

Chapter 15

Amines

Chapter 15 suggested problems: 28, 30, 36, 38, 40, 44, 46, 50, 52, 54, 60, 62

Class Notes

I. Amines: general information

A. Amines: alkyl-substituted ammonia

1. NH_3 vs. NR_3 - R can be H, alkyl, aryl

B. A comparison of the chemistry of C, N, and O

1. All three are sp^3 hybridized when forming single bonds
2. Carbon: tetravalent, no nbp, Td geometry
3. Nitrogen: trivalent, 1 nbp, pyramidal geometry
4. Oxygen: divalent, 2 nbp, bent geometry

C. Classification of amines: classified according to the degree of substitution at the nitrogen atom or according to the nature of the alkyl groups

1. Primary (1°) amines
2. Secondary (2°) amines
3. Tertiary (3°) amines
4. Quaternary (4°) amine salts
5. Aryl and aliphatic amines, depending on the nature of R groups
6. Examples

II. Nomenclature of amines

- A. Amines can be named as alkylamines or as alkanamines in the IUPAC system

B. Note: amino ($-\text{NH}_2$) groups rank lower than hydroxyl and carbonyl groups when naming compounds

1. In alcohols and carbonyl compounds amino groups are indicated as substituents
 - a. 2-amino-2-propanol
 - b. 1-amino-3-chloro-1-phenyl-2-hexanone

C. Primary amines

1. Alkylamine system: alkyl group + "amine"
2. Alkanamine system: name of alkyl group as an alkane - "e" + "amine"
 - a. Methyl amine and methanamine
 - b. Propyl amine and propanamine

D. Aniline

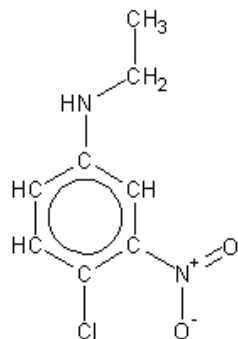
1. Numbering begins at the carbon bearing the amino group
2. Substituents are listed in alphabetical order
3. Arylamines may also be named as arenamines: aniline vs. benzenamine

E. Diamines

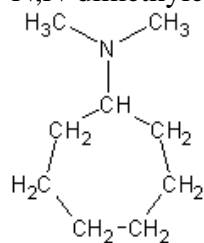
1. Compounds with two amino groups are named by using locants to indicate the position of the amino groups and by suffixing "diamine" to the name of the parent compound
 - a. 1,3-butane diamine
 - b. 1,5-pentane diamine

F. Secondary and tertiary amines: named as N-substituted derivatives of primary amines

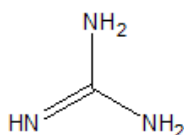
1. The parent primary amine is the one with the longest carbon backbone
2. "N-" is added as a locant to identify the other substituents bonded to the amino nitrogen
 - a. N-methylethylamine
 - b. N,N-dimethylethylamine
 - c. 4-chloro-N-ethyl-3-nitroaniline



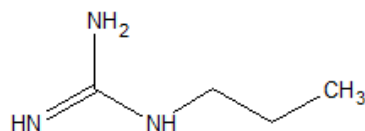
d. N,N-dimethylcycloheptylamine



e. an odd tertiary amine: guanidine



guanidine



1-propylguanidine

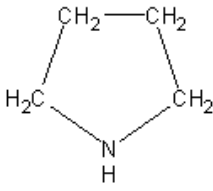
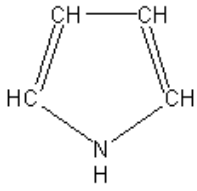
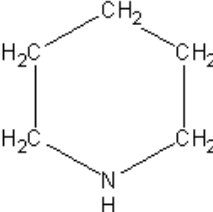
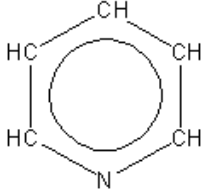
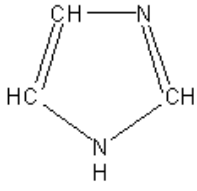
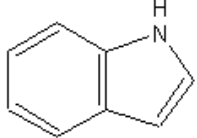
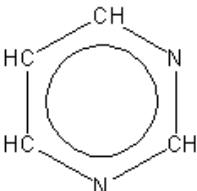
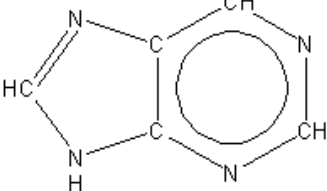
note the imine group (C=N); 1-propylguanidine is the side chain for the amino acid arginine

G. Naming compounds that contain both an amino group and an oxygen-containing functional group

1. The oxygen-containing functional group takes weight
2. NH_2 - amino; NHR - N-alkylamino; NR_2 - N,N-dialkylamino
3. Examples: 4-amino-2-butanone, 4-(N-methylamino)-2-butanone, 4-(N,N-dimethylamino)-2-butanone

H. Heterocyclic compounds and alkaloids

1. Cyclic compounds with one or more carbon atoms replaced by atoms other than carbon (most commonly N, O, S) are called heterocyclic compounds
2. Examples

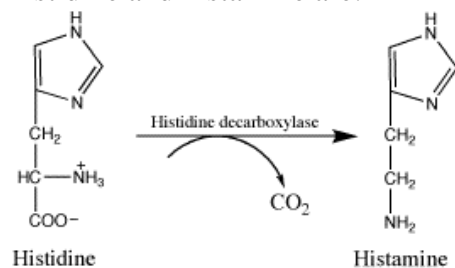
 <p style="text-align: center;">pyrrolidine</p> <p>this compound is the basis for the amino acid proline</p>	 <p style="text-align: center;">pyrrole</p> <p>2-methyl-1-pyrrole is the side chain for the amino acid histidine</p>
 <p style="text-align: center;">piperidine</p>	 <p style="text-align: center;">pyridine</p>
 <p style="text-align: center;">imidazole</p> <p>this is the side chain for the amino acid histidine</p>	 <p style="text-align: center;">indole</p> <p>this is the side chain for the amino acid tryptophan; a phenyl group and a fused pyrrole group</p>
 <p style="text-align: center;">pyrimidine</p>	 <p style="text-align: center;">purine</p> <p>this is pyrimidine with a fused imidazole</p>

- a. "Pyrrolidine: pyrrolidine and piperidine nitrogen heterocycles occur widely in nature as components of pyrrolizidine, indolizidine and quinolizidine alkaloids and are of considerable biochemical, pharmaceutical and agricultural importance because of their diverse biological activities. Their toxicity and halucinatory activities are well known, but probably more important are their antibiotic, antibacterial, antifungal and cytotoxic effects, since they offer the opportunities for

the development of novel pharmacological agents." (source: "Synthesis Of Biologically Relevant Compounds" @ "http://www.chem.ox.ac.uk/dp/mgm/natprod.html")

- b. "Pyrrole is a heterocyclic aromatic organic compound, a five-membered ring with the formula C₄H₅N. Pyrroles are components of larger aromatic rings, including the porphyrins of heme, the chlorins and bacteriochlorins of chlorophyll, and the corrin ring of vitamin B12. In a 1994 report released by five top cigarette companies, pyrrole is one of the 599 additives to cigarettes. Its use or purpose, however, is unknown, like most cigarette additives." ("Pyrrole." *Wikipedia, The Free Encyclopedia*. 18 Apr 2007, 14:07 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)
- c. "Imidazole is a heterocyclic aromatic organic compound. It is further classified as an alkaloid. Imidazole refers to the parent compound C₃H₄N₂, while imidazoles are a class of heterocycles with similar ring structure but varying substituents. This ring system is present in important biological building blocks such as histidine and histamine. Imidazole can act as a base and as a weak acid. . . . Many drugs contain an imidazole ring, such as antifungal drugs and nitroimidazole.

"Imidazole is incorporated into many important biological molecules. The most obvious is the amino acid histidine, which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin. Histidine can be decarboxylated to histamine, which is also a common biological compound. It is a component of the toxin which causes urticaria, which is basically an allergic reaction. The structures of both histidine and histamine are:



("Imidazole." *Wikipedia, The Free Encyclopedia*. 6 Mar 2007, 18:57 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

- d. "Pyridine is important in industrial organic chemistry as both a fundamental building block and as a solvent and reagent in organic synthesis. It is also a starting material in the synthesis of compounds used as an intermediate in making insecticides, herbicides, pharmaceuticals, food flavorings, dyes, rubber chemicals, adhesives, paints, explosives and disinfectants. Pyridine is also used as a denaturant for antifreeze mixtures, for ethyl alcohol, and for fungicides, and as a dyeing aid for textiles." ("Pyridine." *Wikipedia, The Free Encyclopedia*. 14 Apr 2007, 23:45 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

- e. "Piperidine is an organic compound with the molecular formula $C_5H_{11}N$. It is a heterocyclic amine with a six-membered ring containing five carbon atoms and one nitrogen atom. It is a clear liquid with a semen-like odor.

"The piperidine structural motif is present in numerous natural alkaloids such as piperine and quinine, and is the main active chemical agent in black pepper and relatives (*Piper* sp.), hence the name. Piperidine is also a structural element of many pharmaceutical drugs such as raloxifene and minoxidil.

"Piperidine is listed as a Table II precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances

due to its use (peaking in the 1970s) in the clandestine manufacture of PCP. It is also a byproduct of burning phencyclidine (PCP, phenylcyclohexylpiperidine).

"Piperidine is naturally found in fire ant venom, and is the cause of the burning sensation associated with the bite of these insects."

("Piperidine." *Wikipedia, The Free Encyclopedia*. 12 Apr 2007, 16:40 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

- f. "Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. The participation of the nitrogen lone electron pair in the aromatic ring means that indole is not a base, and it does not behave like a simple amine.

"Indole is solid at room temperature. It occurs naturally in human feces and has an intense fecal smell. At very low concentrations, however, it has a flowery smell, and is a constituent of many flower scents (such as orange blossoms) and perfumes. It also occurs in coal tar.

"The indole structure can be found in many organic compounds like the amino acid tryptophan and in tryptophan-containing protein, in alkaloids, and in pigments. Substituted indoles are structural elements of (and for some compounds the synthetic precursors for) the tryptophan-derived tryptamine alkaloids like the neurotransmitter serotonin, melatonin, the hallucinogens psilocybin, DMT, 5-MeO-DMT, or the ergolines like LSD. Other indolic compounds include the plant hormone Auxin (indolyl-3-acetic acid, IAA), the anti-inflammatory drug indomethacin, and the betablocker pindolol.

"The name *indole* is derived from a combination of the words indigo and oleum, since indole was first isolated by treatment of the indigo dye with oleum.

"Natural jasmine oil, used in the perfume industry, contains around 2.5% of indole. Since 1 kg of the natural oil requires processing several million jasmine blossoms and costs around \$10,000, it is not surprising that indole (among other things) is used in the manufacture of synthetic

jasmine oil (which costs around \$10/kg)." ("Indole." *Wikipedia, The Free Encyclopedia*. 5 Apr 2007, 20:04 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

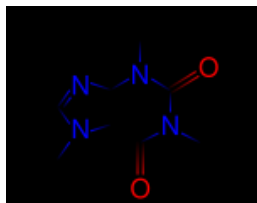
"Skatole or 3-methylindole is a mildly toxic white crystalline organic compound with chemical formula C_9H_9N and CAS number 83-34-1. The compound belongs to the indole family and has a methyl substituent in position 3 of the indole ring. It occurs naturally in feces (it is produced from tryptophan in the mammalian digestive tract), beets, and coal tar, and has a strong fecal odor. In low concentrations it has a flowery smell and is found in several flowers and essential oils, including those of orange blossoms, jasmine, and *Ziziphus mauritiana*. It is used as a fragrance and fixative in many perfumes and as an aroma compound. Its name is derived from *skato*, the Greek word for 'dung'." ("Skatole." *Wikipedia, The Free Encyclopedia*. 27 Mar 2007, 15:26 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

g. Pyrimidine:

h. Purine: "The purine is the most widely distributed nitrogen containing heterocycle in nature. The quantity of naturally occurring purines produced on earth is enormous, as 50 % of the bases in nucleic acids, adenine and guanine, are purines. In DNA, these bases form hydrogen bonds with their complementary pyrimidines thymine and cytosine. In RNA, the complement of adenine is uracil (U) instead of thymine. Other notable purines are hypoxanthine, xanthine, theobromine, caffeine, uric acid and isoguanine." ("Purine." *Wikipedia, The Free Encyclopedia*. 25 Mar 2007, 06:49 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

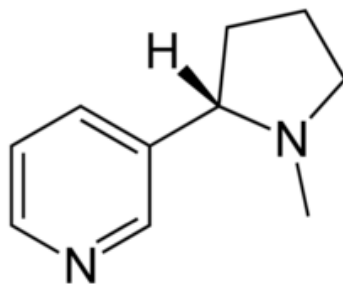
3. Alkaloids: naturally produced bioactive amines, usually heterocyclics (see Section 15.6 for examples)

a. Caffeine



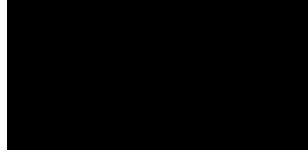
("Caffeine." *Wikipedia, The Free Encyclopedia*. 18 Apr 2007, 23:30 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

b. Nicotine

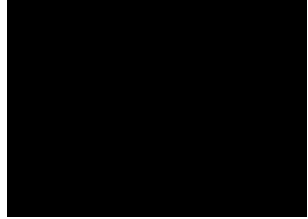


("Nicotine." *Wikipedia, The Free Encyclopedia*. 18 Apr 2007, 12:22 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

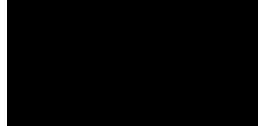
- c. Atropine ("Atropine." *Wikipedia, The Free Encyclopedia*. 8 Apr 2007, 14:18 UTC. Wikimedia Foundation, Inc. 19 Apr 2007),



scopolamine ("Scopolamine." *Wikipedia, The Free Encyclopedia*. 18 Apr 2007, 16:55 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

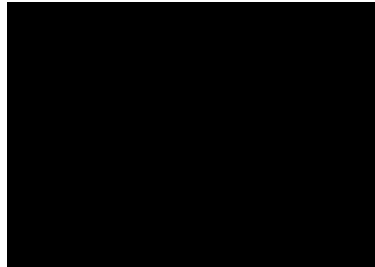


hyoscyamine ("Hyoscyamine." *Wikipedia, The Free Encyclopedia*. 5 Apr 2007, 02:49 UTC. Wikimedia Foundation, Inc. 19 Apr 2007):

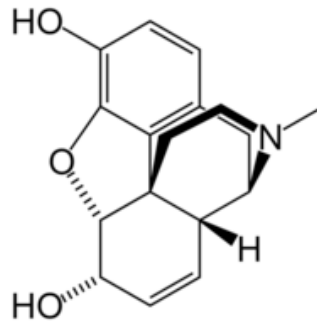


are found in nightshade, henbane, and jimson weed alkaloids.

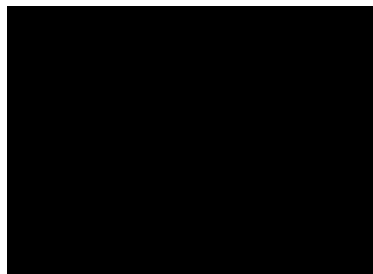
- d. Cocaine ("Cocaine." *Wikipedia, The Free Encyclopedia*. 18 Apr 2007, 15:48 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)



- e. Opium alkaloids

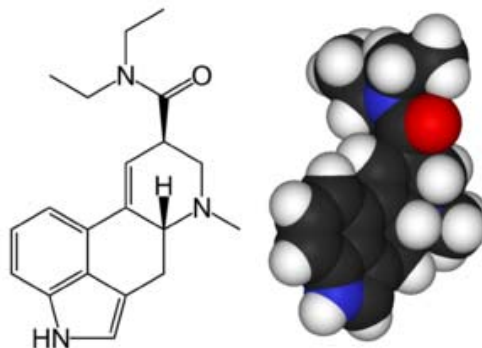


morphine ("Morphine." *Wikipedia, The Free Encyclopedia*. 18 Apr 2007, 13:42 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)



codeine ("Codeine." *Wikipedia, The Free Encyclopedia*. 15 Apr 2007, 01:21 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)

- f. LSD, or
 (6a*R*,9*R*)-*N,N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo-[4,3-*fg*]quinoline
 ("Lysergic acid diethylamide." *Wikipedia, The Free Encyclopedia*. 19 Apr 2007, 02:39 UTC. Wikimedia Foundation, Inc. 19 Apr 2007)



III. Properties of amines

A. Amines and hydrogen bonding

1. 1° and 2° amines can hydrogen bond, 3° amines cannot
2. The N-H bond is less polar than the O-H bond, so amine hydrogen bonds are not quite as strong as those for oxygen compounds
3. All amines have aqueous solubilities comparable to those of aldehydes/ketones and slightly less than alcohols
 - a. Amines with 3-4 carbons are soluble in all proportions, but as C# increases solubility decreases
4. 1° and 2° amines have MP/BP comparable to those of aldehydes/ketones and slightly less than alcohols
5. 3° amines have MP/BP comparable to those of ethers/hydrocarbons

B. Basicity of amines

1. Review of acid-base theories, strong and weak bases
2. Ammonia is both a Brønsted base and a Lewis base, as are all amines
 - a. $\text{NR}_3 + \text{H}_2\text{O} \rightarrow \text{NR}_3\text{H}^+ + \text{OH}^-$

3. Amines are, in general, better bases than water but poorer bases than hydroxide ion
4. N is a better base than O because while O has two electron pairs, as a more electronegative atom it holds its pairs more tightly, which makes it a poorer proton acceptor / electron pair donor than N

IV. Amine salts

A. As weak bases, amines react with strong acids

1. The reaction of an amine and a strong acid (e.g., HCl) produces an amine salt from the free amine (free base)
2. Amine salts are ionic compounds and are soluble in aqueous solution, whereas the underivatized amines are often only soluble in moderately polar solvents and not in aqueous solution - a drawback if the amine is to be used in biological systems
3. "Freebasing" is the opposite process: an amine salt is neutralized with NaOH and the amine is extracted from the aqueous solution with a solvent like diethyl ether
4. As ionic compounds increased MP/BP and aqueous solubility

B. Nomenclature: as per all ionic compounds, cation named first, then anion

1. Aliphatic amine cations: ending of amine name is changed from "amine" to ammonium"
 - a. Methylamine and methylammonium chloride
 - b. Ethyl methylamine and ethyl methylammonium bromide
2. Aromatic and heterocyclic amine cations: final "e" of the name is replaced with "ium"
 - a. Aniline and anilinium chloride
 - b. Pyridine and pyridinium iodide

C. Quaternary ammonium salts

1. The reaction of alkyl halides and tertiary amines result in the formation of ammonium salts bearing four alkyl groups
2. These salts are more stable in the presence of acids and bases

[Chemistry 1120 Index Page]

Last Modified 04/18/2007 21:53:35
