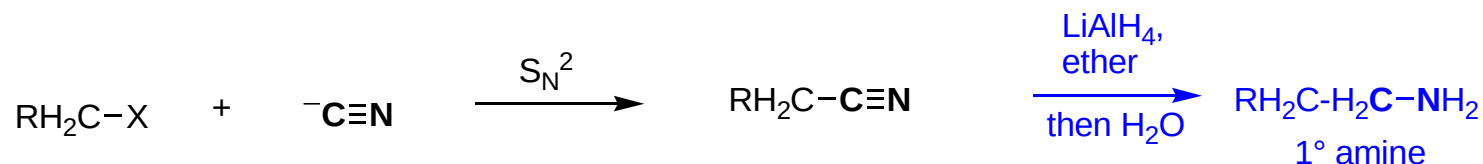
- Treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent



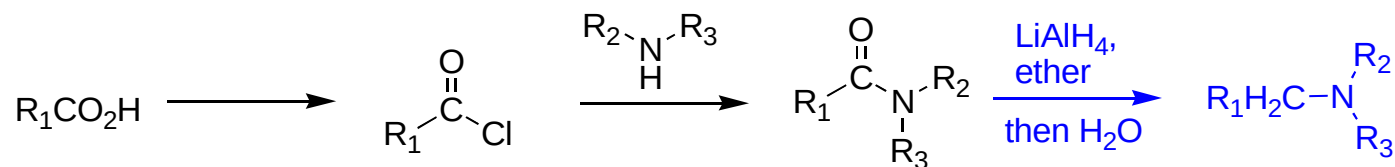


6. Reduction of nitriles and amides

LiAlH_4 reduces nitriles to 1° amines



LiAlH_4 reduces amides to 1° , 2° or 3° amines





Amines, reactions

Amines are similar to ammonia in their reactions.

Like ammonia, amines are basic.

Like ammonia, amines are nucleophilic and react with alkyl halides, acid chlorides, and carbonyl compounds.

The aromatic amines are highly reactive in electrophilic aromatic substitution.



Amine, reactions:

- 1. As bases**
- 2. Alkylation**
- 3. Reductive amination**
- 4. Conversion into amides**
- 5. Reactions with nitrous acid**
- 6. EAS**

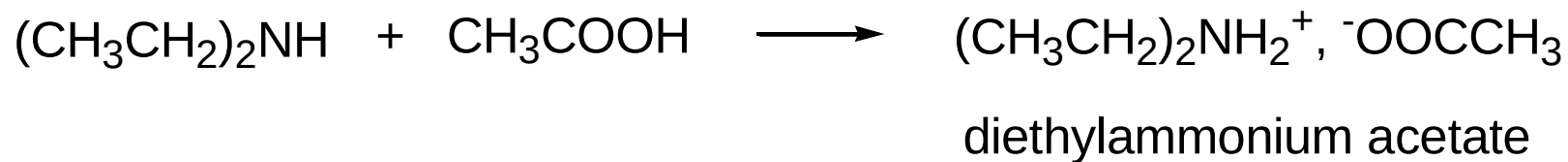
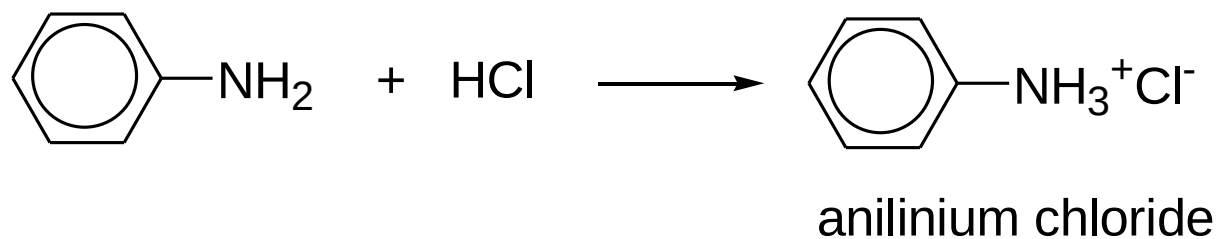


1. As bases

- a) with acids
- b) relative base strength
- c) K_b
- d) effect of groups on base strength



a) with acids





b) relative base strength



K_b ionization of the base in water



$$K_b = \frac{[\text{H:Base}^+][\text{OH}^-]}{[\text{:Base}]}$$

K_b

aliphatic amines $10^{-3} - 10^{-4}$

ammonia 1.8×10^{-5}

anilines 10^{-9} or less



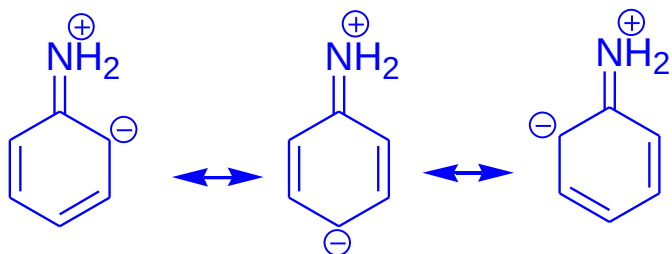
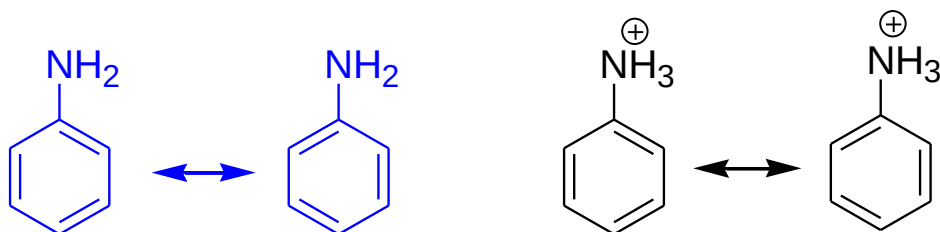
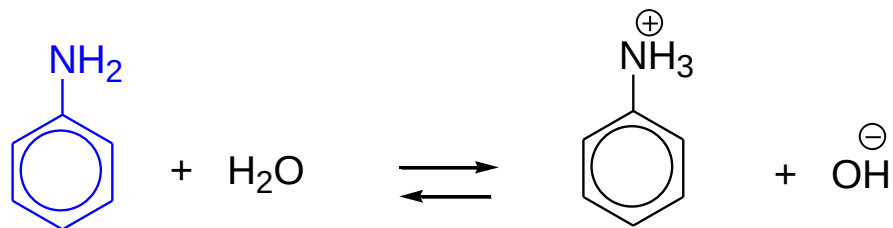
Why are aliphatic amines more basic than ammonia?



The alkyl group, -R, is an electron donating group. The donation of electrons helps to stabilize the ammonium ion by decreasing the positive charge, lowering the ΔH , shifting the ionization farther to the right and increasing the basicity.

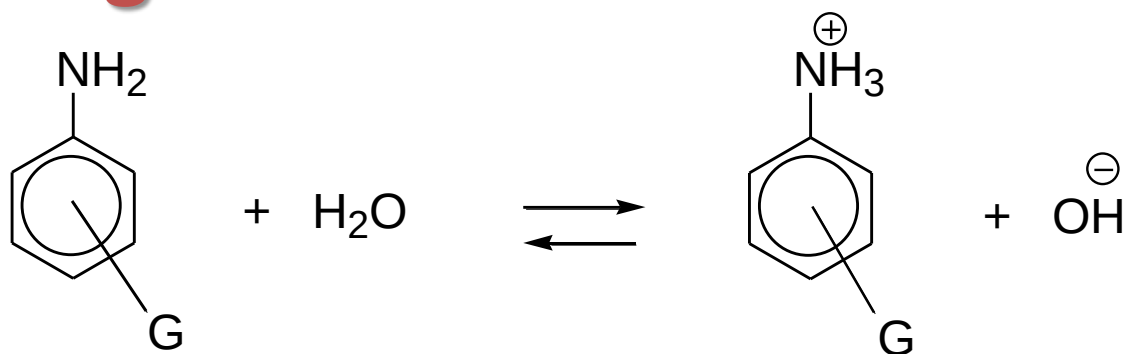


Why are aromatic amines less basic than aliphatic amines?



resonance stabilization of the free base, increases the ΔH , shifts the ionization to the left, decreasing base strength.

d) Effect of substituent groups on base strength:



Electron donating groups will stabilize the anilinium ion, decreasing the ΔH , shifting the ionization farther to the right and making the compound a **stronger base**.

Electron withdrawing groups destabilize the anilinium ion, increasing the ΔH , shifting the ionization towards the reactants, making the compound a **weaker base**.



Common substituent groups:

-NH₂, -NHR, -NR₂

-OH

-OR

-NHCOCH₃

-C₆H₅

-R

-H

-X

-CHO, -COR

-SO₃H

-COOH, -COOR

-CN

-NR₃⁺

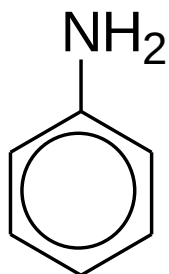
-NO₂

electron donating groups

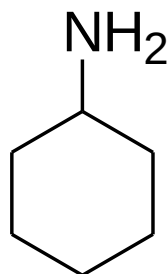
electron withdrawing groups



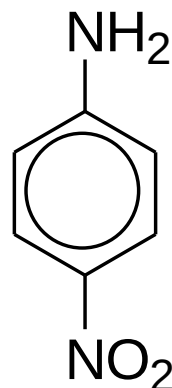
Number the following in decreasing order of base strength (let #1 = most basic, etc.)



4

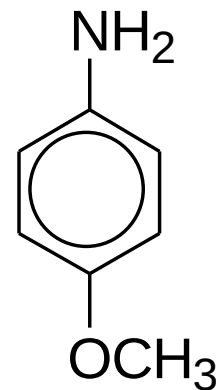


1



5

3

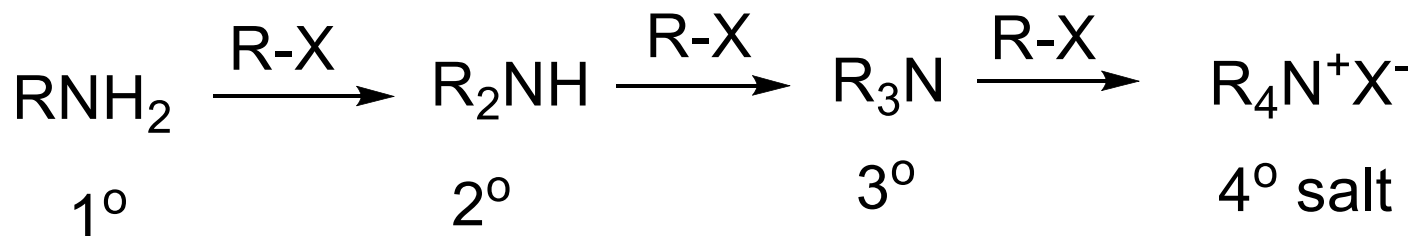


2

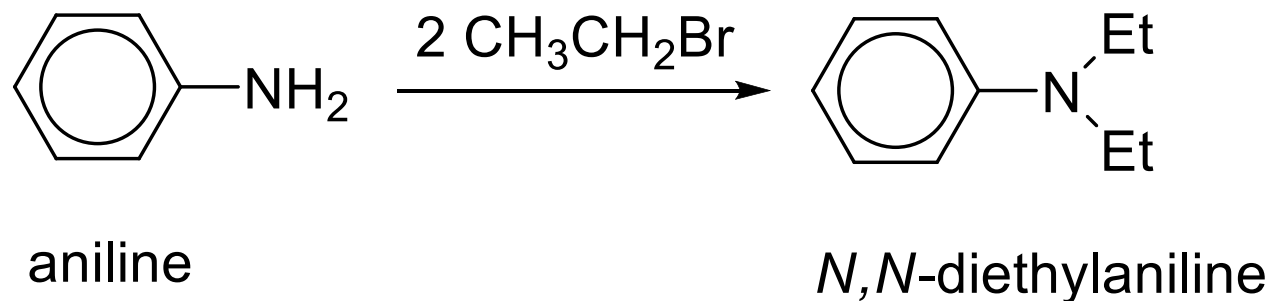
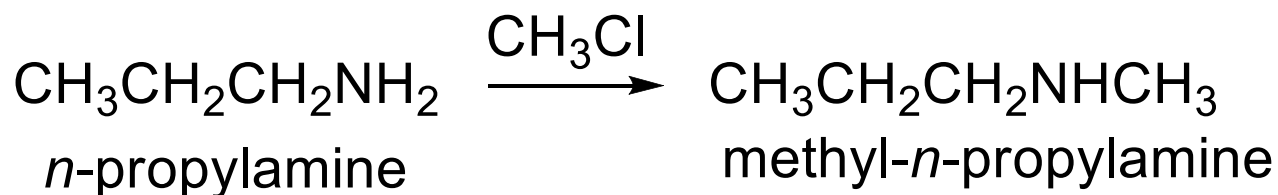




2. Alkylation (ammonolysis of alkyl halides)

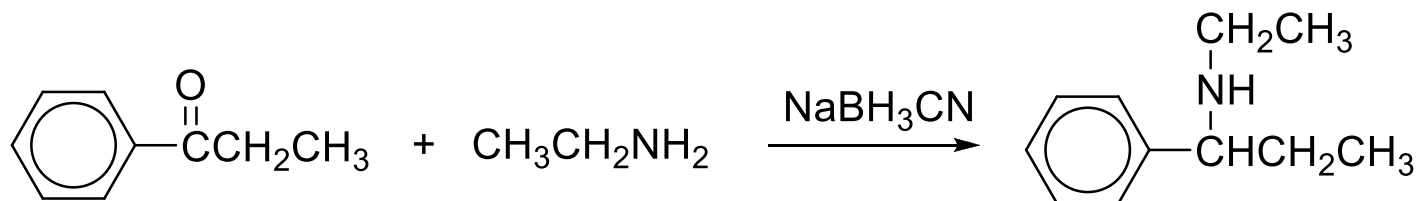
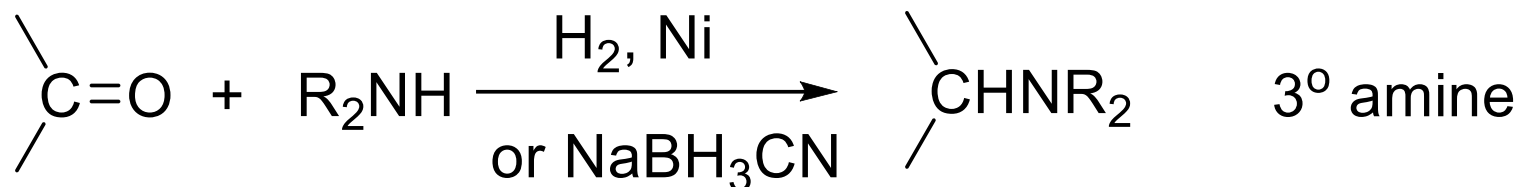
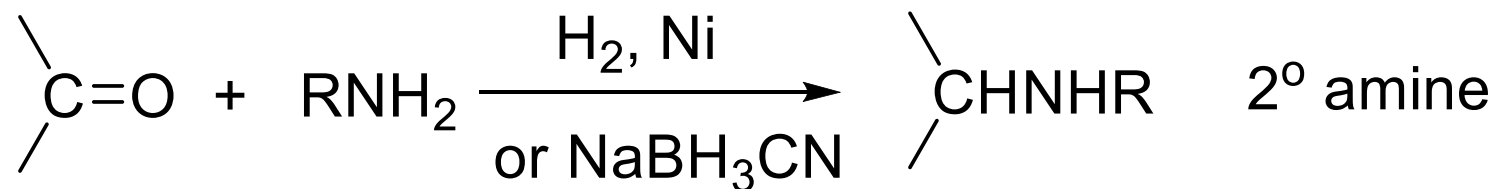


$\text{S}_\text{N}2$: R-X must be 1° or CH_3



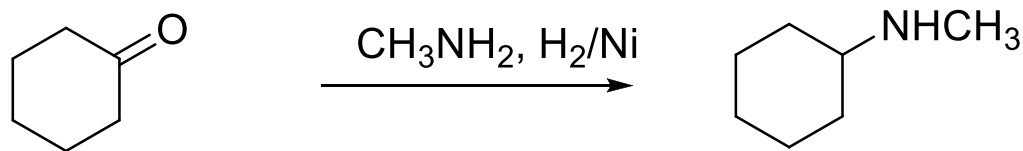


3. Reductive amination



propiophenone

1-(N-ethylamino)-1-phenylpropane



cyclohexanone

cyclohexylmethylamine



4. Conversion into amides



1°

N-subst. amide

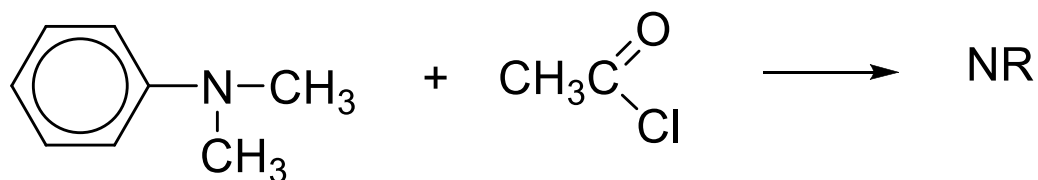
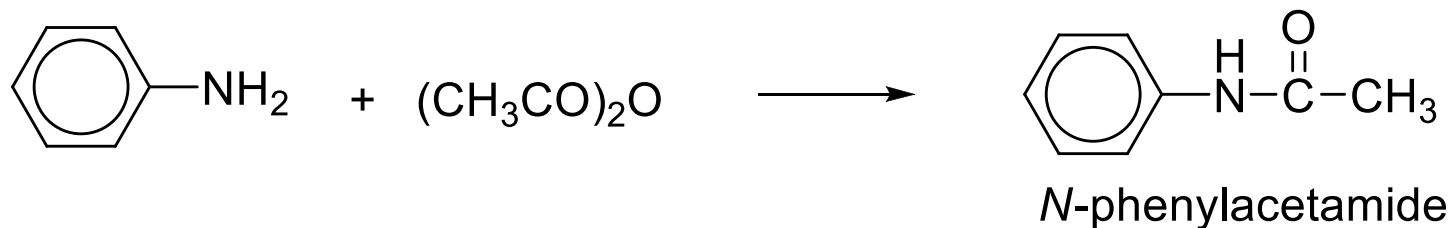


2°

N,N-disubst. amide



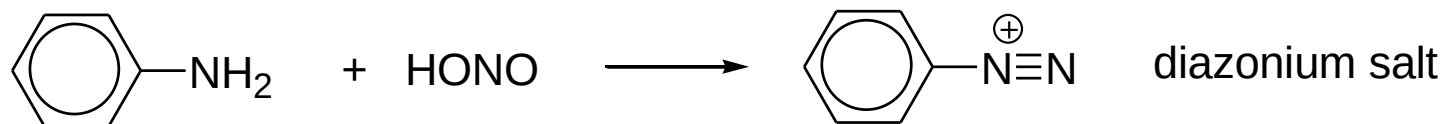
3°



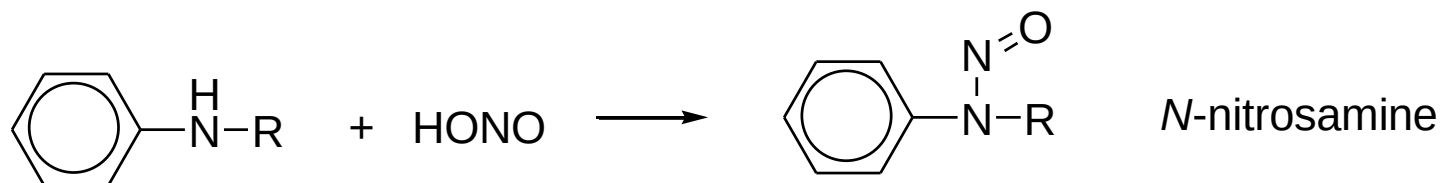


5. Reactions with nitrous acid

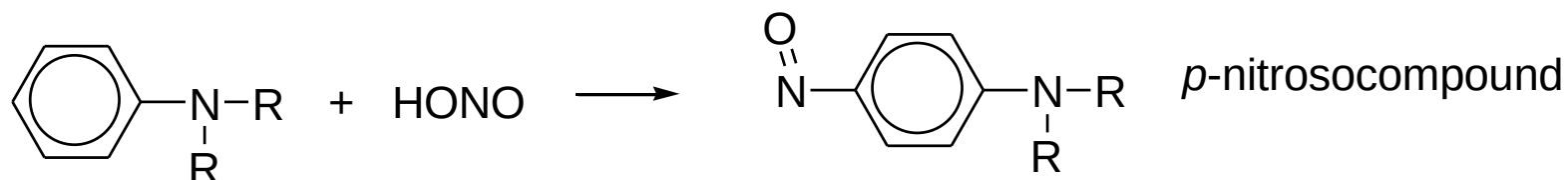
primary amines



secondary amines



tertiary amines





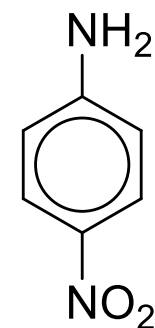
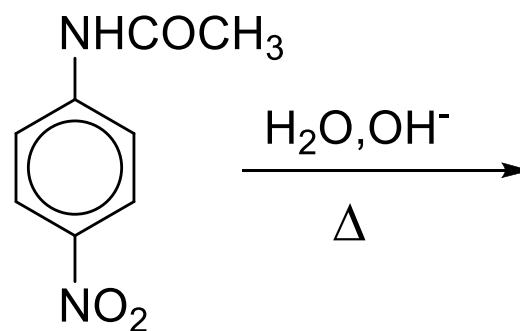
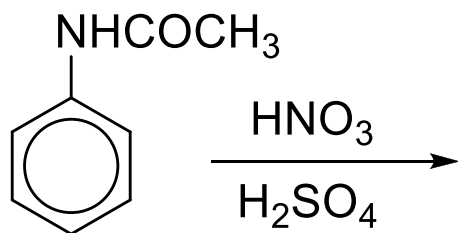
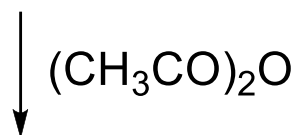
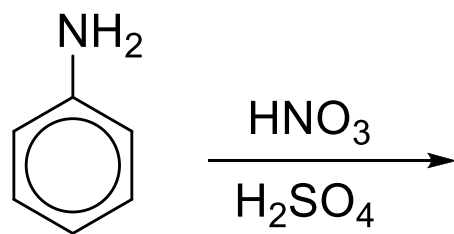
6. EAS

-NH₂, -NHR, -NR₂ are powerful activating groups and *ortho/para* directors

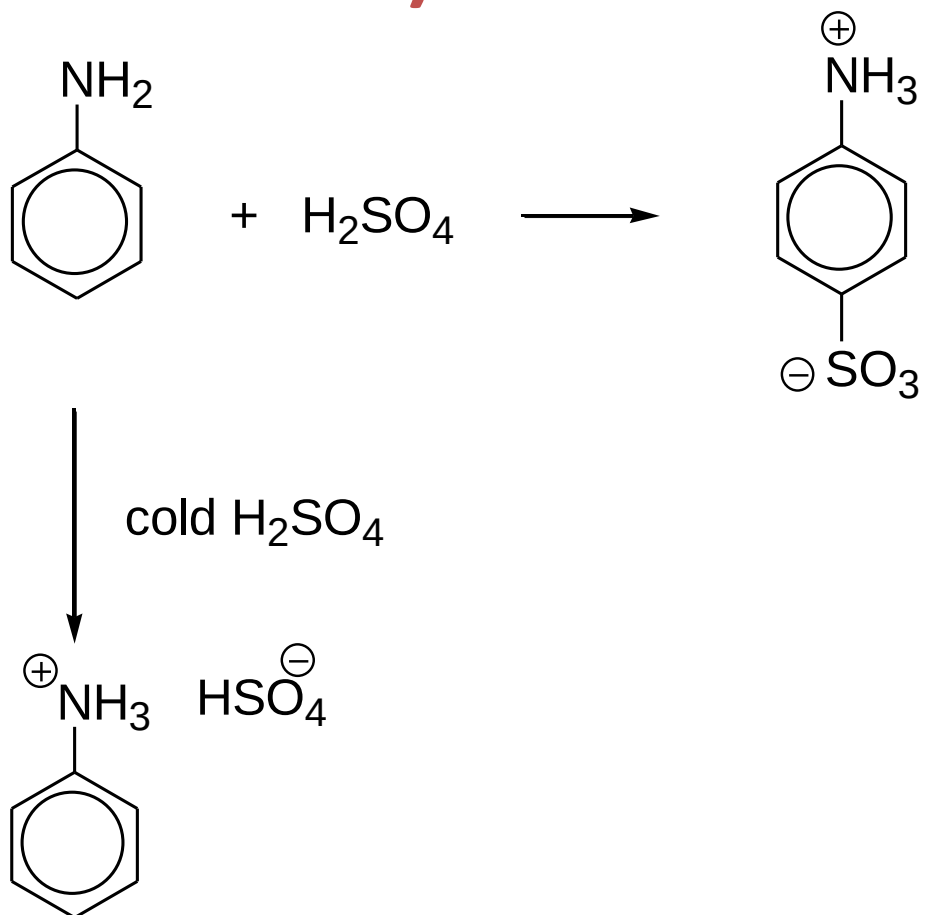
- a) nitration**
- b) sulfonation**
- c) halogenation**
- d) Friedel-Crafts alkylation**
- e) Friedel-Crafts acylation**



a) Nitration

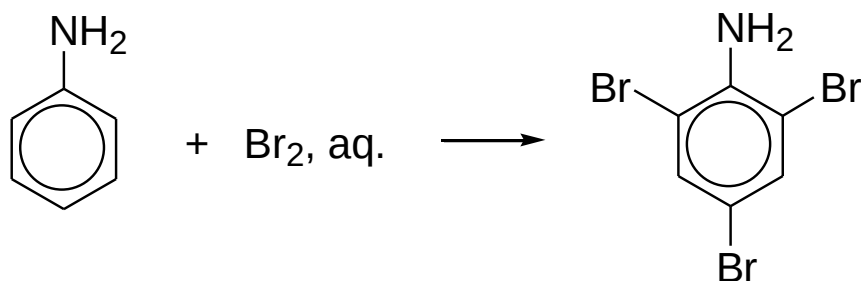


b) Sulfonation



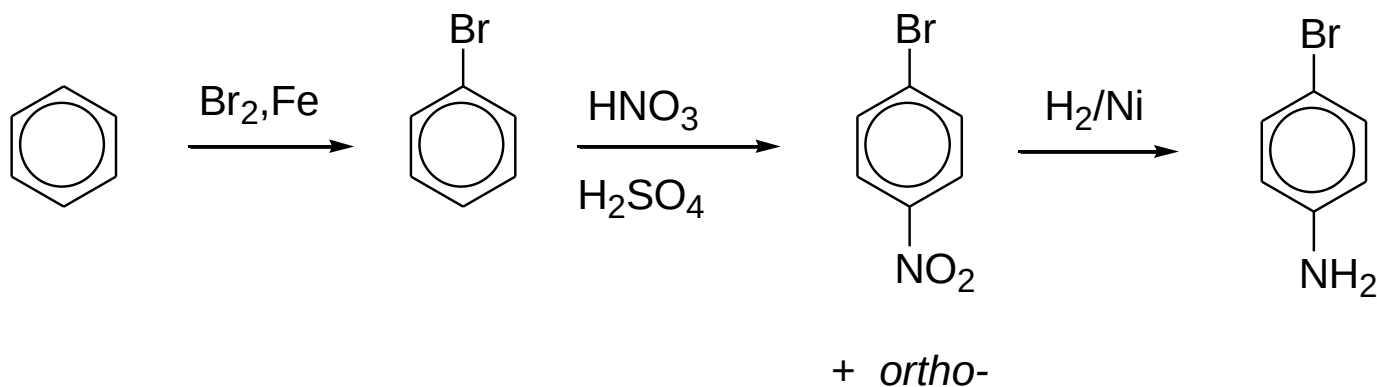


c) Halogenation



polyhalogenation!

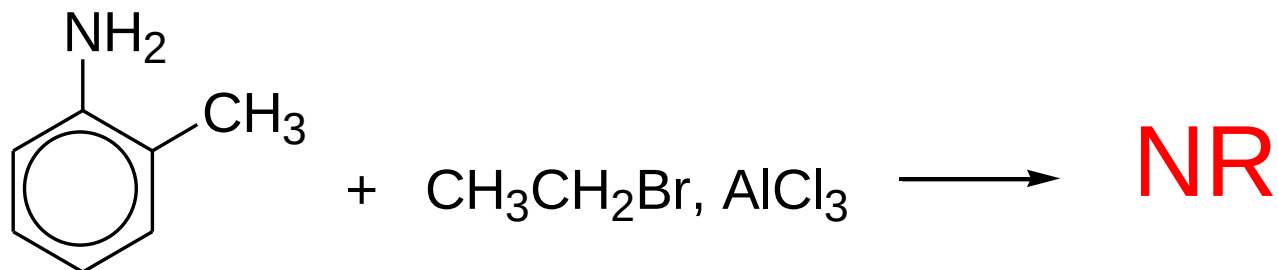
no catalyst needed
use polar solvent



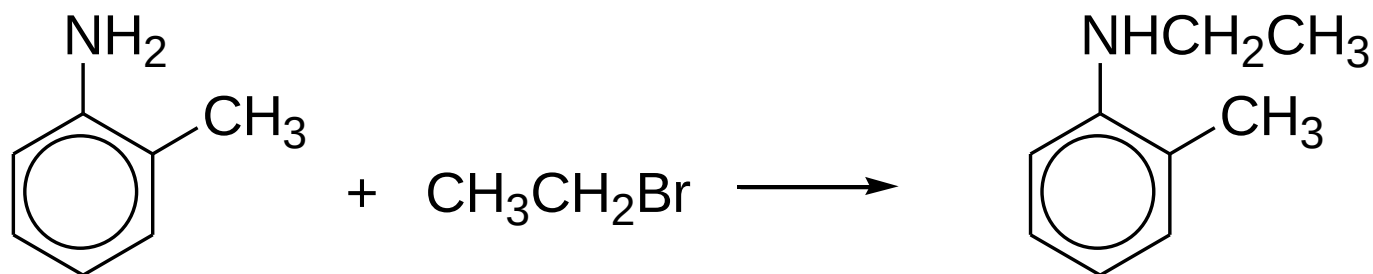


d) Friedel-Crafts alkylation

NR with $-\text{NH}_2$, $-\text{NHR}$, $-\text{NR}_2$



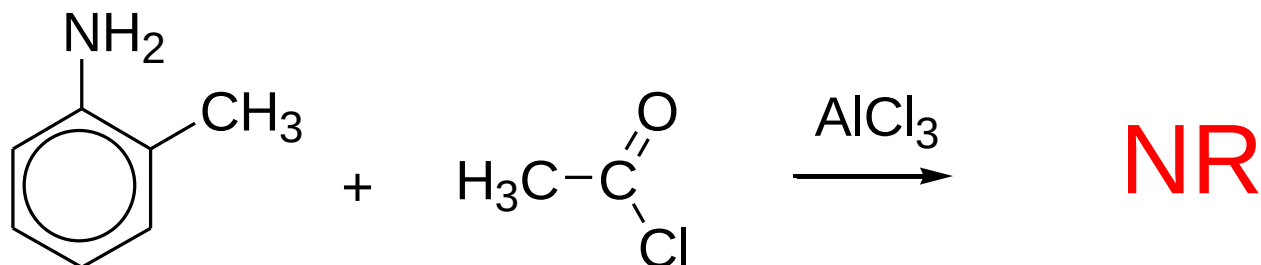
Do not confuse the above with the alkylation reaction:



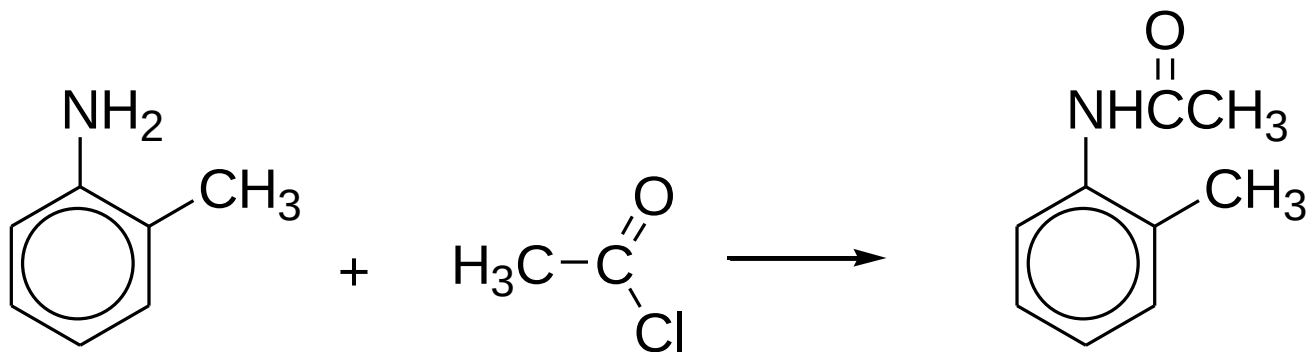


e) Friedel-Crafts acylation

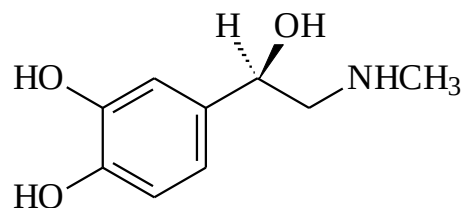
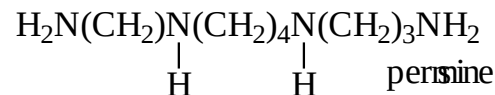
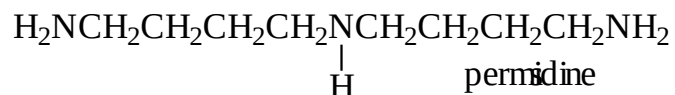
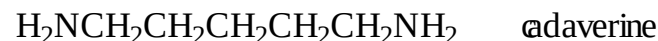
NR with $-\text{NH}_2$, $-\text{NHR}$, $-\text{NR}_2$



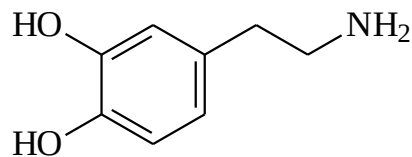
Do not confuse the above with the formation of amides:



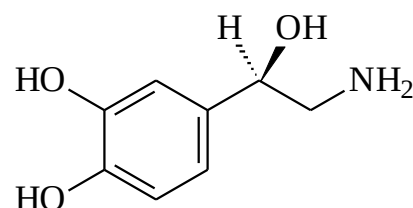
Example of biologically active amines



epinephrine
(adrenaline)



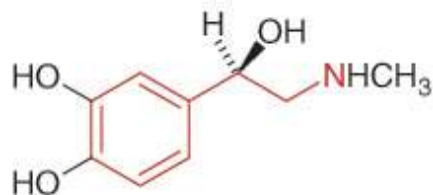
dopamine



norepinephrine
(noradrenaline)

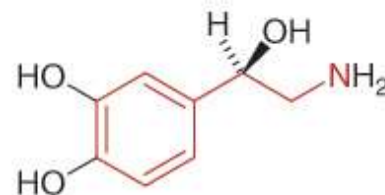


- A large number of physiologically active compounds are derived from 2-phenethylamine ($\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2$). These compounds include adrenaline, noradrenaline, methamphetamine, and mescaline. Each contains a benzene ring bonded to a two-carbon unit with a nitrogen atom (shown in red).



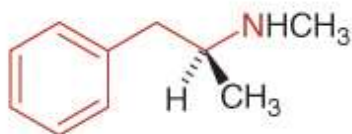
adrenaline
(epinephrine)

a hormone secreted in response to stress
(Chapter 7, introductory molecule)



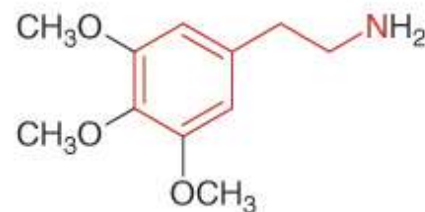
noradrenaline
(norepinephrine)

a neurotransmitter that increases heart rate
and dilates air passages



methamphetamine

an addictive stimulant sold as
speed, meth, or crystal meth

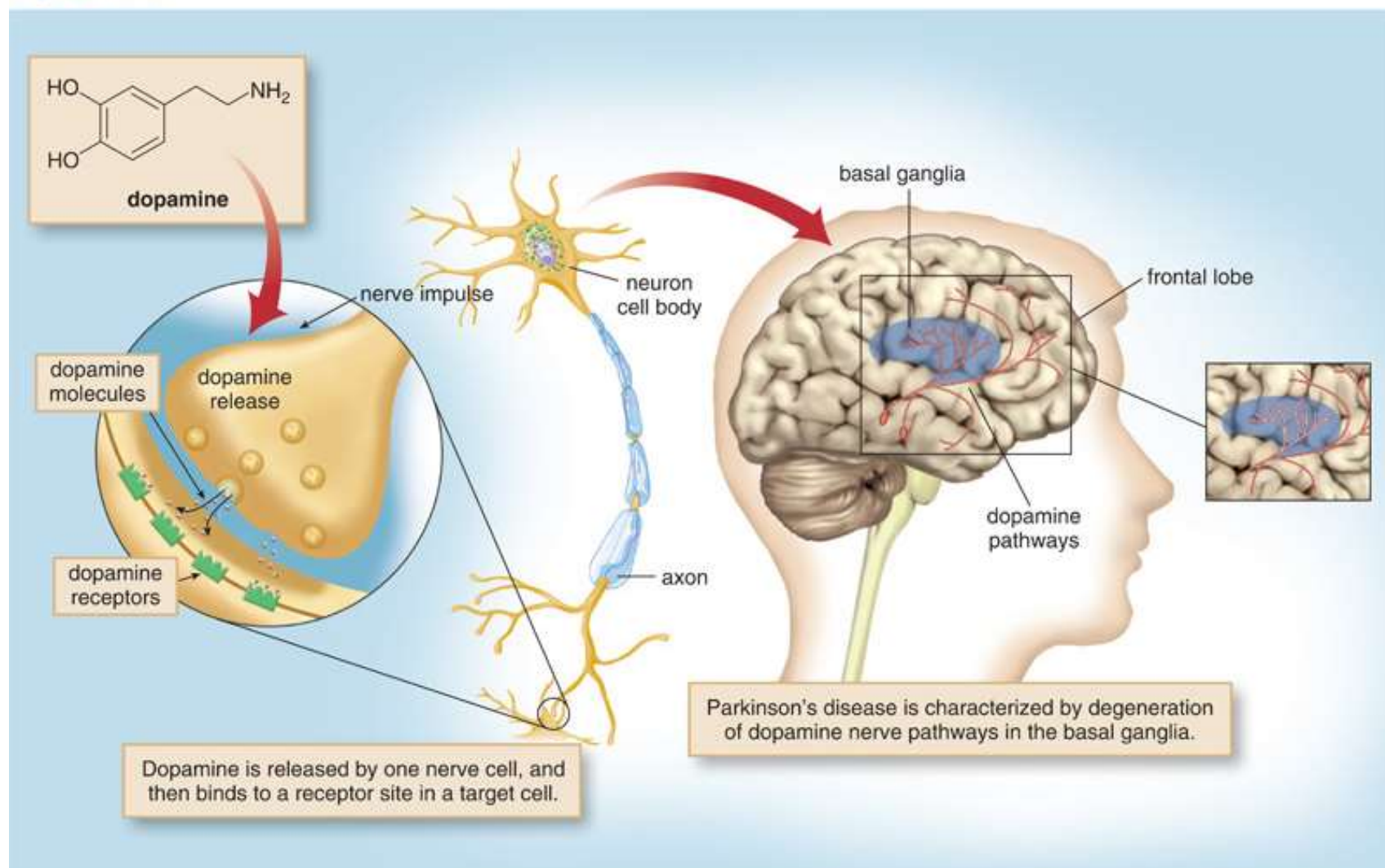


mescaline

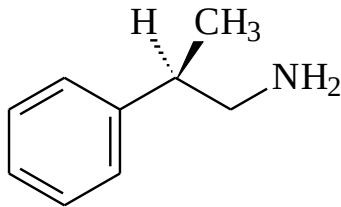
a hallucinogen isolated from peyote, a cactus native
to the southwestern United States and Mexico

the Neurotransmitter Dopamine.

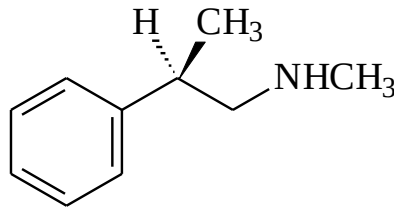
Figure 25.6 Dopamine—A neurotransmitter



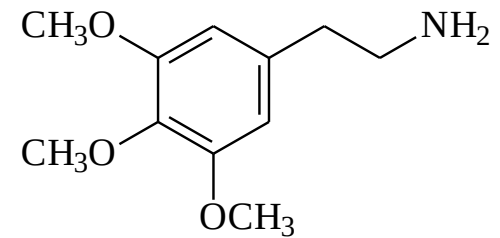
More biologically active amines...



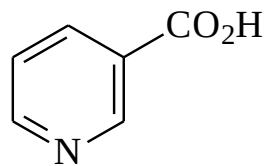
amphetamine
(benzadrine)



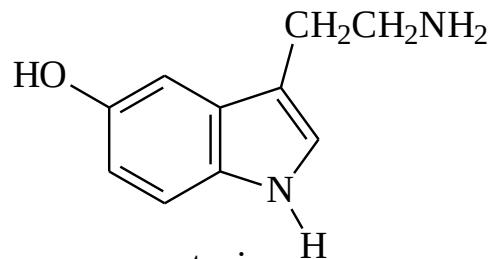
methamphetamine
(speed)



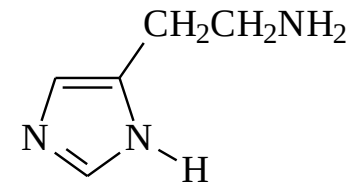
mescaline



nicotinic acid
(niacin)



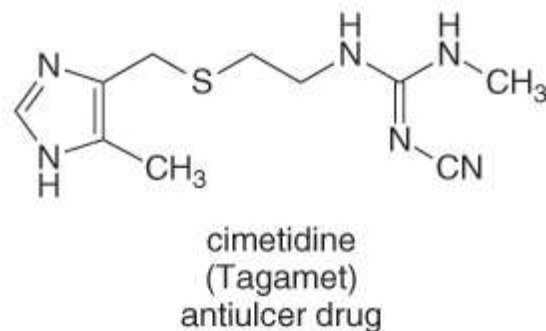
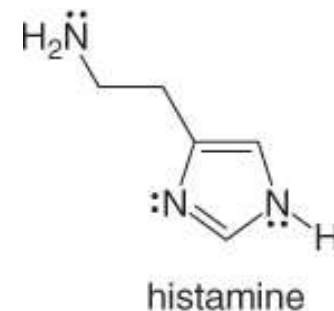
serotonin

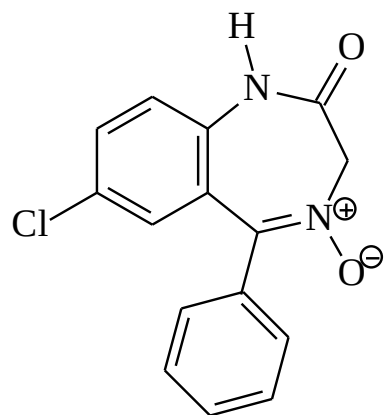


histamine

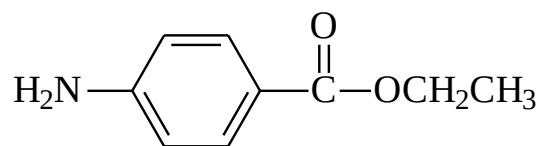


- Histamine, a rather simple triamine that is present in many tissues, is responsible for a wide variety of physiological effects.
- Understanding the physiological properties of histamine has helped chemists design drugs to counteract some of its undesirable effects. Antihistamines bind to the same active site as histamine in the cell, but they evoke a different response. Examples are brompheniramine and cimetidine.

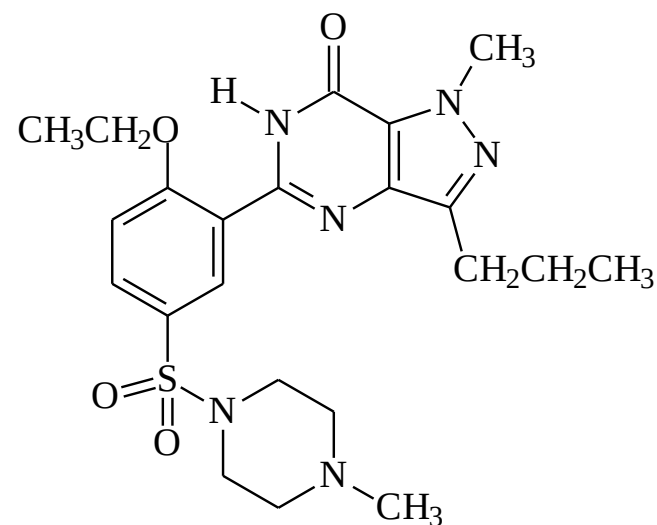




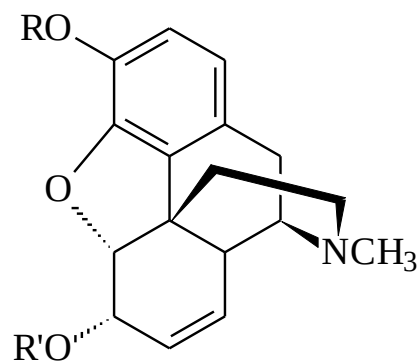
diazepam (Valium)



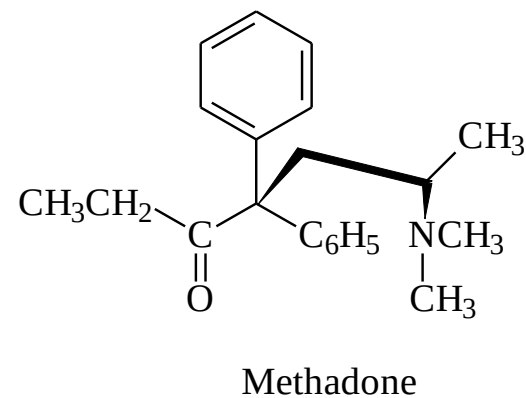
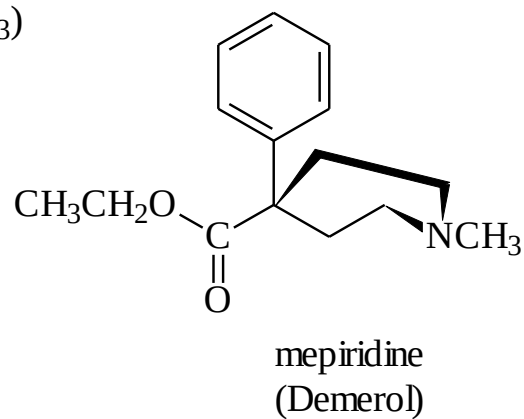
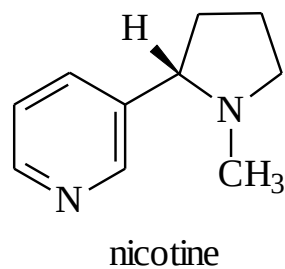
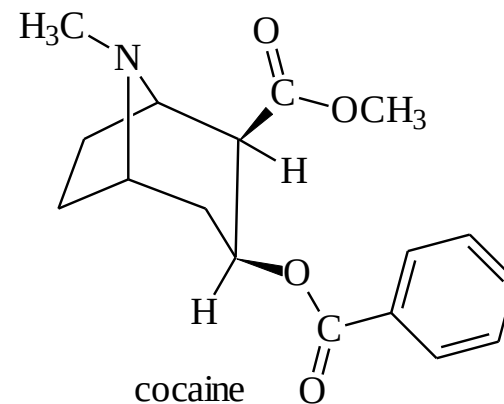
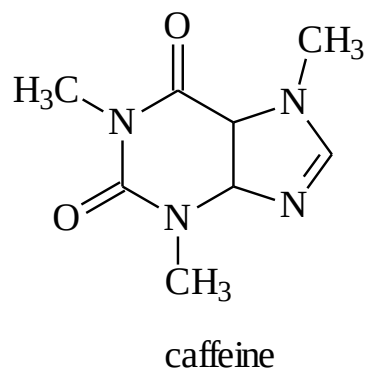
benzocaine
(a topical anesthetic)



Sildenafil (Viagra)

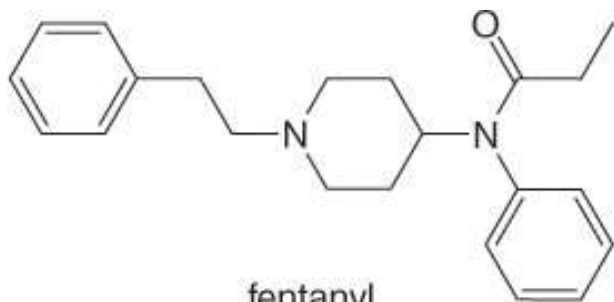


codeine ($R = \text{CH}_3$, $R' = \text{H}$)
 morphine (R and $R' = \text{H}$)
 heroin (R and $R' = \text{COCH}_3$)

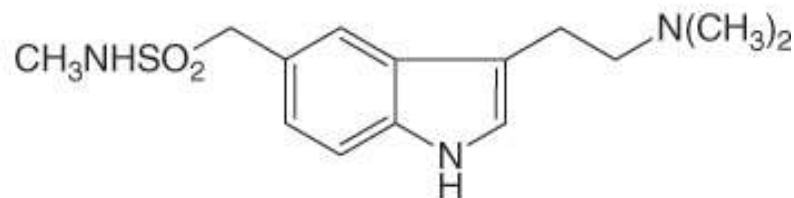




- Cocaine, amphetamines, and several other addicting drugs increase the level of dopamine in the brain, which results in a pleasurable “high.” With time, the brain adapts to increased dopamine levels, so more drug is required to produce the same sensation.
- Understanding the neurochemistry of these compounds has led to the synthesis and availability of several useful drugs. Examples are fentanyl and sumatriptan.



fentanyl
a narcotic pain reliever

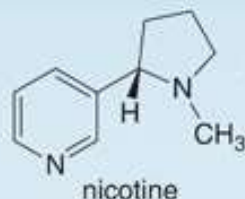


sumatriptan
Trade name: Imitrex

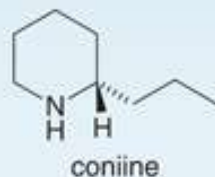
Figure 25.5 Three common alkaloids—Caffeine, nicotine, and coniine



coffee

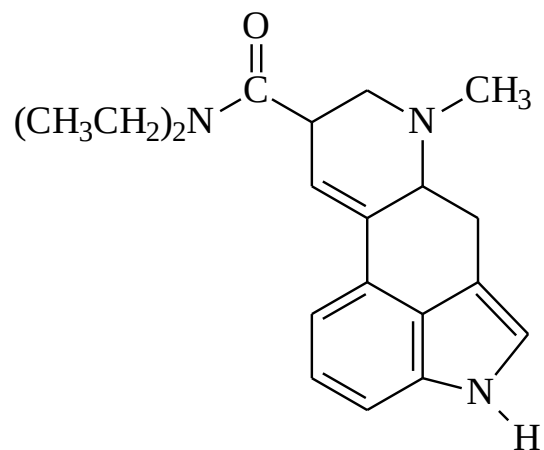


tobacco

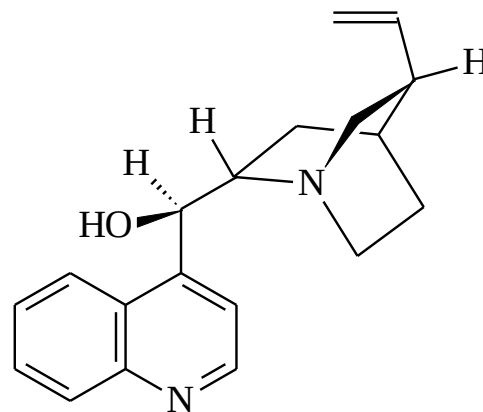


hemlock

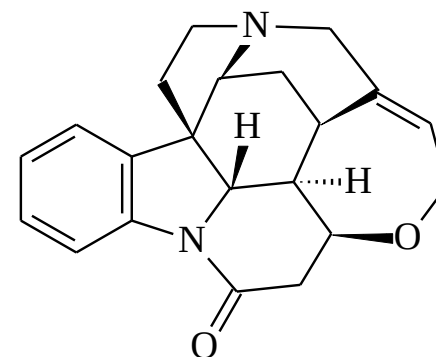
- **Caffeine** is a bitter alkaloid found in coffee, tea, cola beverages, and chocolate. Caffeine is a mild stimulant, usually imparting a feeling of alertness after consumption. It also increases heart rate, dilates airways, and stimulates the secretion of stomach acid. Excessive use can result in insomnia.
- **Nicotine** is an addictive and highly toxic compound isolated from tobacco. In small doses it acts as a stimulant, but in large doses it causes depression, nausea, and even death. Nicotine is synthesized in plants as a defense against insect predators, and is used commercially as an insecticide.
- **Coniine**, a poisonous alkaloid isolated from the seeds, leaves, and roots of hemlock (*Conium maculatum*), has been known since ancient times. Ingestion causes weakness, paralysis, and finally death. The Greek philosopher Socrates was executed by being forced to drink a potion prepared from hemlock in 339 B.C.



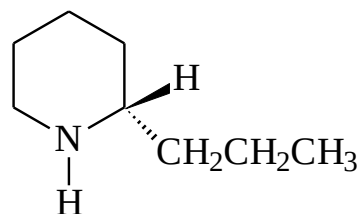
lysergic acid diethylamide (LSD)



quinine



strychnine



coniin (the poison from
hemlock used to kill Socrates)