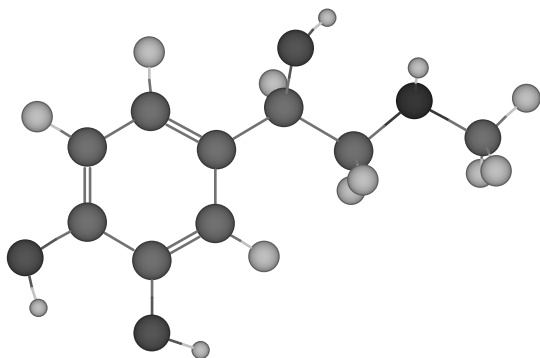


Amines

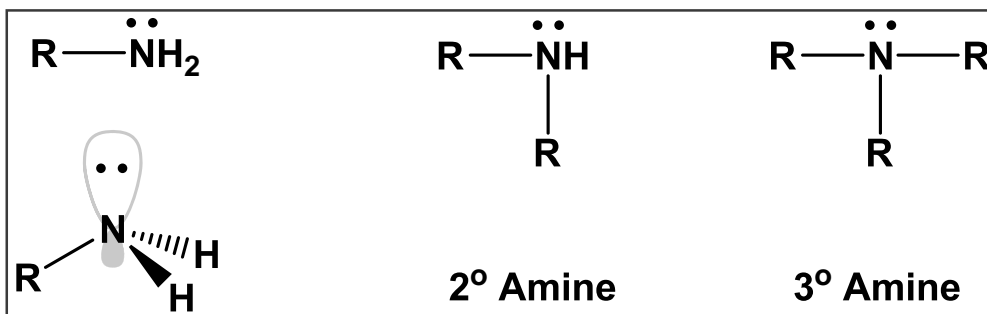


Epinephrine (adrenaline)

Chapter 23 1

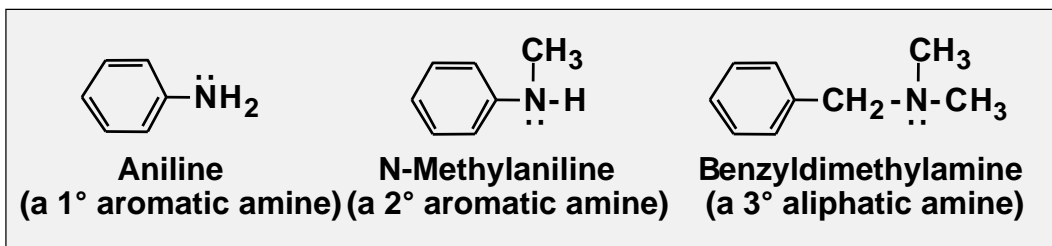
Structure & Classification

- Amines are classified as
 - 1°, 2°, or , 3° amines:** amines in which 1, 2, or 3 hydrogens of NH_3 are replaced by alkyl or aryl groups



Structure & Classification

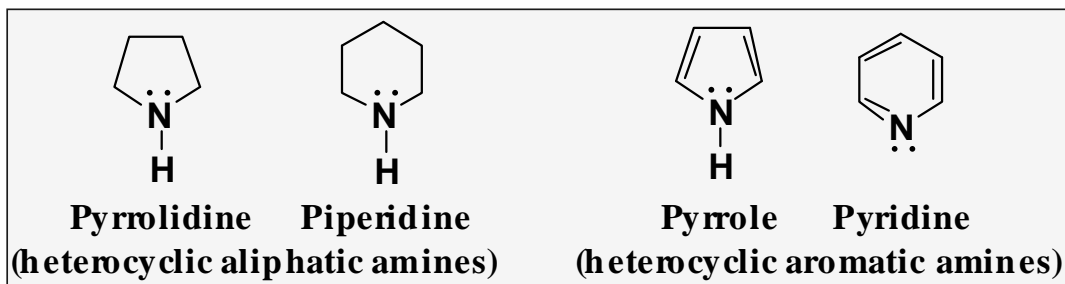
- Amines are further divided into aliphatic, aromatic, and heterocyclic amines:
 - aliphatic amine:** an amine in which nitrogen is bonded only to alkyl groups
 - aromatic amine:** an amine in which nitrogen is bonded to one or more aryl groups



3

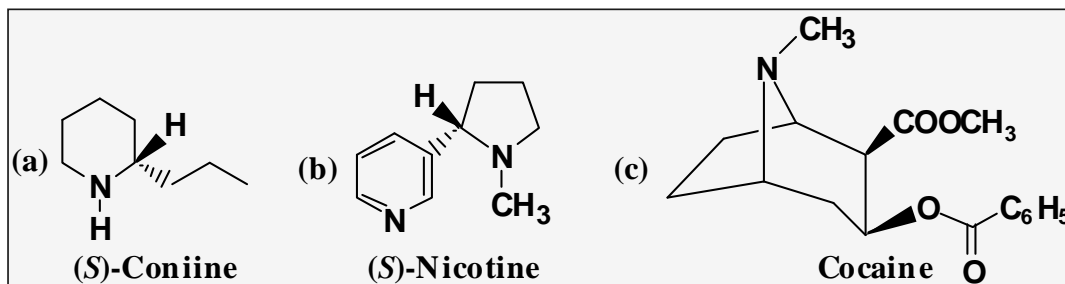
Structure & Classification

- heterocyclic amine:** an amine in which nitrogen is one of the atoms of a ring

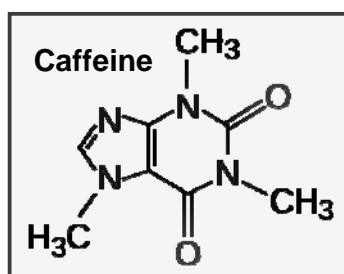


4

Structure & Classification



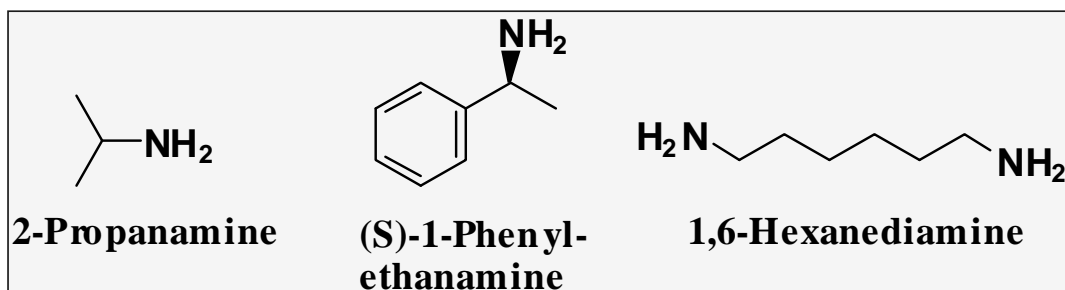
Coniine is a poisonous alkaloid found in poison hemlock and the Yellow Pitcher Plant, and contributes to hemlock's fetid smell. It is a neurotoxin which disrupts the peripheral nervous system.



5

Nomenclature

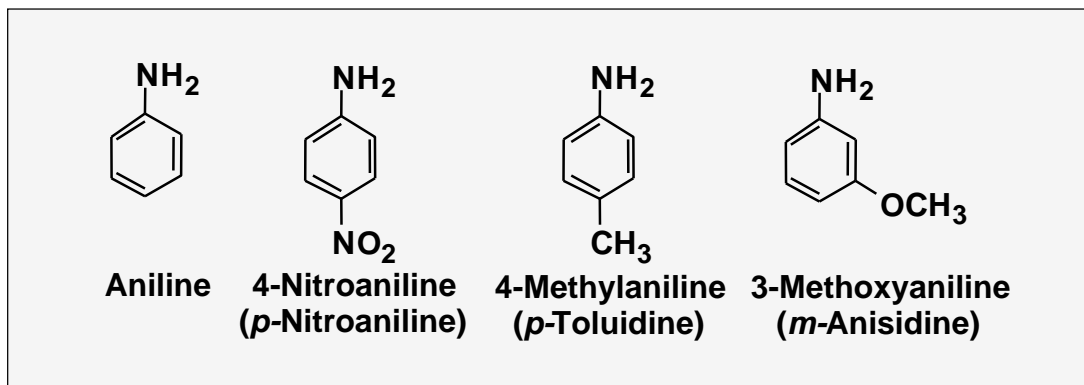
- Aliphatic amines: replace the suffix -e of the parent alkane by -amine



6

Nomenclature

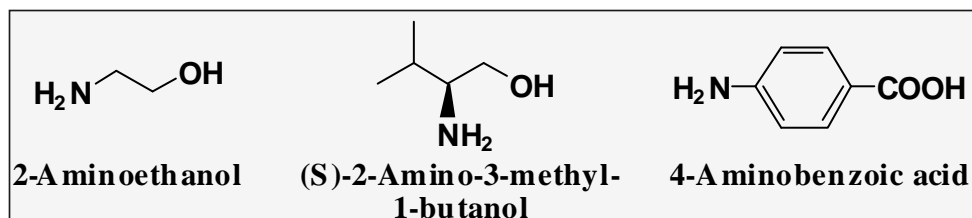
- The IUPAC system retains the name **aniline**:



7

Nomenclature

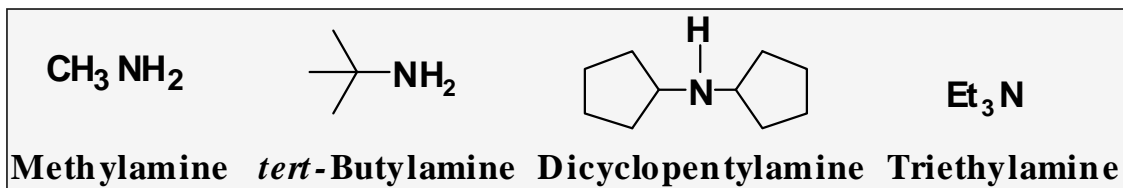
- Among the various functional groups discussed in the text, -NH_2 is one of the lowest in order of precedence



8

Nomenclature

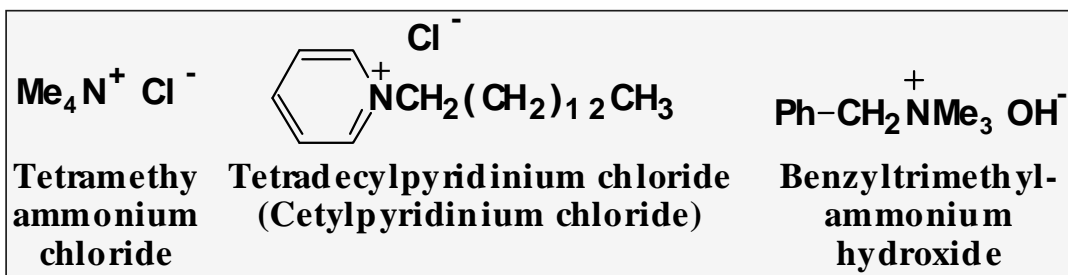
- **Common names** for most aliphatic amines are derived by listing the alkyl groups bonded to nitrogen in one word ending with the suffix -amine



9

Nomenclature

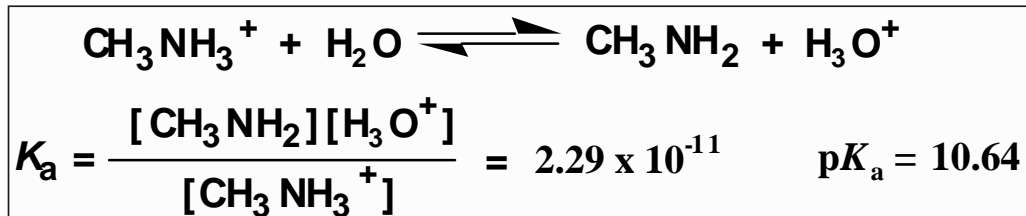
- When four groups are bonded to nitrogen, the compound is named as a **salt** of the corresponding amine



10

Basicity

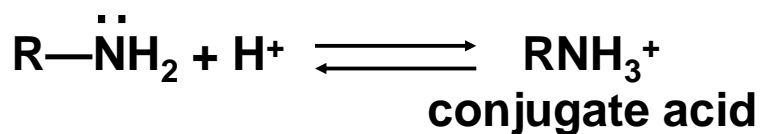
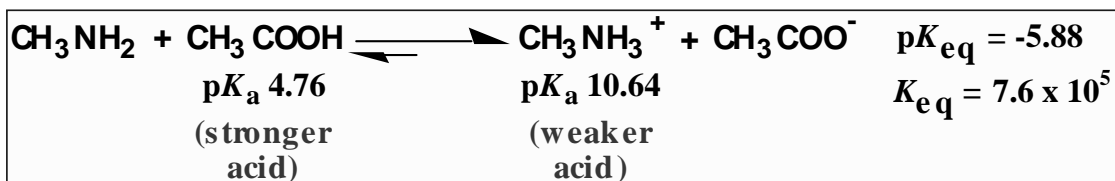
- it is common to discuss their basicity by reference to the acid ionization constant of the conjugate acid:



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Basicity

- using values of $\text{p}K_a$, comparisons of the acidities of amine conjugate acids with other acids can be made:

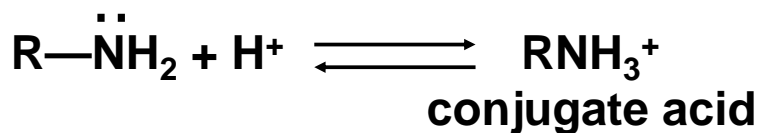


14

Basicity-Aliphatic Amines

ORGANIC LECTURE SERIES

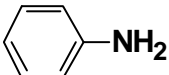

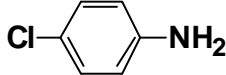
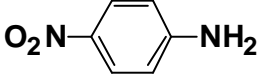
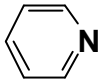
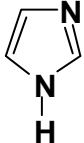
Amine	Structure	pK_a	pK_b
Ammonia	NH_3	9.26	4.74
Primary Amines			
methylamine	CH_3NH_2	10.64	3.36
ethylamine	$CH_3CH_2NH_2$	10.81	3.19
cyclohexylamine	$C_6H_{11}NH_2$	10.66	3.34
Secondary Amines			
dimethylamine	$(CH_3)_2NH$	10.73	3.27
diethylamine	$(CH_3CH_2)_2NH$	10.98	3.02
Tertiary Amines			
trimethylamine	$(CH_3)_3N$	9.81	4.19
triethylamine	$(CH_3CH_2)_3N$	10.75	3.25



15

Basicity-Aromatic Amines

ORGANIC LECTURE SERIES

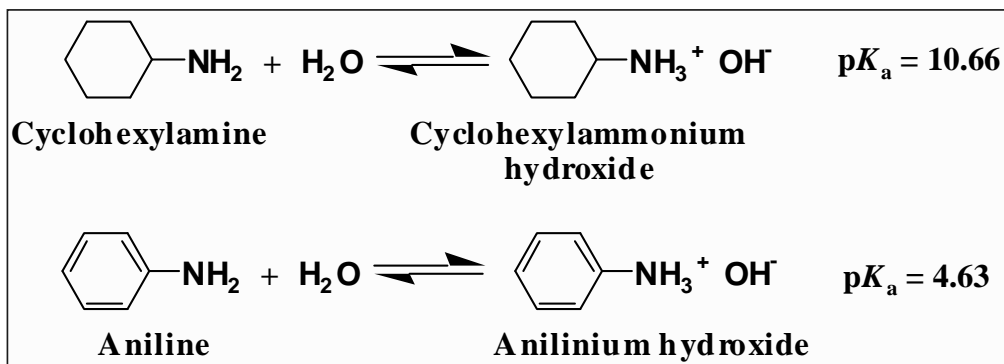
Amine	Structure	pK_a of Conjugate Acid
Aromatic Amines		
Aniline		4.63
4-Methylaniline		5.08
4-Chloroaniline		4.15
4-Nitroaniline		1.0
Heterocyclic Aromatic Amines		
Pyridine		5.25
Imidazole		6.95

Note the effect of Ar-X on the acidity:
The stronger the e^- withdrawing effect, the weaker the base & stronger the conjugate acid.

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Basicity-Aromatic Amines

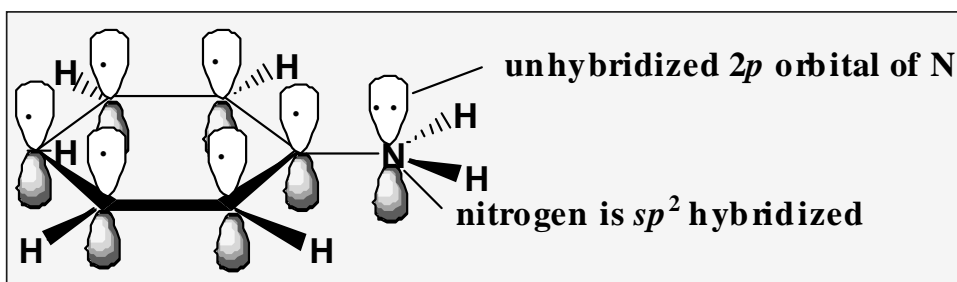
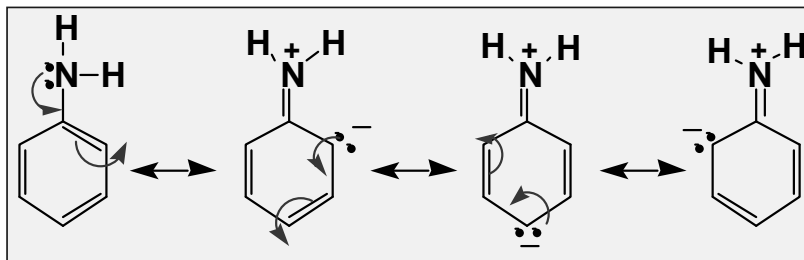
- aromatic amines are considerably weaker bases than aliphatic amines



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Basicity-Aromatic Amines

- Aromatic amines are **weaker bases** than aliphatic amines because of two factors
 - **resonance stabilization of the free base**, which is lost on protonation



18

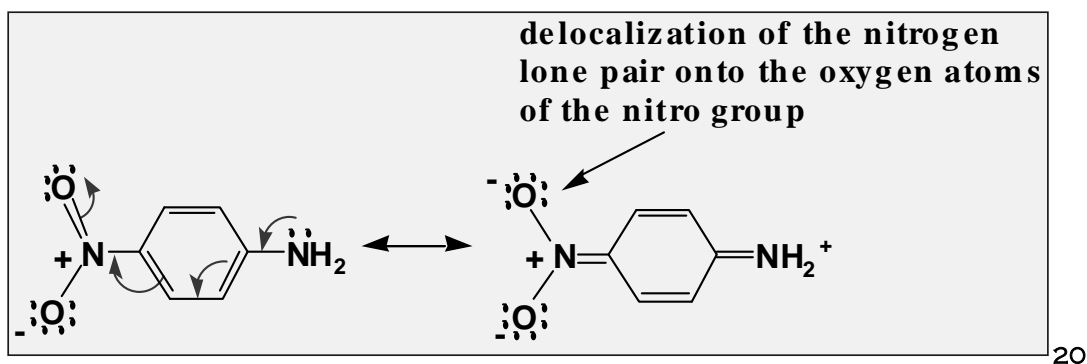
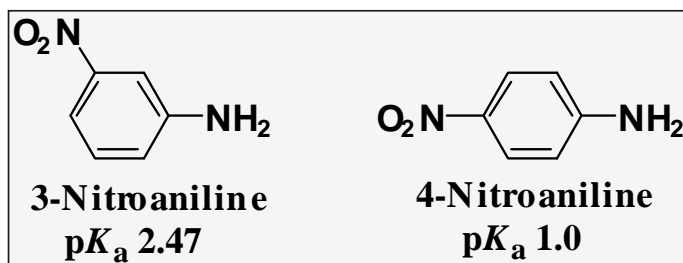
Basicity-Aromatic Amines

- the greater electron-withdrawing inductive effect of the sp^2 -hybridized carbon of an aromatic amine compared with the sp^3 -hybridized carbon of an aliphatic amine also decreases basicity
- Electron-releasing, such as alkyl groups, increase the basicity of **aromatic** amines
- Electron-withdrawing groups, such as halogens, the nitro group, and a carbonyl group decrease the basicity of aromatic amines by a combination of resonance and inductive effects

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Basicity-Aromatic Amines

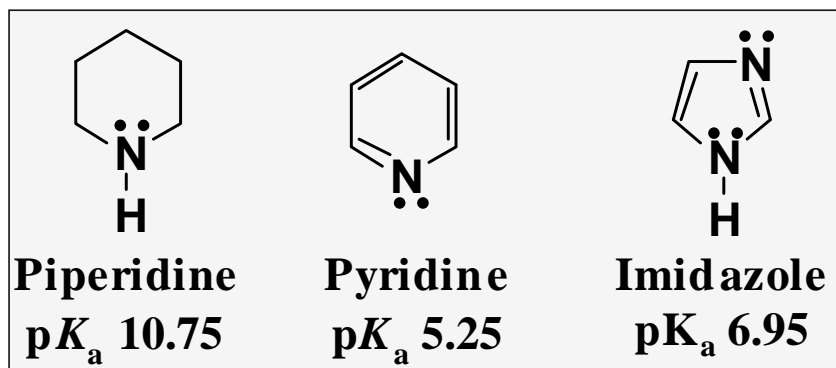
4-nitroaniline is a weaker base than 3-nitroaniline



20

Basicity-Aromatic Amines

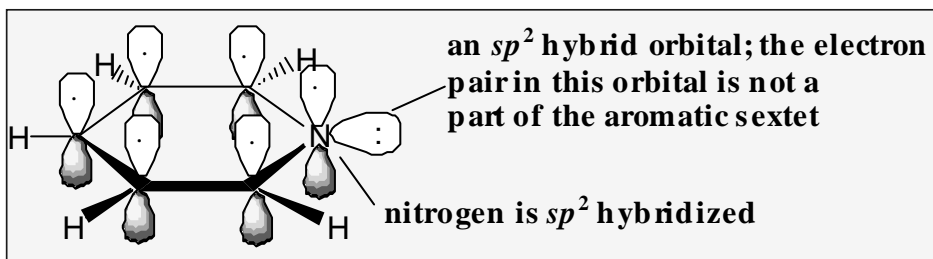
- Heterocyclic aromatic amines are weaker bases than heterocyclic aliphatic amines



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Basicity-Aromatic Amines

- in pyridine, the unshared pair of electrons on N is **not** part of the aromatic sextet

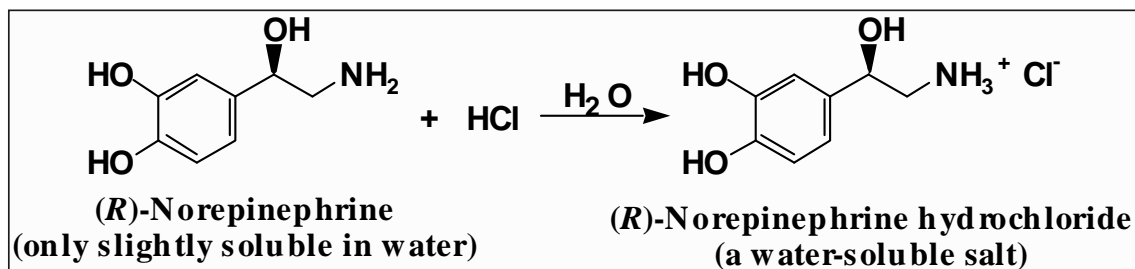


- pyridine is a weaker base than heterocyclic aliphatic amines because the free electron pair on N lies in an sp^2 hybrid orbital (33% s character) and is held more tightly to the nucleus than the free electron pair on N in an sp^3 hybrid orbital (25% s character)

22

Reaction with Acids

- All amines, whether soluble or insoluble in water, react quantitatively with strong acids to form water-soluble salts



23

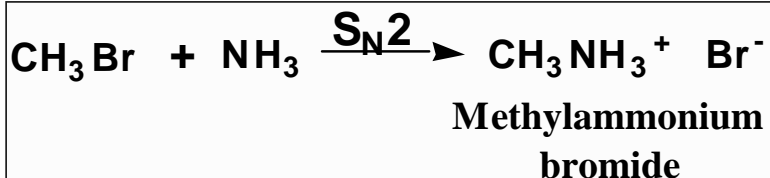
Preparation

- A summary of synthetic methods:
 - nucleophilic ring opening of epoxides by ammonia and amines (**11.9B**)
 - addition of nitrogen nucleophiles to aldehydes and ketones to form imines (**Section 16.8**)
 - reduction of imines to amines (**16.8A**)
 - reduction of amides by LiAlH_4 (**18.10B**)
 - reduction of nitriles to a 1° amine (**18.10C**)
 - nitration of arenes followed by reduction of the NO_2 group to 1° amines (**22.1B**)

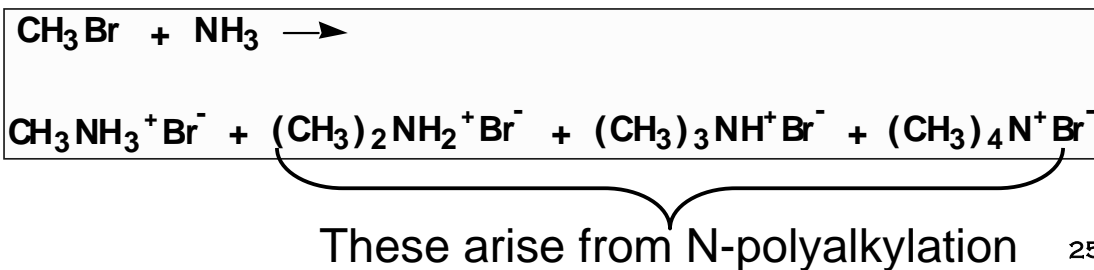
24

Preparation

- Alkylation of ammonia and amines by S_N2

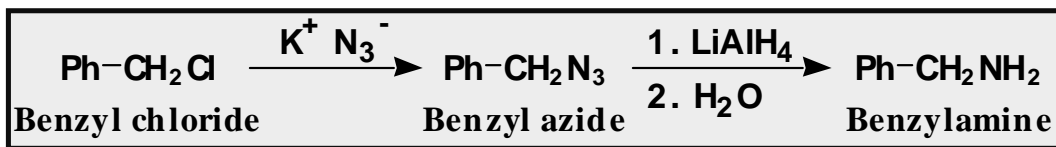


- unfortunately, such alkylations give mixtures of products through a series of proton transfer and nucleophilic substitution reactions



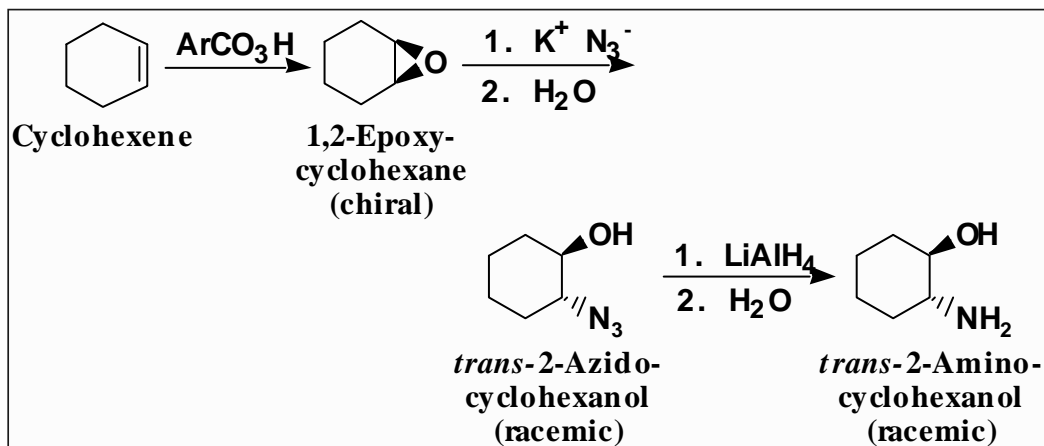
Preparation via Azides

- Alkylation of azide ion, N_3^-



Preparation via Azides

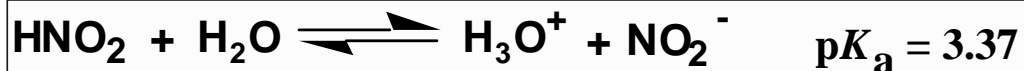
– alkylation of azide ion



27

Reaction with HNO_2

- **Nitrous acid**, a weak acid, is most commonly prepared by treating NaNO_2 with aqueous H_2SO_4 or HCl



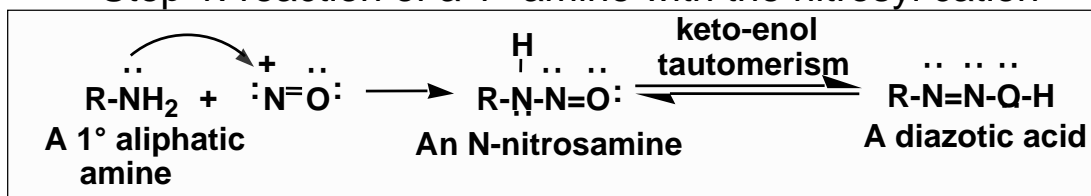
- In its reactions with amines, nitrous acid
 - participates in proton-transfer reactions
 - is a source of the nitrosyl cation, NO^+ , a weak electrophile

28

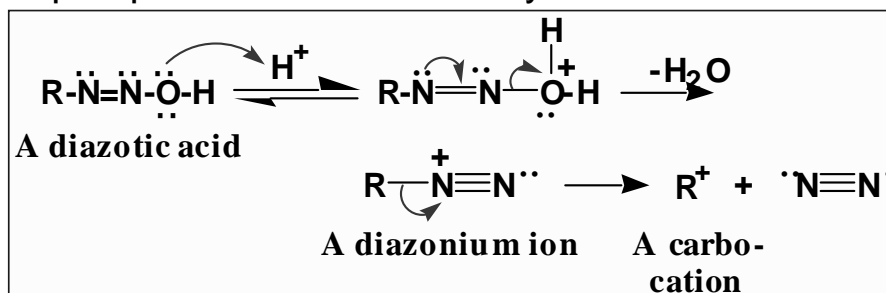
1° RNH₂ with HNO₂

- Formation of a diazonium ion

Step 1: reaction of a 1° amine with the nitrosyl cation



Step 2: protonation followed by loss of water

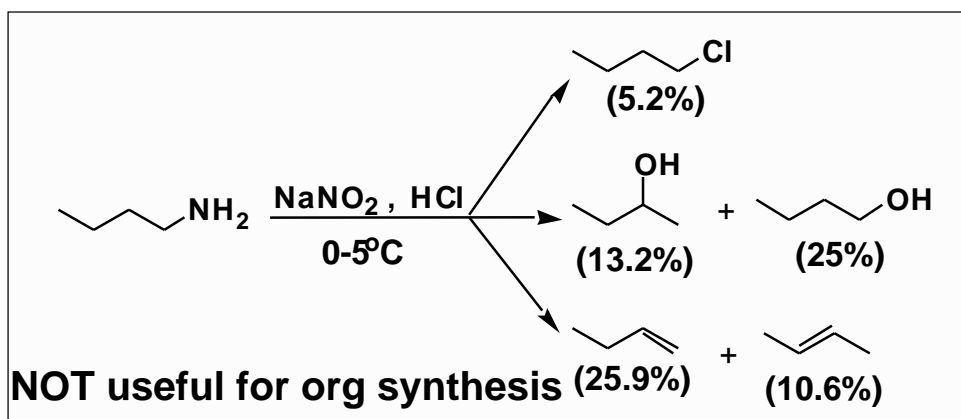


NOT responsible for mechanism

31

1° RNH₂ with HNO₂

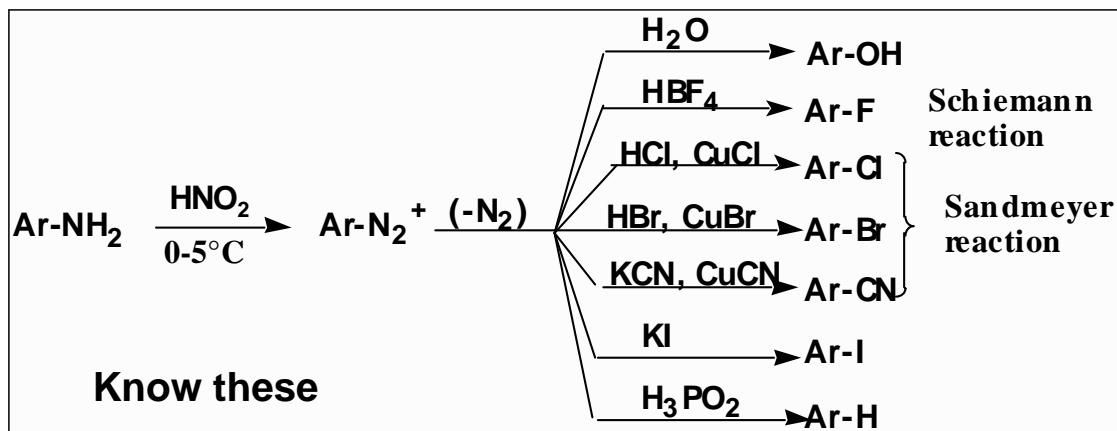
- Aliphatic diazonium ions are unstable and lose N₂ to give a carbocation which may
 - lose a proton to give an alkene
 - react with a nucleophile to give a substitution product
 - rearrange and then react by 1 and/or 2



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1° ArNH₂ with HNO₂

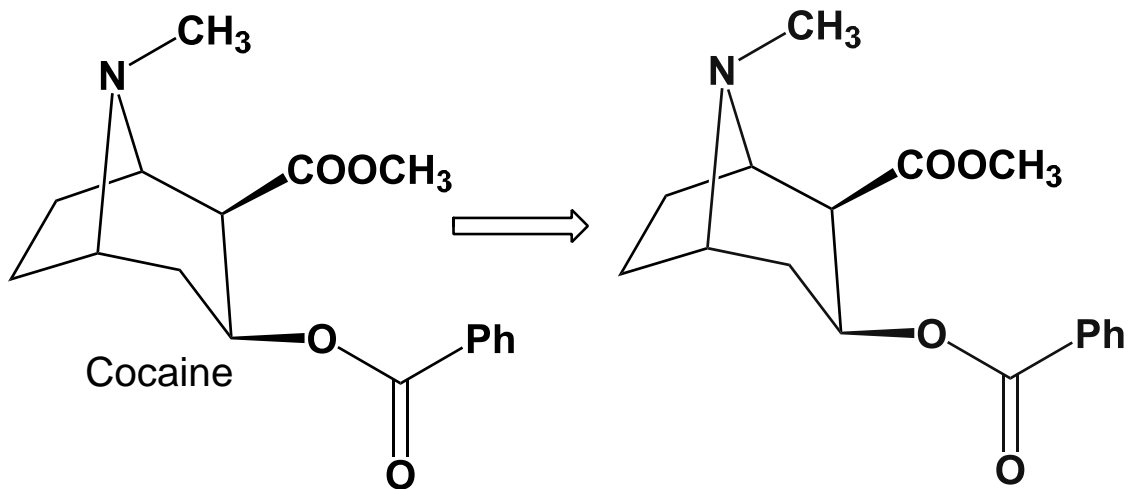
- The -N₂⁺ group of an arenediazonium salt can be replaced in a regioselective manner by these groups



33

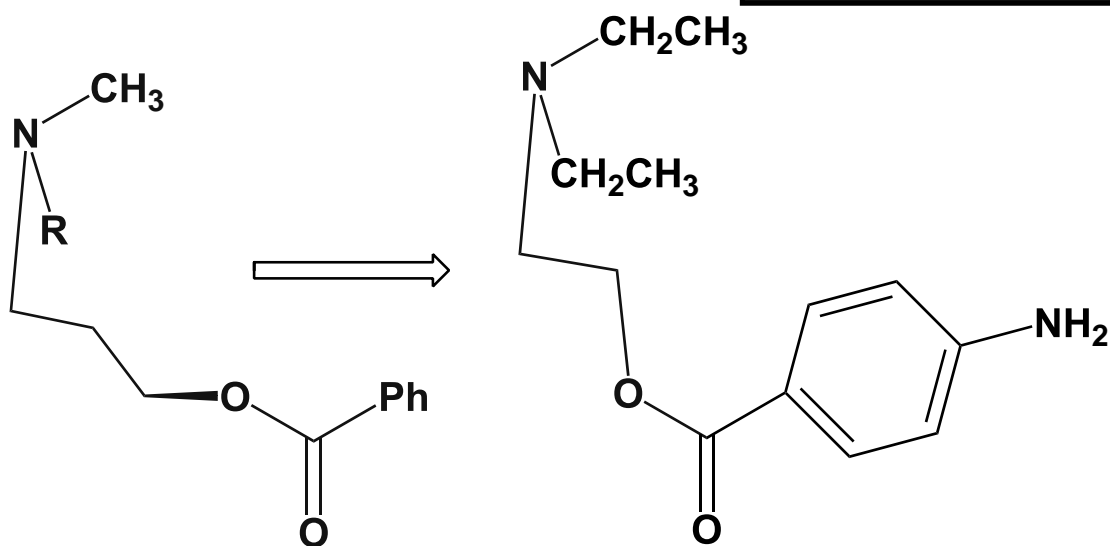
Local Anesthetics

34



Topical anesthetic (local)
CNS stimulant

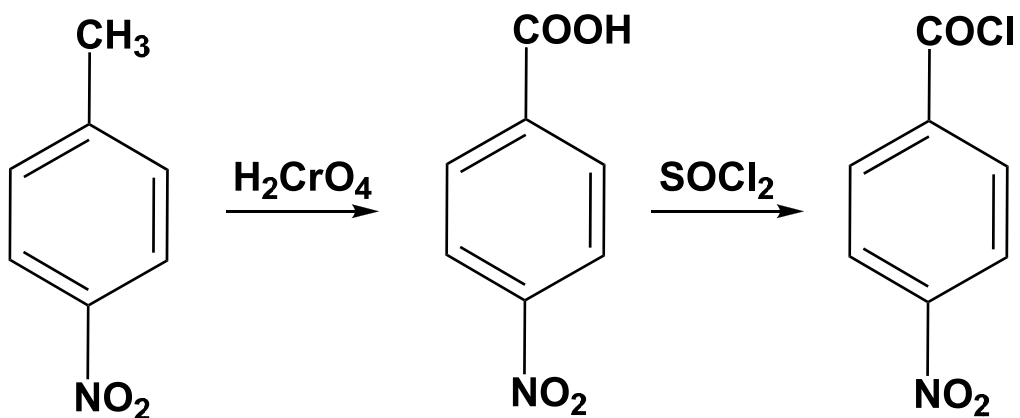
35



Alkanolamines
(Ethanolamines)
Procaine

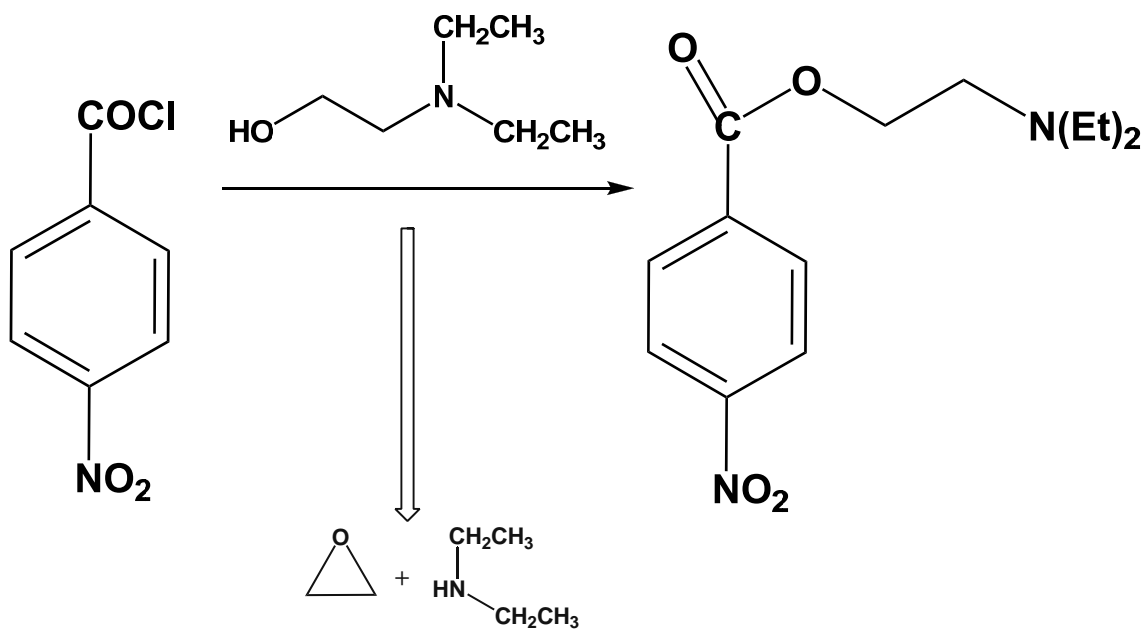
36

Synthesis of Procaine



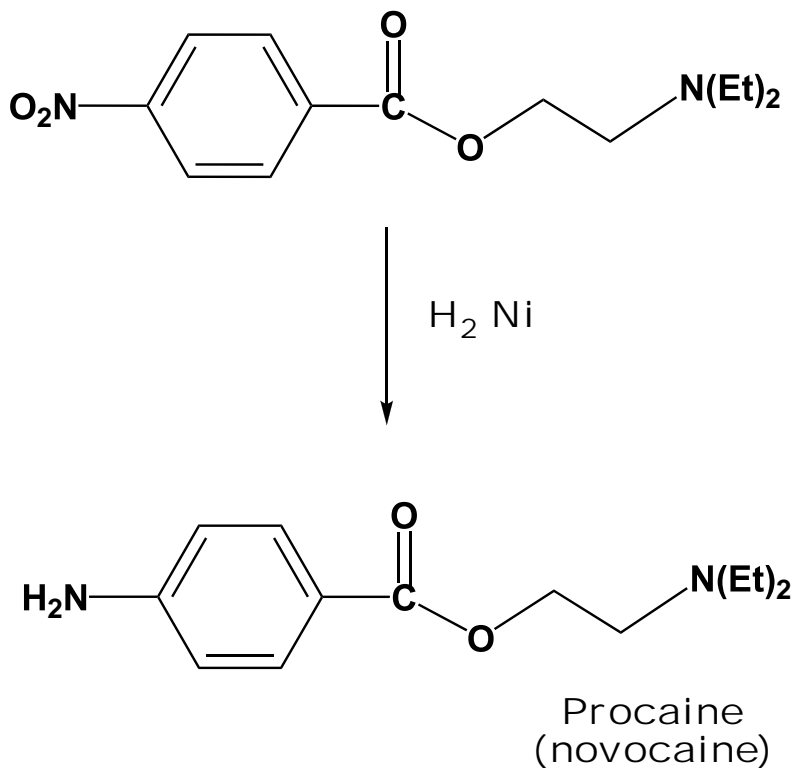
37

Synthesis of Procaine

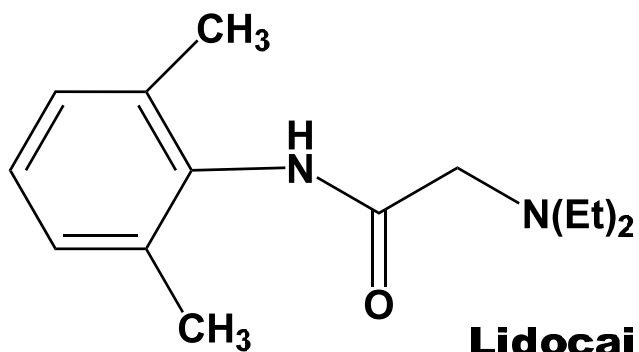
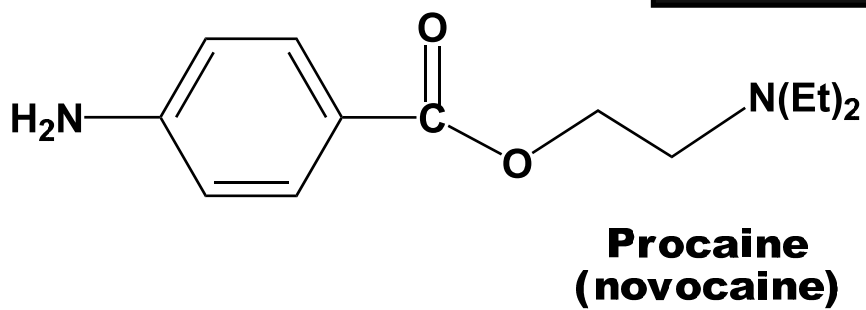


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Synthesis of Procaine



39



**Lidocaine
Xylocaine®**

40