Chemistry 121(01) Winter 2010-11

Introduction to Organic Chemistry and Biochemistry

Instructor Dr. Upali Siriwardane (Ph.D. Ohio State)
E-mail: upali@chem.latech.edu
Office: 311 Carson Taylor Hall ; Phone: 318-257-4941;
Office Hours: MWF 8:00 am - 10:00 am;
TT 9:00 – 10:00 am & 1:00-2:00 pm.

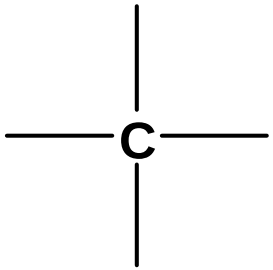
December 17, 2010 Test 1 (Chapters 12-13)
January 19, 2011 Test 2 (Chapters 14,15 & 16)
February 7, 2011 Test 3(Chapters 17, 18 & 19)
February 23, 2011 Test 4 (Chapters 20, 21 & 22)
February 24, 2011 Comprehensive Make Up Exam:

Chapter 17: Amines and Amides

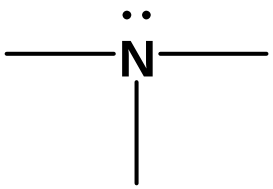
Chapter 17: Amines and Amides

Bonding Characteristics of Nitrogen

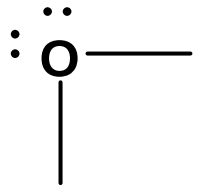
- **Nitrogen is a member of Group VA of the periodic table**
- **Nitrogen has five valence electrons**
- **Nitrogen can form three covalent bonds to complete its octet of electrons**



4 Valence electrons
4 Covalent bonds
No nonbonding electron pairs



5 Valence electrons
3 Covalent bonds
1 No nonbonding electron pairs



6 Valence electrons
2 Covalent bonds
2 No nonbonding electron pairs

Amine: Organic derivative of ammonia (NH_3)

Molecule of ammonia (NH_3) in which one or more alkyl, cycloalkyl, or aryl groups are attached to the nitrogen atom are called amines

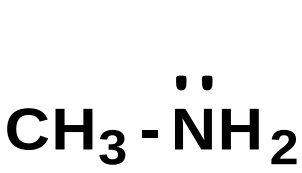
Classification:

- **Primary amines (1^o): Nitrogen with one R group**
- **Secondary amines (2^o): Nitrogen with two R groups**
- **Tertiary amines (3_o): Nitrogen with three R groups**

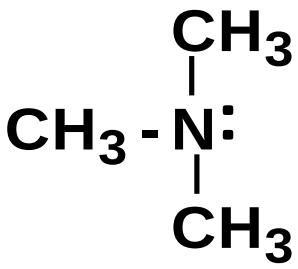
Structure & Classification

Classification

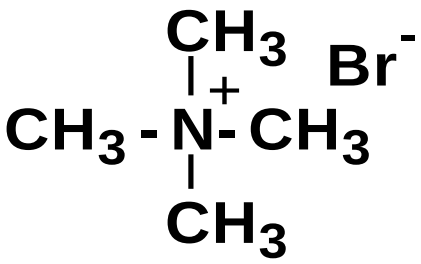
- **1°, 2°, or , 3° amines: amines in which 1, 2, or 3 hydrogens of NH_3 are replaced by alkyl or aryl groups**
- **4° amines: ions in which nitrogen is bonded to four carbons and bears a positive charge**



Methylamine (a 1° amine)



Trimethylamine (a 3° amine)



Tetramethylammonium bromide (a 4° ammonium salt)

Cyclic Amines

- Cyclic amines either secondary or tertiary amines
- Cyclic amines are designated as heterocyclic compounds
- Numerous heterocyclic amines are found in biochemical systems

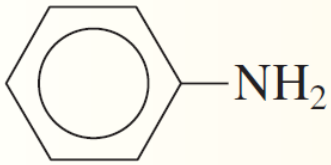
Practice Exercise

Classify each of the following amines as a primary, secondary, or tertiary amine.

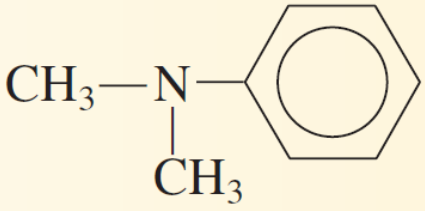
a. $CH_3—CH_2—CH_2—NH_2$

b. $CH_3—NH—CH_2—CH_3$

c.



d.



Answers:

a. Primary

b. Secondary

c. Primary

d. Tertiary

IUPAC Rules for Naming Primary Amines

Rule 1: Select as the parent carbon chain the longest chain to which the nitrogen atom is attached.

Rule 2: Name the parent chain by changing the *-e* ending of the corresponding *alkane* name to *-amine*.

Rule 3: Number the parent chain from the end nearest the nitrogen atom.

Rule 4: The position of attachment of the nitrogen atom is indicated by a number in front of the parent chain name.

Rule 5: The identity and location of any substituents are appended to the front of the parent chain name.

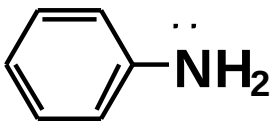
NH_2 group the amino group

- **Secondary and tertiary amines are named as N-substituted primary amines.**
- **The largest carbon group bonded to the nitrogen is used as the parent amine name.**
- **The names of the other groups attached to the nitrogen are appended to the front of the base name.**
  - **N- or N,N- prefixes are used to indicate that these groups are attached to the nitrogen atom**

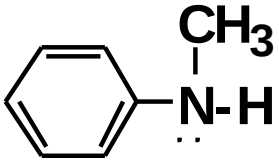
Structure & Classification

Amines are further divided into aliphatic, aromatic, and heterocyclic amines

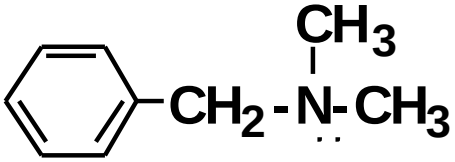
- **aliphatic amine:** an amine in which nitrogen is bonded only to alkyl groups
- **aromatic amine:** an amine in which nitrogen is bonded to one or more aryl groups



Aniline
(a 1° aromatic amine)



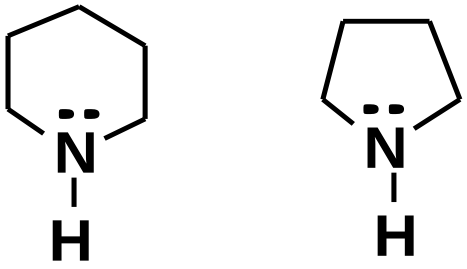
***N*-Methylaniline**
(a 2° aromatic amine)



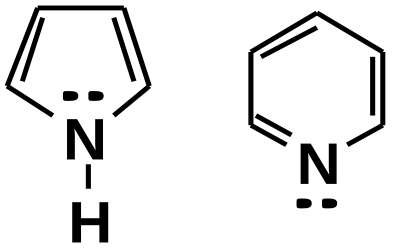
Benzyldimethylamine
(a 3° aliphatic amine)

Structure & Classification

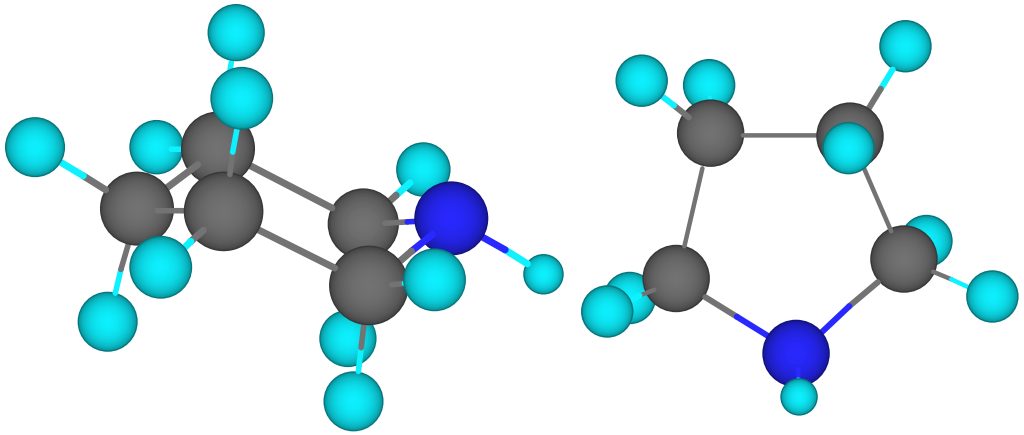
- **heterocyclic amine: an amine in which nitrogen is one of the atoms of a ring**



Piperidine Pyrrolidine (heterocyclic aliphatic amines)



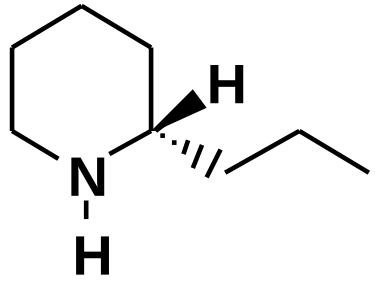
Pyrrole Pyridine (heterocyclic aromatic amines)



Structure & Classification

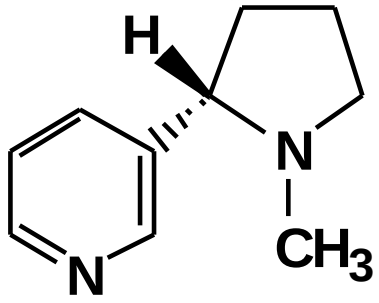
Example: classify each amino group by type

(a)



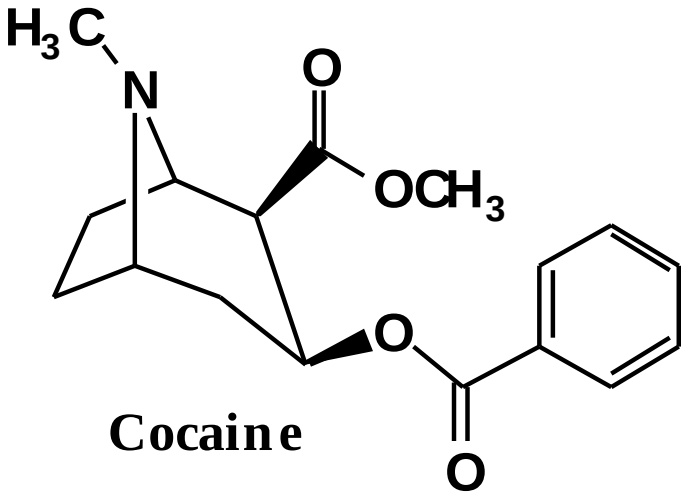
(S)-(+)-Coniine

(b)



(S)-(-)-Nicotine

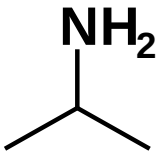
(c)



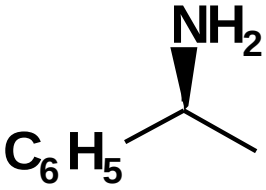
Cocaine

Nomenclature

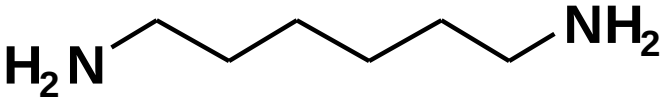
Aliphatic amines: replace the suffix -e of the parent alkane by -amine



2-Propanamine

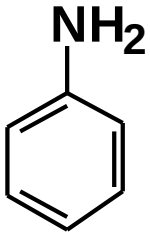


(S)-1-Phenylethanamine

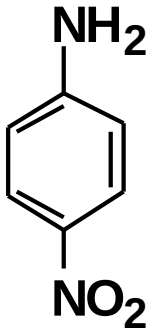


1,6-Hexanediamine

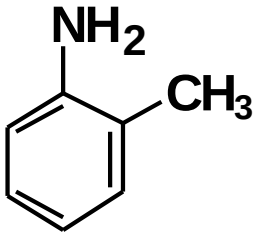
The IUPAC system retains the common name aniline



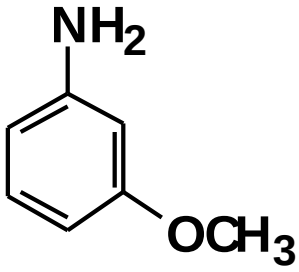
Aniline



4-Nitroaniline (*p*-Nitroaniline)



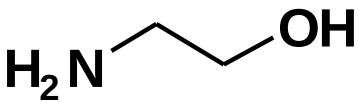
2-Methylaniline (*o*-Toluidine)



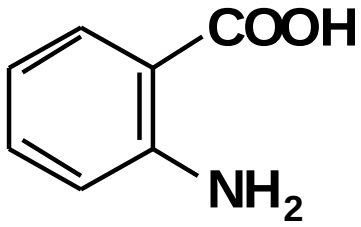
3-Methoxyaniline (*m*-Anisidine)

Nomenclature

Among the various functional groups discussed in the text, -NH_2 has one of the lowest priorities



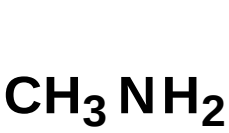
2-Aminoethanol



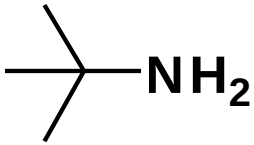
2-Aminobenzoic acid
(Anthranilic acid)

Nomenclature

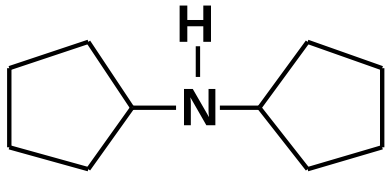
Common names for most aliphatic amines are derived by listing the alkyl groups bonded to nitrogen in one word ending with the suffix -amine



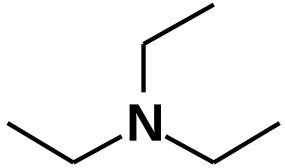
Methylamine



tert- Butylamine



Dicyclopentylamine



Triethylamine

Aromatic Amine-Aniline

- In amines with additional functional groups are present, the amine group is treated as a substituent, E.g, an —NH_2 group is called an amino group.
- The simplest aromatic amine, a benzene ring bearing an amino group, is called *aniline* and the other simple aromatic amines are named as derivatives of aniline.
- In secondary and tertiary aromatic amines, the additional group or groups attached to the nitrogen atom are located using a capital *N*-.

Constitutional isomerism of amines

Constitutional isomerism in amines can arise from several causes. Different carbon atom arrangements produce isomers

Different positioning of the nitrogen atom on a carbon chain is another cause for isomerism

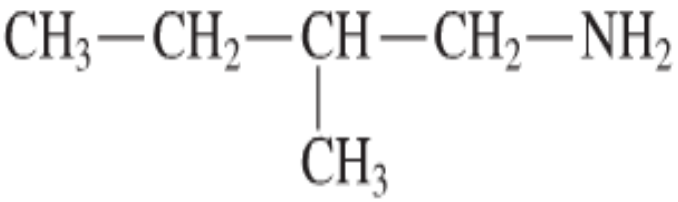
Insecondary and tertiary amines, different partitioning of carbon atoms among the carbon chains present produces constitutional isomers.

- **There are three C_4 secondary amines**
- **Carbon atom partitioning can be two ethyl groups, a propyl group and a methyl group, or an isopropyl group and a methyl group.**

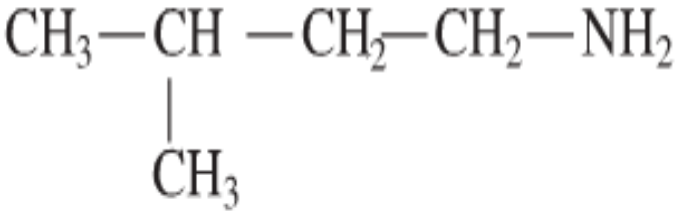
Constitutional Isomers: 1-pentaamine

1-Pentanamine

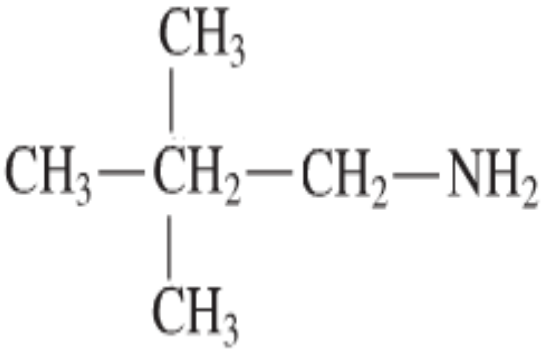
and



2-Methyl-1-butanamine



3-Methyl-1-butanamine



2,2-Dimethypropanmine

Physical Properties

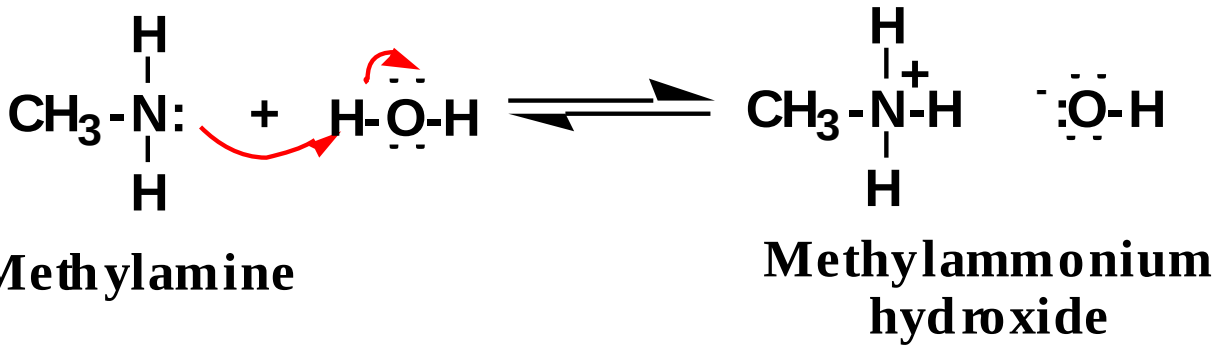
Amines are polar compounds, and both 1° and 2° amines form intermolecular hydrogen bonds

- N-H- - - -N hydrogen bonds are weaker than O-H- - - -O hydrogen bonds 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)

	CH_3CH_3	CH_3NH_2	CH_3OH
molecular weight (g/mol)	30.1	31.1	32.0
boiling point (°C)	-88.6	-6.3	65.0

Basicity

All amines are weak bases, and aqueous solutions of amines are basic



$$K_b = K_{eq}[H_2O] = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2]} = 4.37 \times 10^{-4}$$

Basicity

it is also common to discuss the basicity of amines by reference to the acid ionization constant of the corresponding conjugate acid

$$CH_3NH_3^+ + H_2O \rightleftharpoons CH_3NH_2 + H_3O^+$$

$$K_a = \frac{[CH_3NH_2][H_3O^+]}{[CH_3NH_3^+]} = 2.29 \times 10^{-11} \qquad pK_a = 10.64$$

- **for any acid-conjugate base pair**

$$pK_a + pK_b = 14.00$$

Basicity

- aliphatic amines have about the same base strength, pK_b 3.0 - 4.0, and are slightly stronger bases than ammonia

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

Physical State

- The methylamines (mono-, di-, and tri-) and ethylamine are gases at room temperature
- Most other amines are liquids at room temperature
- Physical state summary for unbranched primary amines at room temperature and room temperature:

Unbranched Primary Amines			
C_1	C_3	C_5	C_7
C_2	C_4	C_6	C_8

Gas Liquid

Odor (Smell)

Methylamines (mono-, di-, and tri-) and ethylamine (gases) have ammonia-like smell.

Most other amines are liquids and have odors resembling that of raw fish (strong, disagreeable odors).

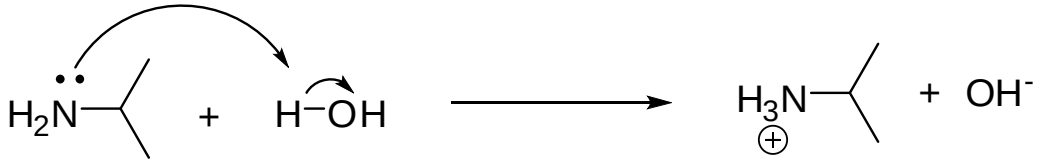
- **Foul smell from dead fish and decaying flesh is due to diamines released by the bacterial decomposition of protein.**
- **Examples: putrescine and cadaverine**

Solubility in Water

- Amines with fewer than six carbon atoms are infinitely soluble in water.
- Solubility results from hydrogen bonding between the amines and water.
- Even tertiary amines are water-soluble because of its ability to form hydrogen bonds

Amines as bases

Amines behave like NH_3 and are basic: This behavior is due to the acceptance of H+ (proton) from an acid.



2-Propanamine

2-Propanammnium ion

In the example above water is acts as an acid

The resulting solution is alkaline due to OH^- ion and a substituted ammonium ion.

- **Ammonium and substituted ammonium ions form four bonds with N ; therefore carries a + charge**
- **Names of substituted ammonium ions are derived from the parent amine in which the "-e" of parent amine is replaced by "ammonium ion".**

Acid and a Base reactions of amines

The reaction between an acid and a base (neutralization) results in a salt

Amines are bases and their reaction with an acid produces a salt (amine salt)

- **Amine + Acid → Amine Salt**

Naming amines salts

Names of amines salts are written in the following order:

- **Substituted amine followed by the name of anion**

Putting vinegar (acid) on fish to remove odor

- **Results in the formation of an odorless amine salts**

All amine slats are water soluble

- **This is why drugs of amines are administered in the form of amine salts**

Preparation and reactions of amines

- **Primary amine is not quickly removed from alkylation reaction mixture, the nitrogen atom of the amine may react with further alkyl halide molecules giving secondary and tertiary amines**

Secondary and Tertiary amines are produced in similar reactions

Tertiary amines react with alkyl halides in the presence of a strong base to produce a quaternary ammonium salt.

Quaternary ammonium salts different from amine salts

- **Addition of strong base does not result in "parent" amine**

Quaternary ammonium salts:

- **Colorless, odorless, crystalline solids that have high melting points and are water-soluble.**

Heterocyclic amine

Heterocyclic amine: An organic compound with nitrogen atoms of amine groups present in a ring system.

Ring systems may be:

- **Saturated, unsaturated, or aromatic**
- **>1 Nitrogen atom may be present in a given ring, and**
- **Fused ring systems often occur.**

Heterocyclic amines are important starting material for medicinal, agricultural, food and products that are important in human body

- **Nicotine and caffeine are two heterocyclic amines - Stimulants**
- **Porphyrin ring, a component of hemoglobin, is a heterocyclic amine**

Neurotransmitters

A neurotransmitter is a chemical substance that is released at the end of a nerve, travels across the synaptic gap between the nerve and another nerve, and then bonds to a receptor site on the other nerve, triggering a nerve impulse

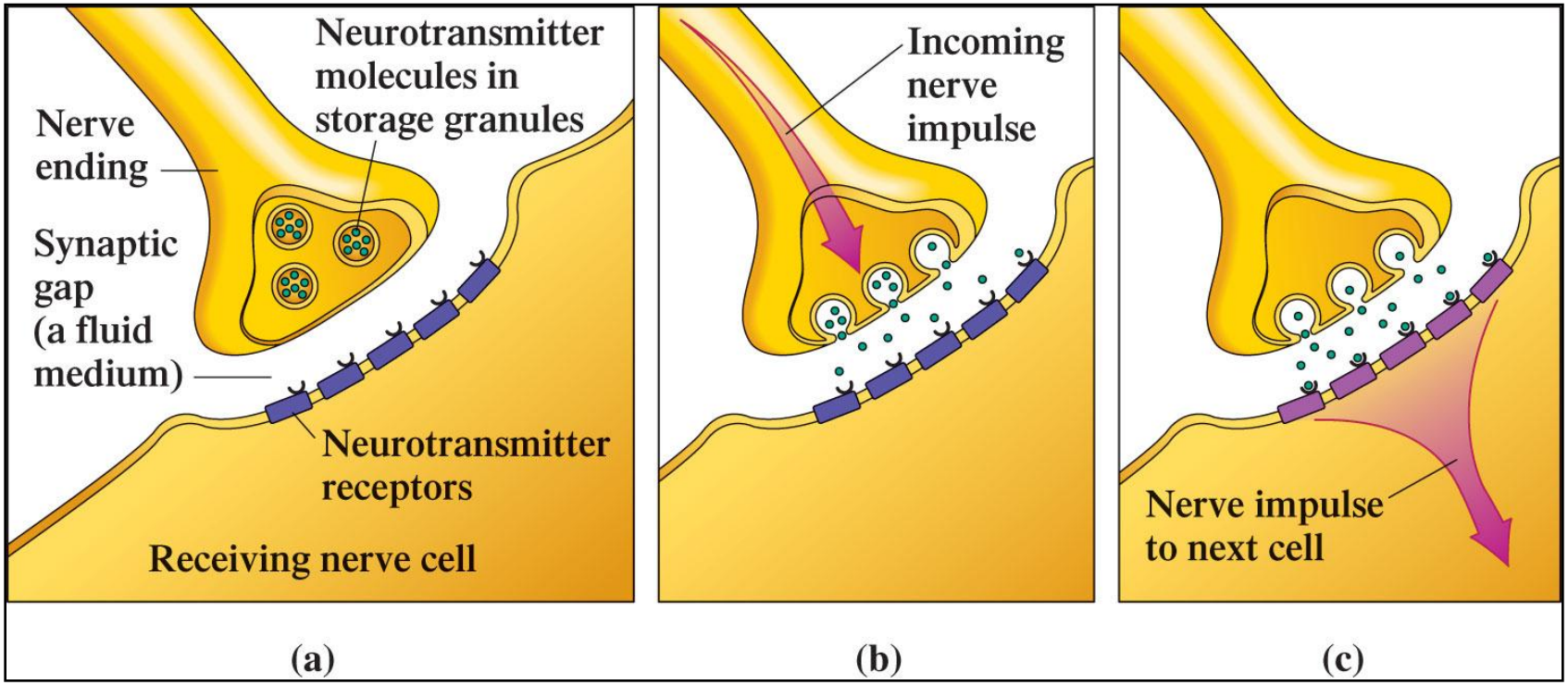
Acetylcholine: Involved in transmission of nerved impulses

Dopamine: Found in brain and its deficiency may cause Parkinson disease

Serotonin: Involved in sleep, sensory perception in mental illness.

Norepinepherine: Helps maintain muscle tone in blood vessels

Neurotransmitters



Epinephrine and Histamine

Epinephrine:

- Important in central nervous system stimulant
- Released into blood in response to pain, excitement and fear.
- Increases rate and force of heart contraction and muscular strength

Histamine:

- Responsible for unpleasant effects during hay fever and pollen allergies
- Antihistamine is used to counter the effects of histamine

Alkaloids

Alkaloid: An alkaloid is a nitrogen-containing organic compounds excreted from plant material

Well known alkaloids:

- **Nicotine (tobacco plant)**
- **Caffeine (coffee beans and tea leaves)**
- **Cocaine (coca plant)**
- **Morphine and codeine (Opium plant)**

Alkaloids as medicine

Many alkaloids are currently used in medicine.

Quinine: Isolated from cinchona tree bark - used to treat malaria.

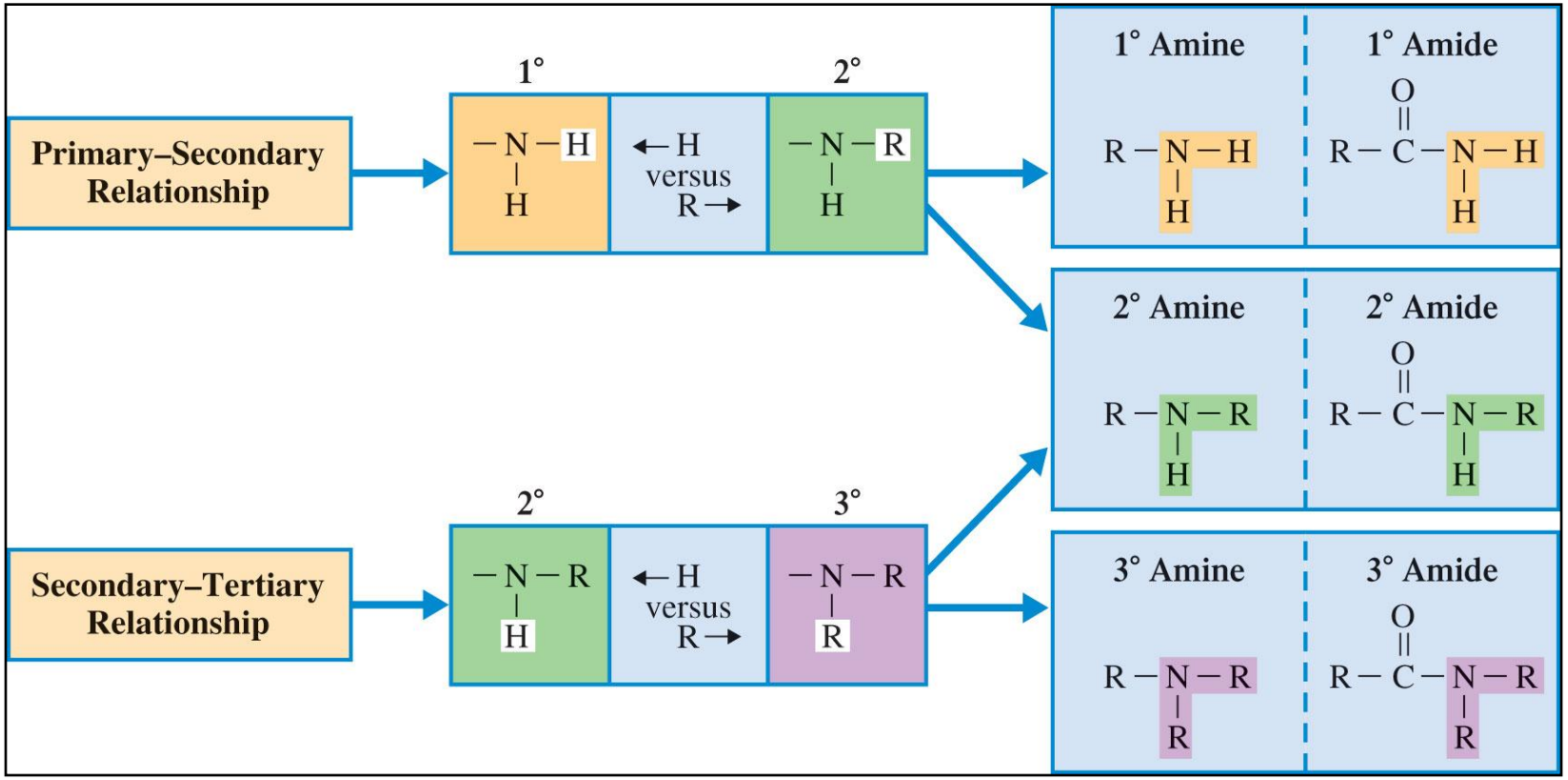
Atropine: Isolated from the belladonna plant - used as a preoperative muscle relaxant

Amides: The carboxylic acid derivatives of amine

- Amides: Derivatives of carboxylic acids in which the "-OH" group of the carboxylic acid is replaced by an NH_2 or NHR or NR_2
- Same rules are that apply to amines to determine if they are primary, secondary or tertiary amines also apply to amides
- Amide groups are considered as -R groups

Primary, Secondary, and Tertiary Amines and Amides

The "H versus R" relationship:



Amide Classification

Primary amides (1º) : Two hydrogen atoms are bonded to the amide nitrogen atom

Secondary amides (2º): An alkyl (or aryl) group and a hydrogen atom are bonded to the amide nitrogen atom

Tertiary amides (3º): Two alkyl (or aryl) groups and no hydrogen atoms are bonded to the amide nitrogen atom

Lactam

The ring size in a lactam is indicated using a Greek letter

A lactam with a four-membered ring : Beta-lactam

- **Beta-carbon from the carbonyl group is bonded to the heteroatom.**

A lactam with a five-membered ring : Gamma-lactam.

The members of the penicillin family of antibiotics have four-membered lactam ring.

Naming amides

Amides are derivatives of carboxylic acids (similar to esters)

Rules:

- **The ending of the name of the carboxylic acid is changed from "-ic" acid (common) or "-oic" acid (IUPAC) to -amide**
- **Example: benzoic acid becomes benzamide**
- **The names of groups attached to the nitrogen (2º and 3º amides) are appended to the front of the base name, using an N- prefix as a locator**

Amides: aliphatic and Aromatic

Secondary and tertiary amides involves use of the "prefix *N*-," a practice we previously used in amine nomenclature

The simplest aromatic amide bears a benzene ring and an unsubstituted amide group

- **Name: Benzamide**

Other aromatic amides are named as benzamide derivatives.

Urea

- Naturally occurring amide, water-soluble white solid produced in the human body from carbon dioxide and ammonia through urea cycle

  $CO_2 + 2NH_3 \rightarrow (H_2N)_2CO + H_2O$

- Human nitrogen waste product
- Kidneys remove it from blood and we excrete it via urine
- Kidneys not functioning properly leads to urea accumulation in blood - Uremia

Melatonin

A polyfunctional amide

A hormone (synthesized by the pineal gland) that regulates the sleep–wake cycle in humans.

Melatonin levels increase in evening hours and decrease as morning approaches (high levels associated with longer and sound sleep)

- Levels in the blood decreases with age
- A six-year-old has a five times more melatonin than an 80-year-old.

Melatonin: Treatment for insomnia and jet lag.

Acetaminophen

Synthetic amides exhibit physiological activity and are used as drugs.

Foremost among them is acetaminophen,

The top-selling over-the-counter pain reliever

Acetaminophen is a derivative of acetamide

Barbiturates

Cyclic amides- derivatives of barbituric acid

First synthesized from urea and malonic acid

Heavily used group of prescription drugs

- **Cause relaxation (tranquilizers), sleep (sedatives), and death in case of overdoses**

Amides do not exhibit basic properties in solution like amines because:

- Electrons not available for hydrogen bonding
- Electrons are pulled by more electronegative atom in the carbonyl group.

Boiling Points

Boiling points of amides:

- **Monosubstituted > Disubstituted > Trisubstituted**

Monosubstituted amides are solids except for formamide

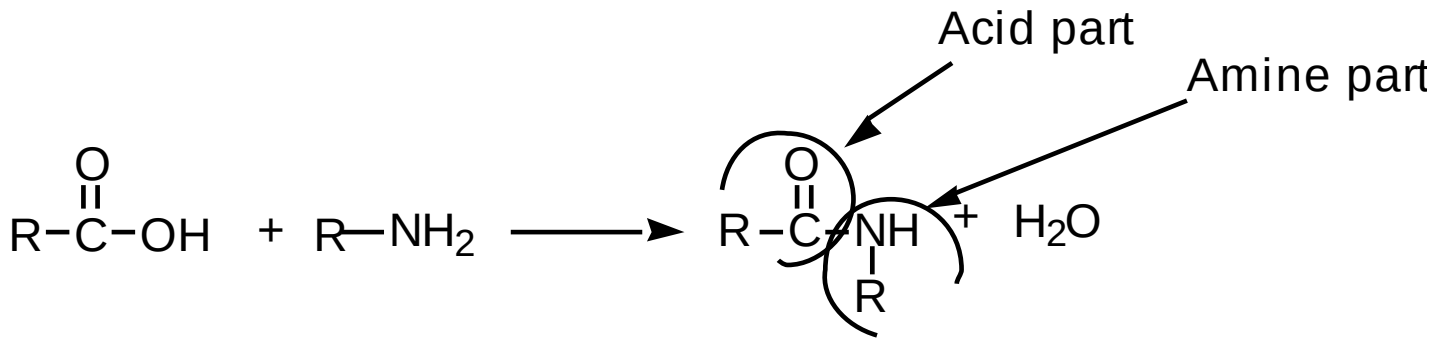
Formamide exhibits hydrogen bonding

Low molecular mass amides with 5-6 Carbon atoms are soluble in water

Reaction of carboxylic acid with ammonia

A primary or a secondary amine produces an amide at elevated temperature

- **A primary amine produces a secondary amide**
- **A Secondary amine produces a tertiary amide**



Amides hydrolysis (acid/base/enzyme catalyzed)

As in the case of esters, amides under go hydrolysis to release free acid and an amine

Amide hydrolysis is catalyzed by:

- **Acids and bases, or certain enzymes**
- **Sustained heating may be needed in certain cases**

Amides under go acid or base hydrolysis

- **Under acidic conditions of hydrolysis the amine is converted to an amine salt**

Under basic conditions of hydrolysis the carboxylic acid is convert to a carboxylic acid salt

Amide polymers:polyamides

Amide polymers or polyamides: Synthesized by combining diamines and dicarboxylic acids in a condensation polymerization reaction.

Nylon is a synthetic polyamide

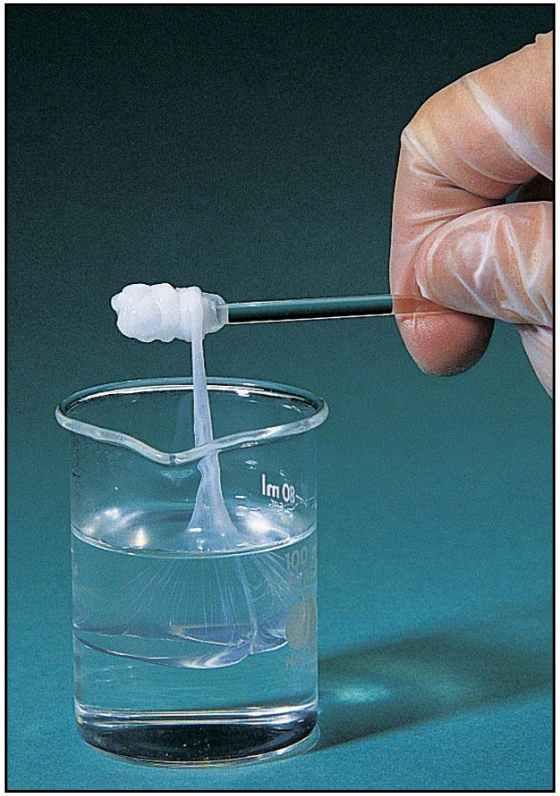
Many different types of Nylons

- **Based on diamine and diacid monomers used**

Nylon 66 – a polymer of 1,6-hexanediamine and hexanedioic acid as monomers

Nylon Polymer

A white strand of a nylon polymer forms between two layers of a solution containing a diacid (bottom layer) and a diamine (top layer):



Applications of polyamides

- Additional stiffness and toughness are imparted to polyamides with the introduction of aromatic rings to the polymer "backbone."
- Polyamide Kevlar is one such polymer and it is used in making bullet-resistant vests
- Silk and wool are examples of naturally occurring polyamide polymers.
- Much of the human body is also polyamide polymer.

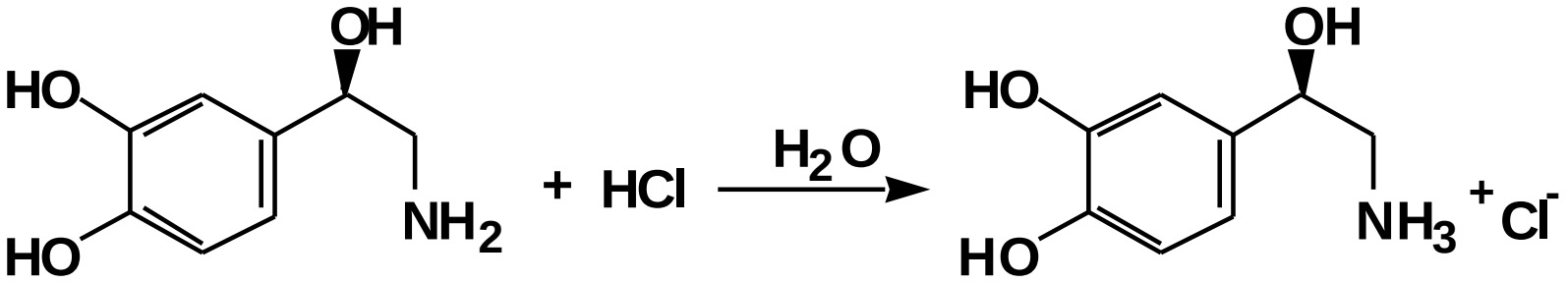
Urethane and Polyurethane

Urethane: A hydrocarbon derivative containing a carbonyl group bonded to both an —OR group and a —NHR (or –NR_2) group.

Polyurethane : A polymer formed from the reaction of dialcohol and diisocyanate monomers.

Reaction with Acids

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



(*R*)-Norepinephrine (only slightly soluble in water)

(*R*)-Norepinephrine hydrochloride (a water-soluble salt)

Reaction with Nitrous Acid

Nitrous acid is a weak acid, most commonly prepared by treating an aqueous solution of $NaNO_2$ with H_2SO_4 or HCl

$$HNO_2 + H_2O \rightleftharpoons H_3O^+ + NO_2^- \qquad K_a = 4.26 \times 10^{-4}$$

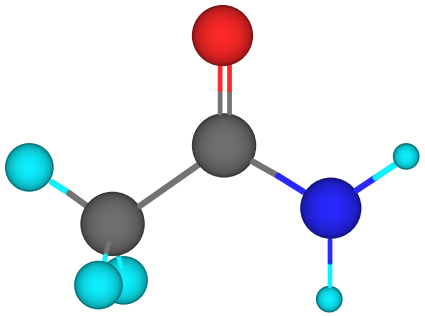
$$pK_a = 3.37$$

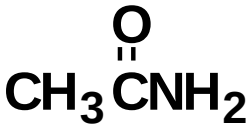
- **nitrous acid reacts with amines of different types, depending on whether the amine is 1°, 2°, 3° and whether it is aliphatic or aromatic**
- **we concentrate on the reaction of nitrous acid with 1° aromatic amines because this reaction is useful in organic synthesis**

Amides

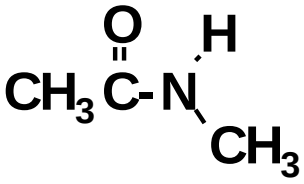
The functional group of an amide is an acyl group bonded to a trivalent nitrogen

- IUPAC: drop -ic acid from the name of the parent acid and add -amide
- if the amide nitrogen is bonded to an alkyl or aryl group, name the group and show its location on nitrogen by *N*-

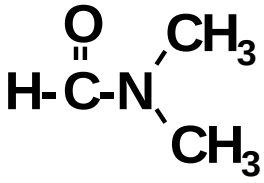




Acetamide
(a 1° amide)



N-Methylacetamide
(a 2° amide)

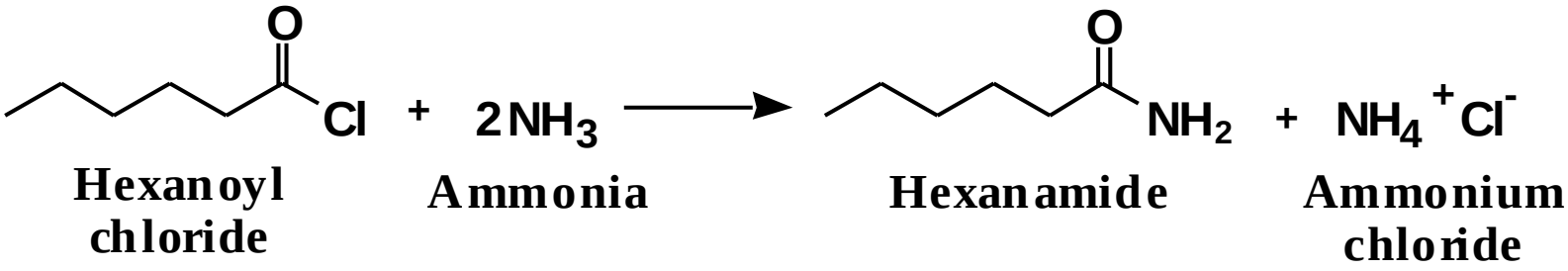


N,*N*-Dimethyl-
formamide (DMF)
(a 3° amide)

Preparation of amides from acid chlorides

Acid halides react with ammonia, 1° amines, and 2° amines to form amides

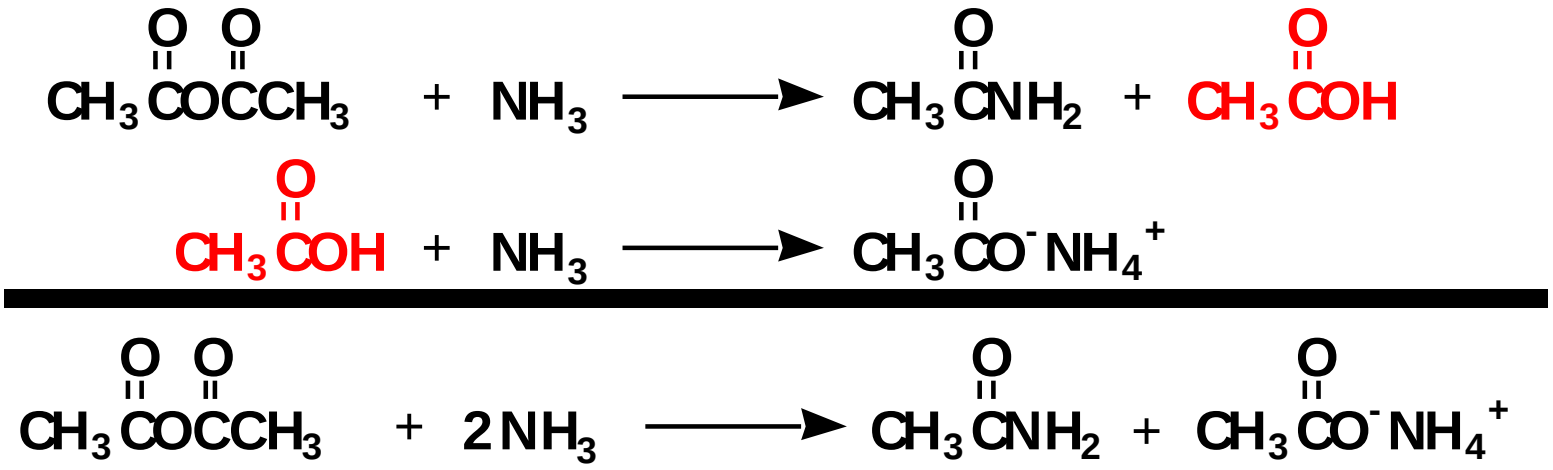
- 2 moles of the amine are required per mole of acid chloride; one to form the amide and one to neutralize the HCl formed



Preparation of amides from acid anhydrides

Acid anhydrides react with ammonia, and with 1° and 2° amines to form amides

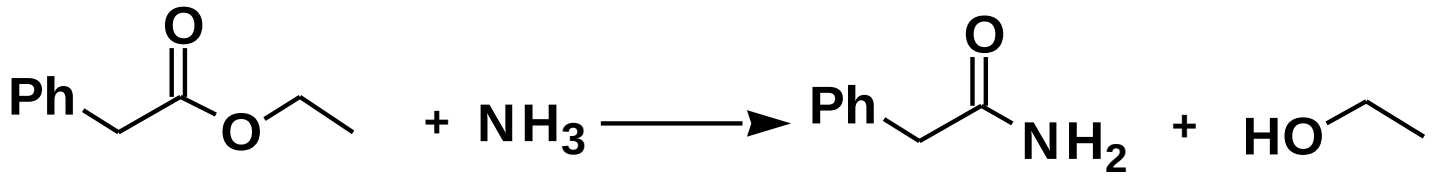
- 2 moles of ammonia or amine are required; one to form the amide and one to neutralize the carboxylic acid byproduct
- here the reaction is broken into two steps



Preparation of amides from esters

Esters react with ammonia, and with 1° and 2° amines to form amides

- esters are less reactive than either acid halides or acid anhydrides

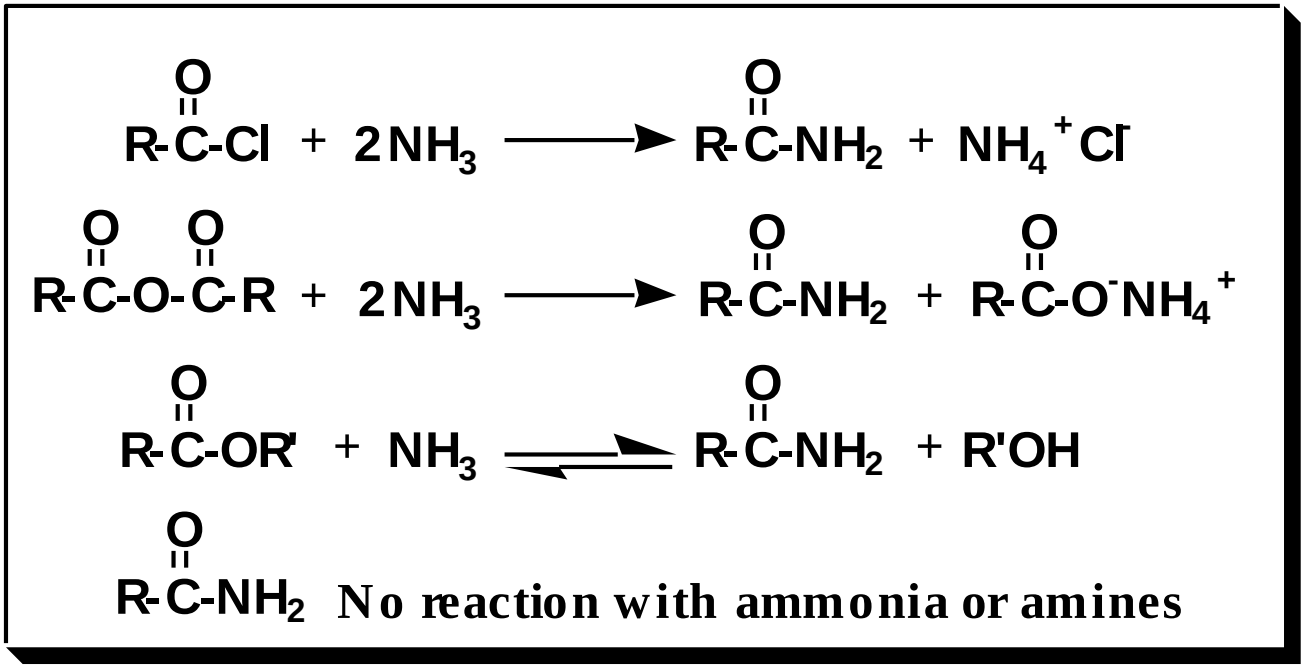


Ethyl phenylacetate Phenyl acetamide Ethanol

Amides do not react with ammonia, or with 1° or 2° amines

Preparation of amides

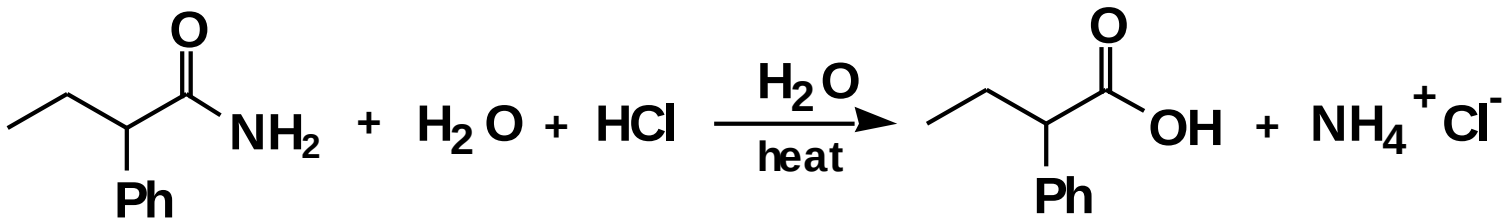
Summary



Reactions of amides: hydrolysis

Hydrolysis of an amide requires much more vigorous conditions than hydrolysis of an ester

- hydrolysis in aqueous acid requires 1 mole of acid for each mole of amide
- the products are a carboxylic acid and an ammonium or an amine salt

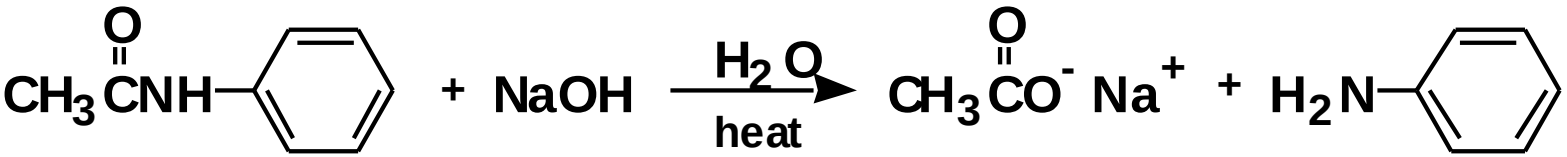


2-Phenylbutanamide

2-Phenylbutanoic acid

Reactions of amides: hydrolysis

- hydrolysis of an amide in aqueous base requires 1 mole of base per mole of amide
- the products are a carboxylate salt and an amine



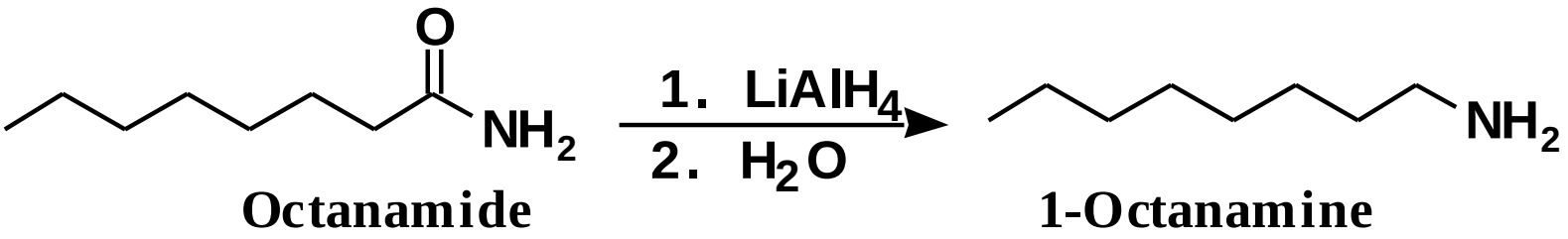
N-Phenylethanamide (*N*-Phenylacetamide, Acetanilide)

Sodium acetate

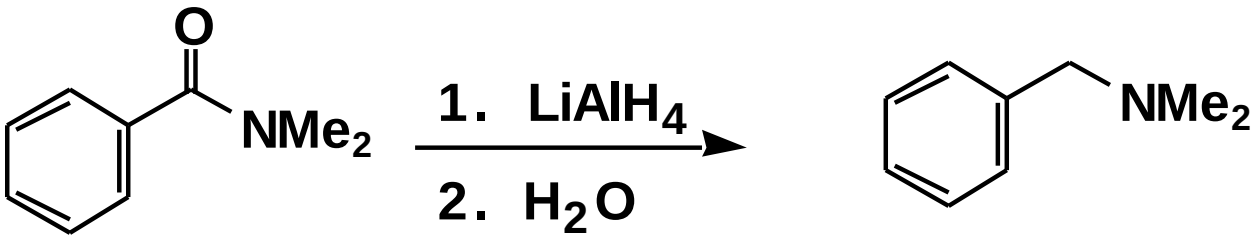
Aniline

Reactions of amides: reduction

- **$LiAlH_4$ reduction of an amide gives a 1°, 2°, or 3° amine, depending on the degree of substitution of the amide**



Octanamide → 1-Octanamine

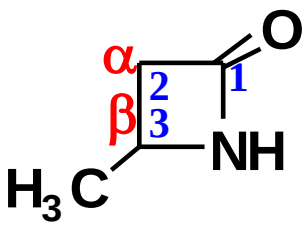


N,*N*-Dimethylbenzamide → *N*,*N*-Dimethylbenzylamine

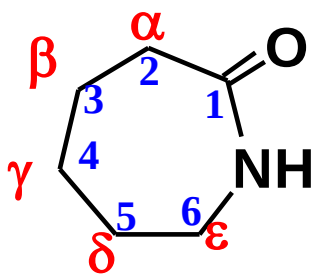
Cyclic amides: Lactam

Lactam: a cyclic amide

- name the parent carboxylic acid, drop the suffix -ic acid and add -lactam
- the location of the nitrogen atom in the ring is commonly indicated by a Greek letter, α, β, etc.



3-Butanolactam
(A β-lactam)



6-Hexanolactam
(An ε-lactone)

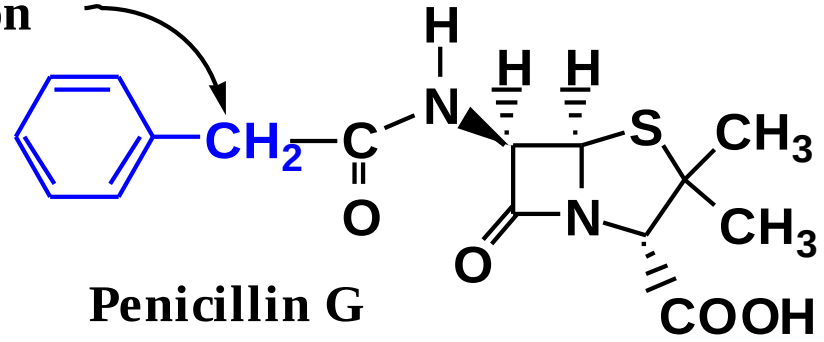
- 6-hexanolactam is an intermediate in the synthesis of nylon 6

The Penicillins: β-lactam

The penicillins are a family of β-lactam antibiotics

- one of the first discovered was penicillin G

the penicillins differ in the group bonded to the acyl carbon



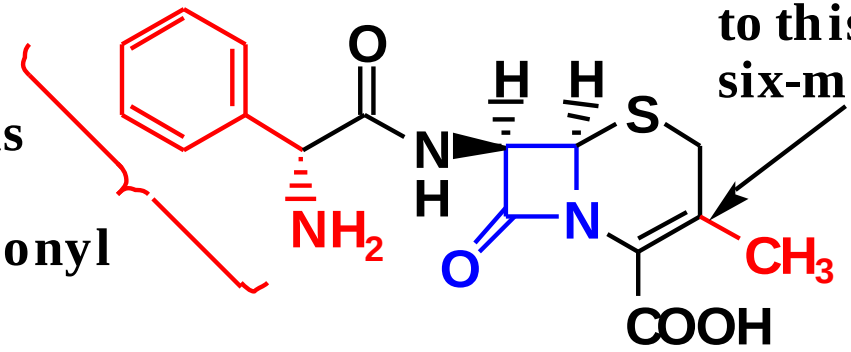
Penicillin G

Cephalosporins

The cephalosporins are also β-lactam antibiotics

The cephalosporins differ in the group bonded to the carbonyl carbon...

...and the group bonded to this carbon of the six-membered ring



Keflex
(a β-lactam antibiotic)