Amines

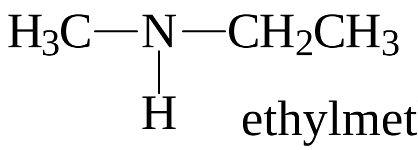
Nomenclature —

1^o: RNH_2, 2^o: RR'NH, 3^o: RR'R''N, 4^o (salt) $RR'R''R'''N^+$

R = alkyl or aryl

Common names –

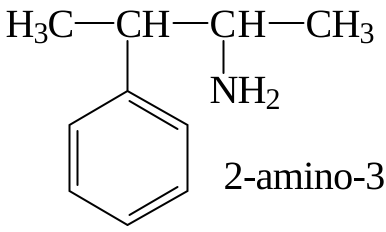
For simple amines name groups attached to N alphabetically; use suffix -amine.



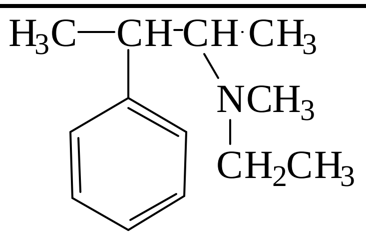
$H_3C-\underset{\underset{\displaystyle H}{|}}{N}-CH_2CH_3$

ethylmethylamine

In complicated structures the prefix amino- may be used for primary amines. For secondary and tertiary amines the most complex group attached to the nitrogen is taken as parent and the N and remaining groups are named as an alkylamino group.



2-amino-3-phenylbutane

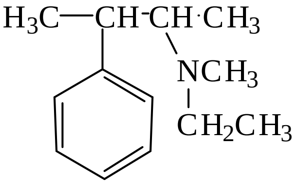


2-(ethylmethylamino)-3-phenylbutane

IUPAC Names –

-NH_2 is considered a substituent, like chloro or nitro, and is called amino. It is located by number in the usual way.

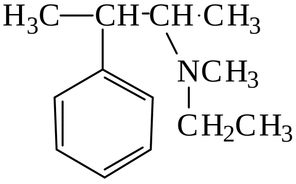
For secondary and tertiary amines, the largest alkyl group is taken as the parent. Smaller groups on N are prefixed to amino, and they, in turn, are prefixed by *N*-.



2-(*N*-ethyl-*N*-methylamino)-3-phenylbutane

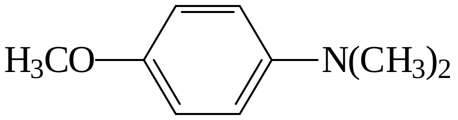
Chemical Abstracts Names –

Similar to alcohols. Longest chain holding N provides parent name with -e of alkane changed to -amine. Chain is numbered as usual; substituents on the chain are numbered. Substituents on the N get the prefix *N*-.



N-ethyl-*N*-methyl-3-phenyl-2-butanamine

Aromatic amines are often named as derivatives of aniline, Ph-NH_2.



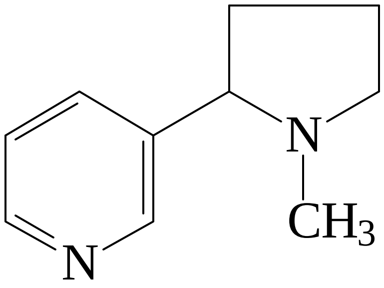
p-methoxy-N,N-dimethylaniline

Low molecular weight amines have fishy odors and in some cases may be quite unpleasant smelling. Two amines, found in rotting flesh, are named for their unpleasant odors —

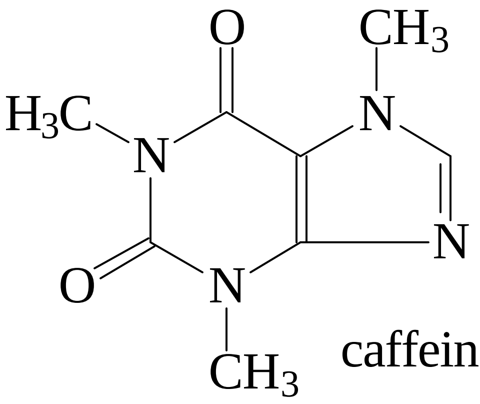
$H_2N(CH_2)_4NH_2$, putrescine,

and $H_2N(CH_2)_5NH_2$, cadaverine.

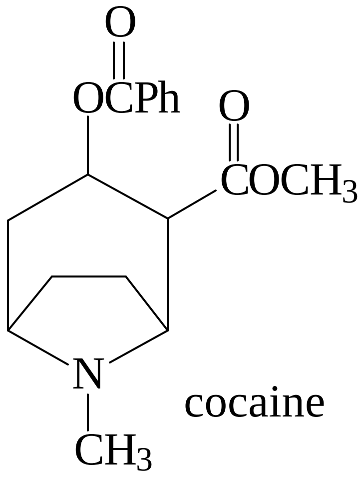
"Alkaloids" are basic nitrogenous plant products. (Reference: Manske & Holmes, "The Alkaloids," Academic Press)



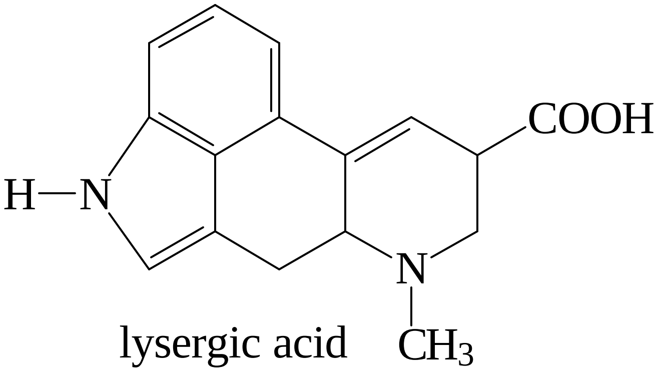
nicotine



caffeine



cocaine



lysergic acid

Preparation of Amines —

Reduction of Nitro Group —

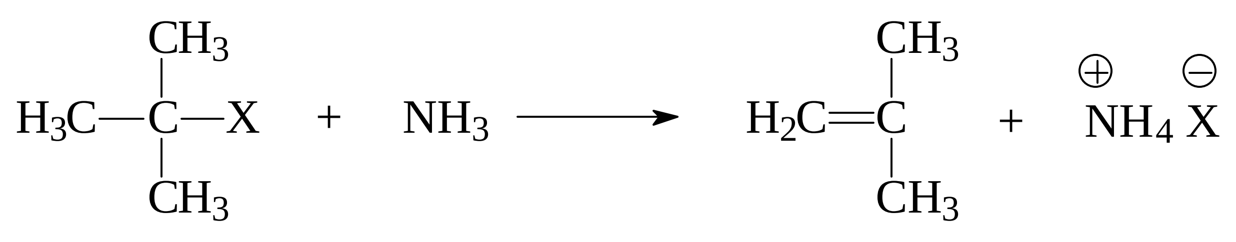
For aromatic amines, reduction of a nitro group is a common method. (Although this method works for aliphatic compounds, the nitro group is less common in these compounds.)

$$\mathrm{ArNO_2} \xrightarrow{\mathrm{Sn,\ HCl}} \mathrm{ArNH_3^{+}\ Cl^{-}} \xrightarrow{\mathrm{B:}} \mathrm{ArNH_2} + \mathrm{BH^{+}} + \mathrm{Cl^{-}}$$

Ammonolysis of Halides —

$$\mathrm{RX} + \mathrm{NH_3} \longrightarrow \overset{\oplus}{\mathrm{RNH_3}}\ \overset{\ominus}{\mathrm{X}} \xrightarrow{:\mathrm{B}} \mathrm{RNH_2} + \overset{\oplus}{\mathrm{H\text{-}B}} + \overset{\ominus}{\mathrm{X}}$$

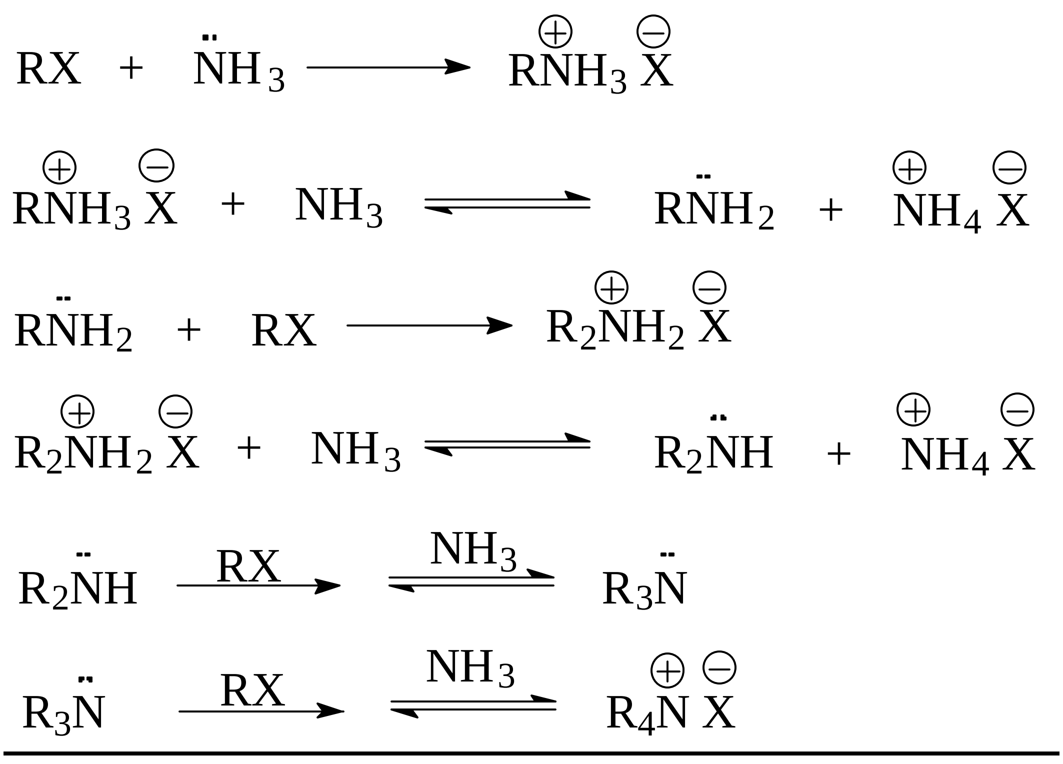
This reaction works best for 1° alkyl halides and may work for 2° halides, but for 3° halides —



$$H_3C-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-X \quad + \quad NH_3 \longrightarrow H_2C=\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}} \quad + \quad \overset{\oplus}{N}H_4\,\overset{\ominus}{X}$$

Vinyl and aryl halides usually do not react.

A severe limitation to ammonolysis in many cases is generation of other classes of amines —



$$RX \quad + \quad \ddot{N}H_3 \longrightarrow R\overset{\oplus}{N}H_3\,\overset{\ominus}{X}$$

$$R\overset{\oplus}{N}H_3\,\overset{\ominus}{X} \quad + \quad NH_3 \rightleftharpoons R\ddot{N}H_2 \quad + \quad \overset{\oplus}{N}H_4\,\overset{\ominus}{X}$$

$$R\ddot{N}H_2 \quad + \quad RX \longrightarrow R_2\overset{\oplus}{N}H_2\,\overset{\ominus}{X}$$

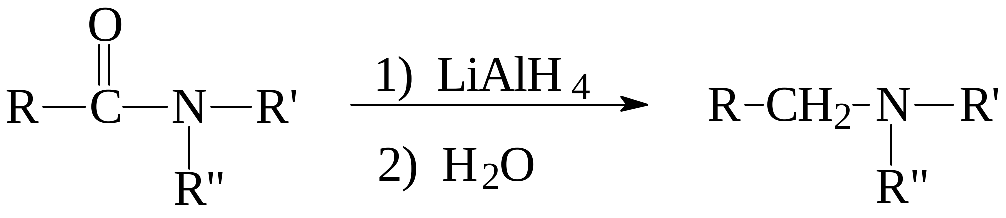
$$R_2\overset{\oplus}{N}H_2\,\overset{\ominus}{X} \quad + \quad NH_3 \rightleftharpoons R_2\ddot{N}H \quad + \quad \overset{\oplus}{N}H_4\,\overset{\ominus}{X}$$

$$R_2\ddot{N}H \xrightarrow{RX} \overset{NH_3}{\rightleftharpoons} R_3\ddot{N}$$

$$R_3\ddot{N} \xrightarrow{RX} \overset{NH_3}{\rightleftharpoons} R_4\overset{\oplus}{N}\,\overset{\ominus}{X}$$

Preparation of Amines *via* Reduction —

A. Reduction of Amides —



$$R-\overset{\overset{O}{\|}}{C}-\underset{\underset{R''}{|}}{N}-R' \xrightarrow[2)\ H_2O]{1)\ LiAlH_4} R-CH_2-\underset{\underset{R''}{|}}{N}-R'$$

The R groups may be H, alkyl, or aryl.

B. Reduction of Nitriles —

$$R-C\equiv N \xrightarrow[\textit{or}\ LiAlH_4]{H_2,\ cat.} R-CH_2-NH_2$$

Reactions of Amines —

Basicity of Amines —

$$\underset{\text{stronger base}}{RNH_2} + H_3\overset{\oplus}{O} \rightleftharpoons R\overset{\oplus}{N}H_3 + \underset{\text{weaker base}}{H_2O}$$

$$R\overset{\oplus}{N}H_3 + \underset{\text{stronger base}}{\overset{\ominus}{O}H} \rightleftharpoons \underset{\text{weaker base}}{RNH_2} + H_2O$$

On a quantitative basis we may measure the basicity of an amine by its ability to accept a proton from water.

$$RNH_2 + H_2O \rightleftharpoons R\overset{\oplus}{N}H_3 + \overset{\ominus}{O}H$$

$$K_b = \frac{\left[R\overset{\oplus}{N}H_3\right]\left[\overset{\ominus}{O}H\right]}{\left[RNH_2\right]}$$

Factors which stabilize the ammonium ion, RNH_3^+, compared to the amine, RNH_2, will increase K_b; factors which destabilize the ammonium ion compared to the amine will decrease K_b.

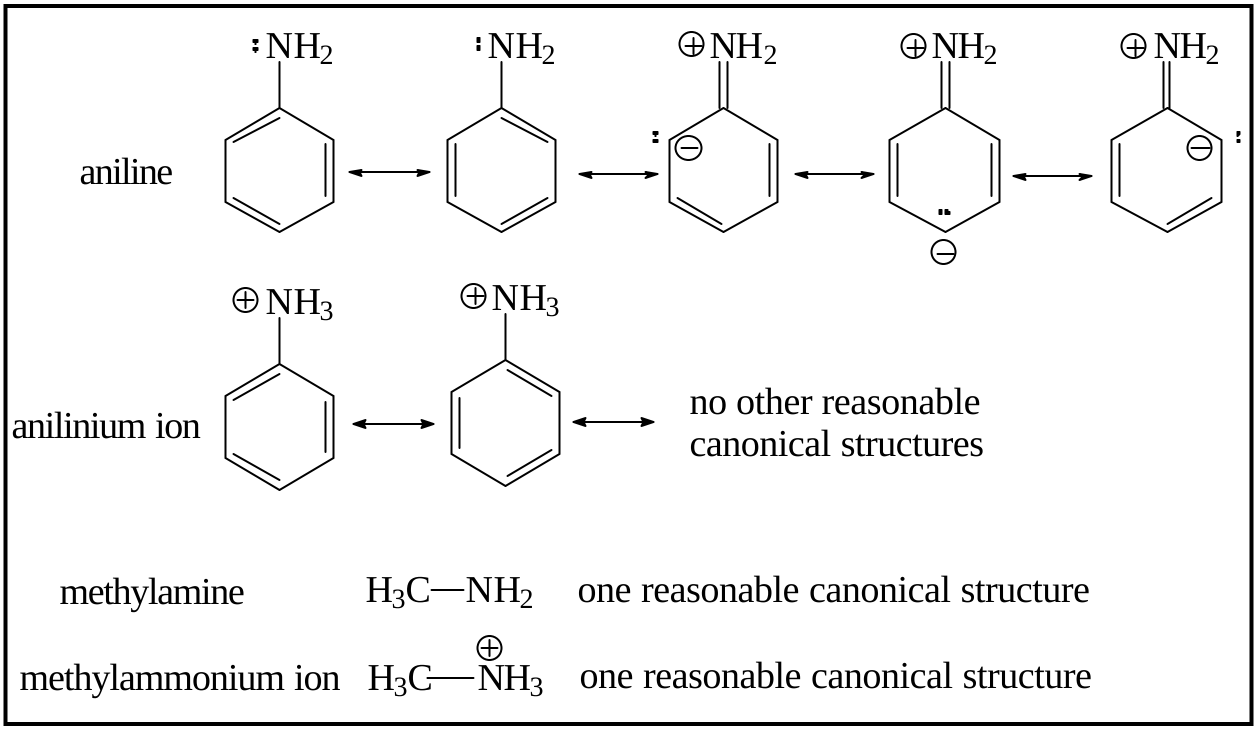
[Sometimes the basicity of an amine, RNH_2, is reported by giving the K_a of its protonated form, RNH_3^+. This K_a and K_b are inversely related.]

Name	Structure	pK_b
triethylamine	Et_3N	2.99
ethylamine	$EtNH_2$	3.19
dimethylamine	Me_2NH	3.27
methylamine	$MeNH_2$	3.34
diethylamine	Et_2NH	3.51
trimethylamine	Me_3N	4.19
ammonia	NH_3	4.74
aniline	$C_6H_5\text{-}NH_2$	9.37

Alkyl amines all have roughly the same basicity. Aryl amines, like aniline, are much less basic.

Effect of Resonance on Basicity —

Aromatic amines are less basic than aliphatic amines, mostly because of resonance. The aromatic amine is more stabilized compared to its ammonium ion than an aliphatic amine is compared to its ammonium ion —



aniline

anilinium ion

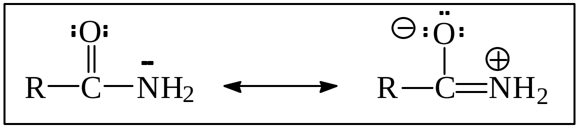
no other reasonable canonical structures

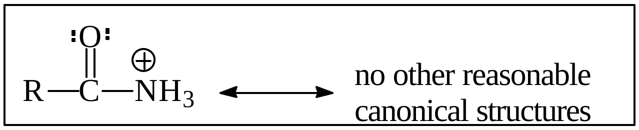
methylamine $H_3C{-}NH_2$ one reasonable canonical structure

methylammonium ion $H_3C{-}\overset{\oplus}{N}H_3$ one reasonable canonical structure

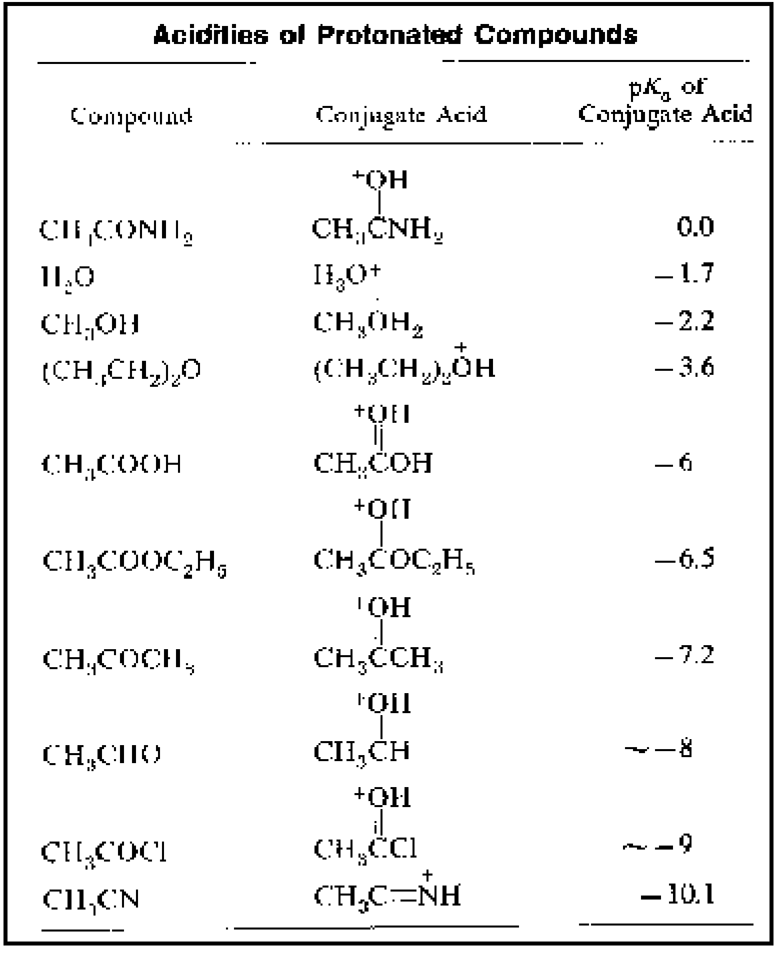
Compound	pK_b
methylamine	3.34
aniline	9.37
diphenylamine	13.2
triphenylamine	not basic

Amides are not basic at the nitrogen mostly because of resonance effects. The amide is stabilized relative to the protonated amide.





On the other hand, amides are slightly basic at the carbonyl oxygen and much more basic at this position than other carbonyl compounds. This can also be explained by resonance.

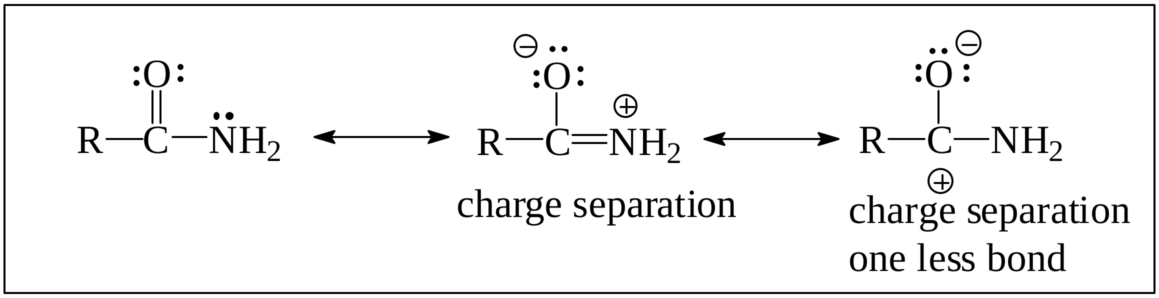


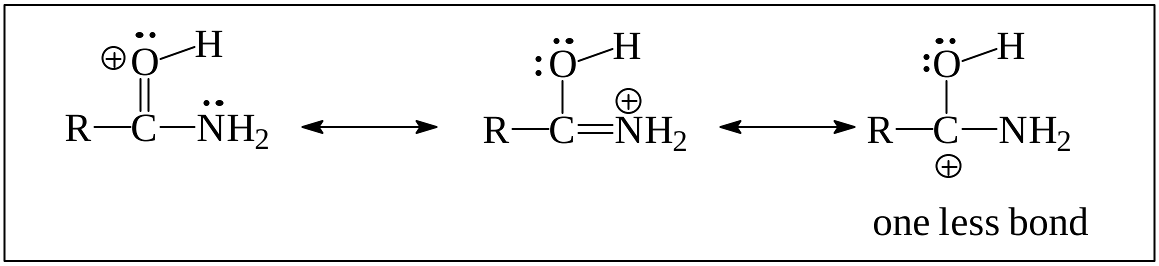
Acidities of Protonated Compounds

Compound	Conjugate Acid	pK_a of Conjugate Acid
CH_3CONH_2	$CH_3\overset{+OH}{C}NH_2$	0.0
H_2O	H_3O^+	−1.7
CH_3OH	$CH_3\overset{+}{O}H_2$	−2.2
$(CH_3CH_2)_2O$	$(CH_3CH_2)_2\overset{+}{O}H$	−3.6
CH_3COOH	$CH_3\overset{+OH}{C}OH$	−6
$CH_3COOC_2H_5$	$CH_3\overset{+OH}{C}OC_2H_5$	−6.5
CH_3COCH_3	$CH_3\overset{+OH}{C}CH_3$	−7.2
CH_3CHO	$CH_3\overset{+OH}{C}H$	∼ −8
CH_3COCl	$CH_3\overset{+OH}{C}Cl$	∼ −9
CH_3CN	$CH_3C{=}\overset{+}{N}H$	−10.1

[In the table to the left, the most basic compound is at the top and the least basic is at the bottom. The conjugate acids of these bases are also shown, along with their pK_as. The weakest conjugate acid is at the top of the list and the strongest is at the bottom.]

As noted above, the reason for amide basicity at the oxygen can also be explained by resonance —



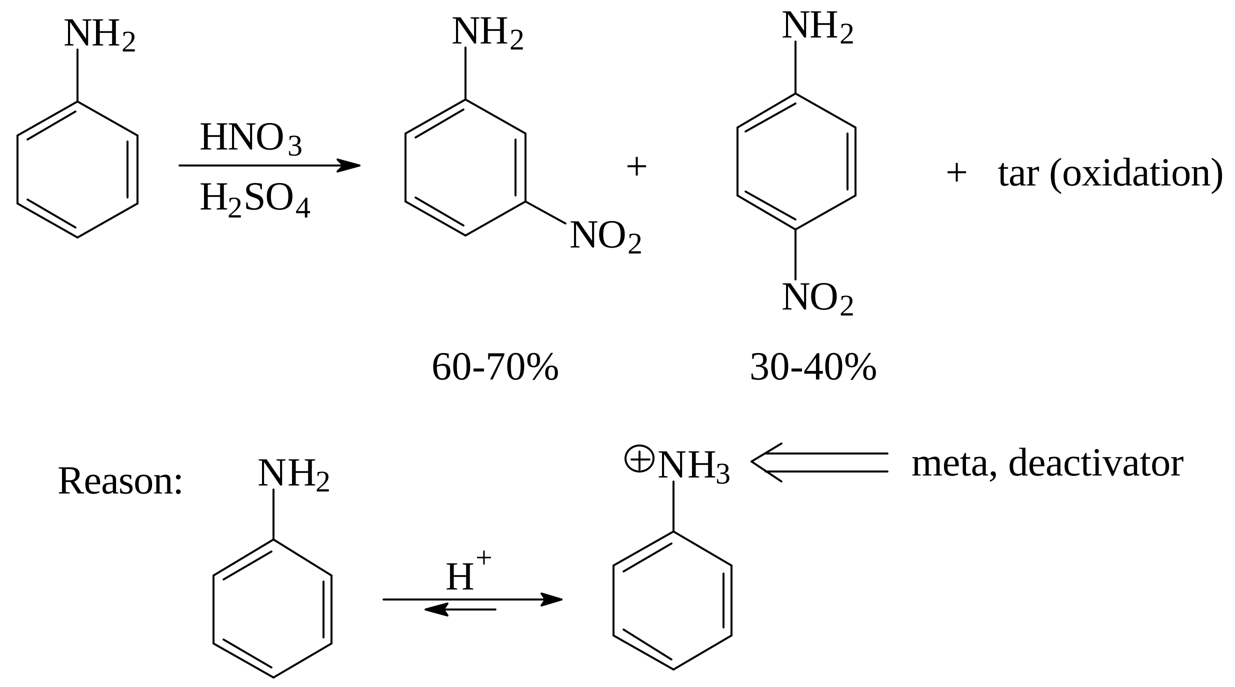


The two resonance structures shown on the right for the amide are not as good as the two comparable structures for the amide protonated on the oxygen, owing to charge separation.

<u>More Reactions of Amines</u> —

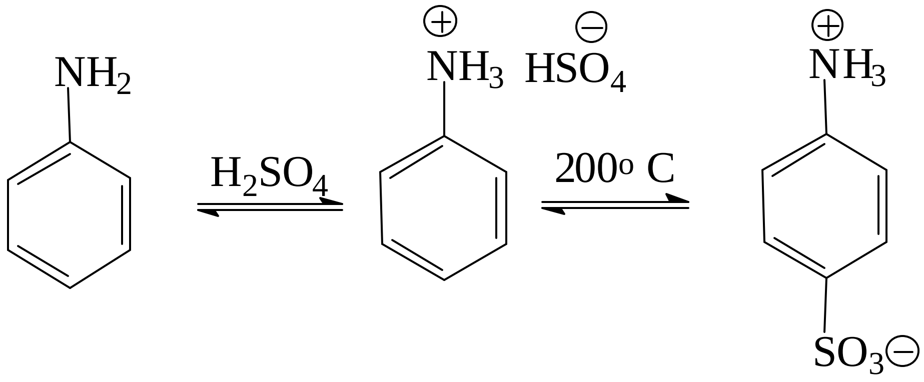
Nitration of Aromatic Amines —

-NH_2 is an o, p-directing activating group for electrophilic substitution. However,



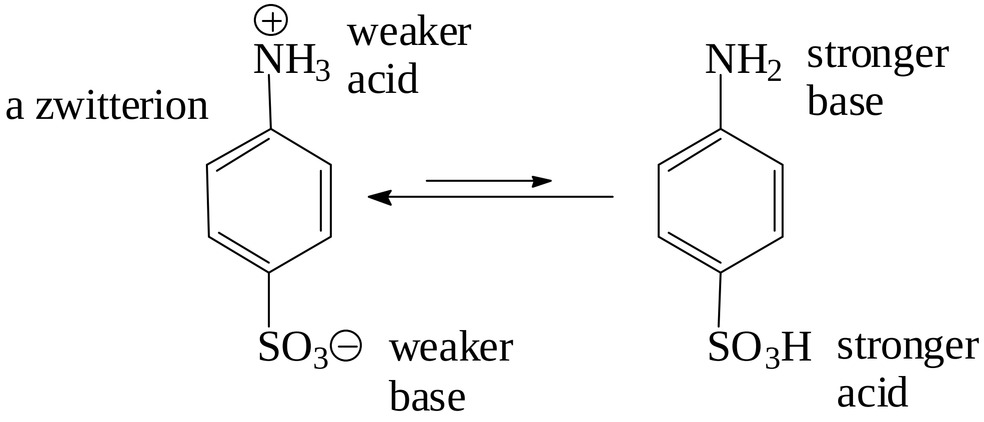
This problem can be avoided by *protecting* the amino group by acetylation, nitrating, and deprotecting the amino group by hydrolysis of the amide.

Sulfonation of Aromatic Amines —



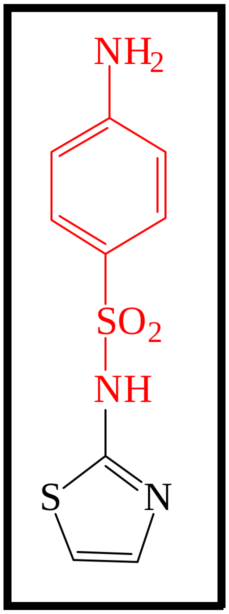
sulfanilic acid

Para isomer is most stable.



Certain N-substituted amides of sulfanilic acid, sulfanilamides, are bacteriostatic and are known as *sulfa* drugs. Sulfathiazole is shown.

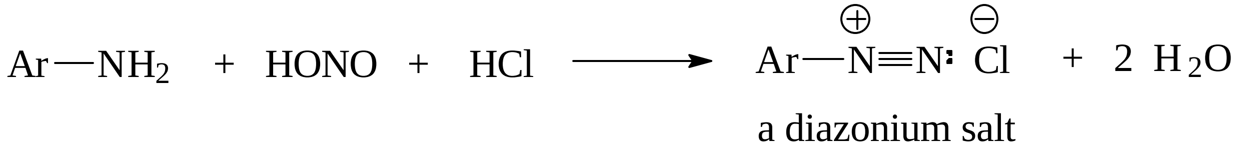
Sulfa drugs were widely used as broad-spectrum antibacterials before penicillin.



Reactions of Amines with Nitrous Acid —

[Nitrous acid, HONO, is not stable and is generated *in situ* from an acid and sodium nitrite:
$NaNO_2$ + HCl ———> HONO + NaCl.]

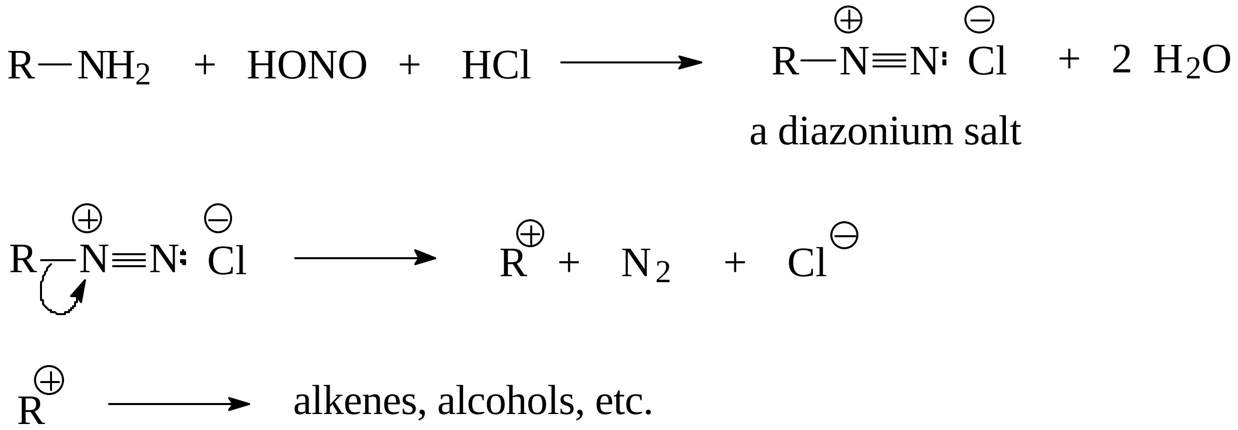
Primary aromatic amines give diazonium salts —



$$Ar{-}NH_2 + HONO + HCl \longrightarrow Ar{-}\overset{\oplus}{N}{\equiv}N{:}\ \overset{\ominus}{Cl} + 2\ H_2O$$

a diazonium salt

Primary aliphatic amines give diazonium salts —
but these compounds are unstable and decompose.



$$R{-}NH_2 + HONO + HCl \longrightarrow R{-}\overset{\oplus}{N}{\equiv}N{:}\ \overset{\ominus}{Cl} + 2\ H_2O$$

a diazonium salt

$$R{-}\overset{\oplus}{N}{\equiv}N{:}\ \overset{\ominus}{Cl} \longrightarrow R^{\oplus} + N_2 + Cl^{\ominus}$$

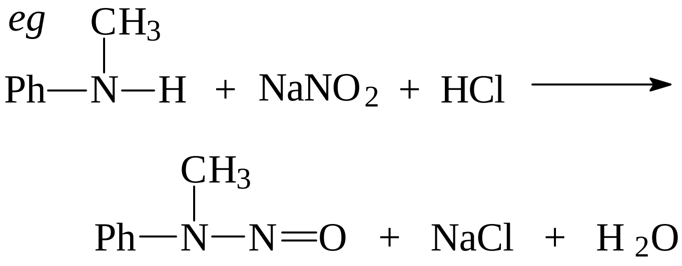
$$R^{\oplus} \longrightarrow \text{alkenes, alcohols, etc.}$$

Secondary aliphatic or aromatic amines give N-nitrosamines —

$$R_2N{-}H + NaNO_2 + HCl \longrightarrow R_2N{-}N{=}O + NaCl + H_2O$$

an N-nitrosamine

eg

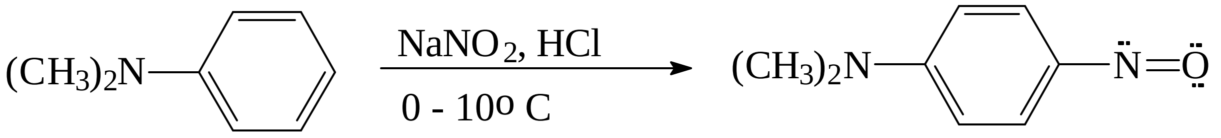


$$Ph{-}\overset{CH_3}{\overset{|}{N}}{-}H + NaNO_2 + HCl \longrightarrow Ph{-}\overset{CH_3}{\overset{|}{N}}{-}N{=}O + NaCl + H_2O$$

N-nitroso-N-methylaniline

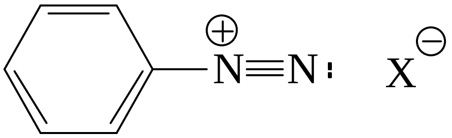
CARCINOGENIC

Tertiary Aromatic Amines —

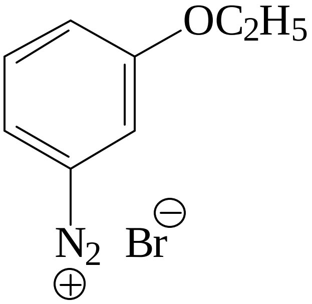


p-nitroso-N,N-dimethylaniline

Aromatic Diazonium Salts —



a diazonium salt

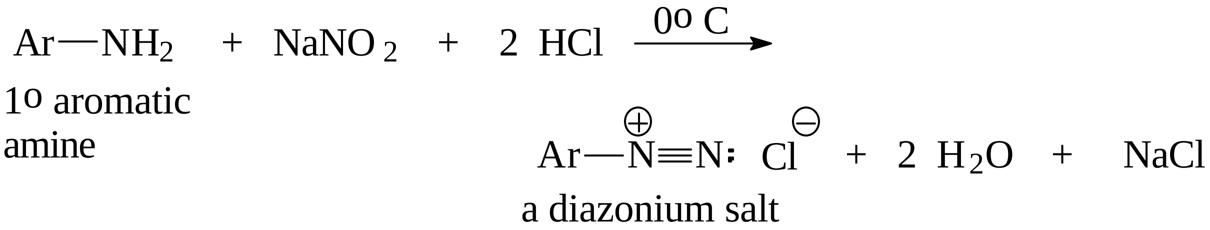


m-ethoxybenzenediazonium bromide

Named by adding -diazonium to the name of the aromatic compound from which they are derived, followed by the anion name.

Physical properties --- crystalline solids, soluble in water, explosive in solid state.

Preparation —



$$\text{Ar—NH}_2 + \text{NaNO}_2 + 2\ \text{HCl} \xrightarrow{0^{\circ}\text{C}} \text{Ar—}\overset{\oplus}{\text{N}}\equiv\text{N:}\ \overset{\ominus}{\text{Cl}} + 2\ \text{H}_2\text{O} + \text{NaCl}$$

1° aromatic amine

a diazonium salt

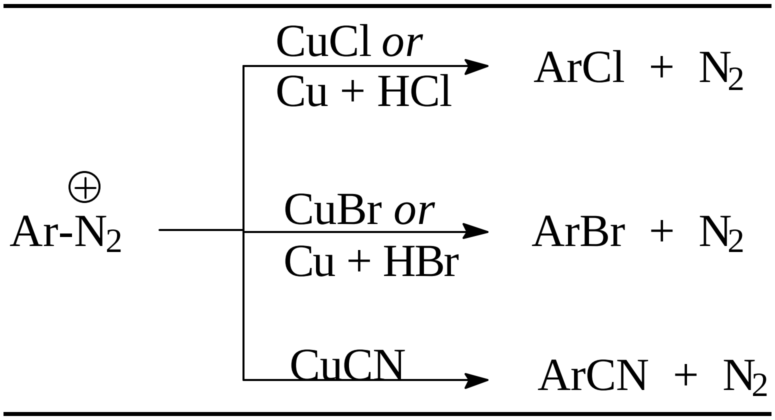
The solution of diazonium salt must be used immediately because it slowly decomposes.

Reactions of Aromatic Diazonium Salts —

Replacement of N_2 —

$Ar\text{-}N_2^+$ + :Z ------> Ar-Z + N_2

1) Replacement by -Cl, -Br, -CN: the Sandmeyer reaction —



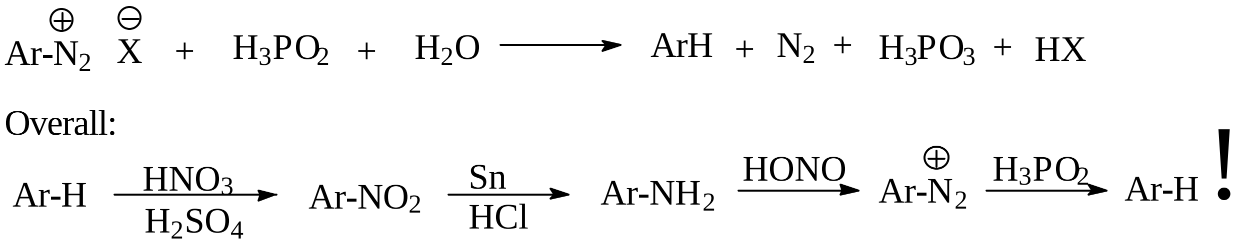
These reactions may proceed through free radical mechanisms.
The nitrile synthesis can lead to aromatic carboxylic acids *via* hydrolysis.

2) Reaction of a diazonium salt with I^- produces an aryl iodide

3) Aryl diazonium salts react with water to produce phenols —
$ArN_2^+ X^-$ + H_2O -------> ArOH + N_2 + H^+
This is a side reaction whenever diazonium salts are formed in aqueous solutions.

To prepare phenols the cold solution of diazonium salt is slowly added to boiling dilute sulfuric acid. This minimizes the formation of Ar-N=N-Ar-OH. [See “coupling” below.]

5) Replacement of $-N_2^+$ by -H —

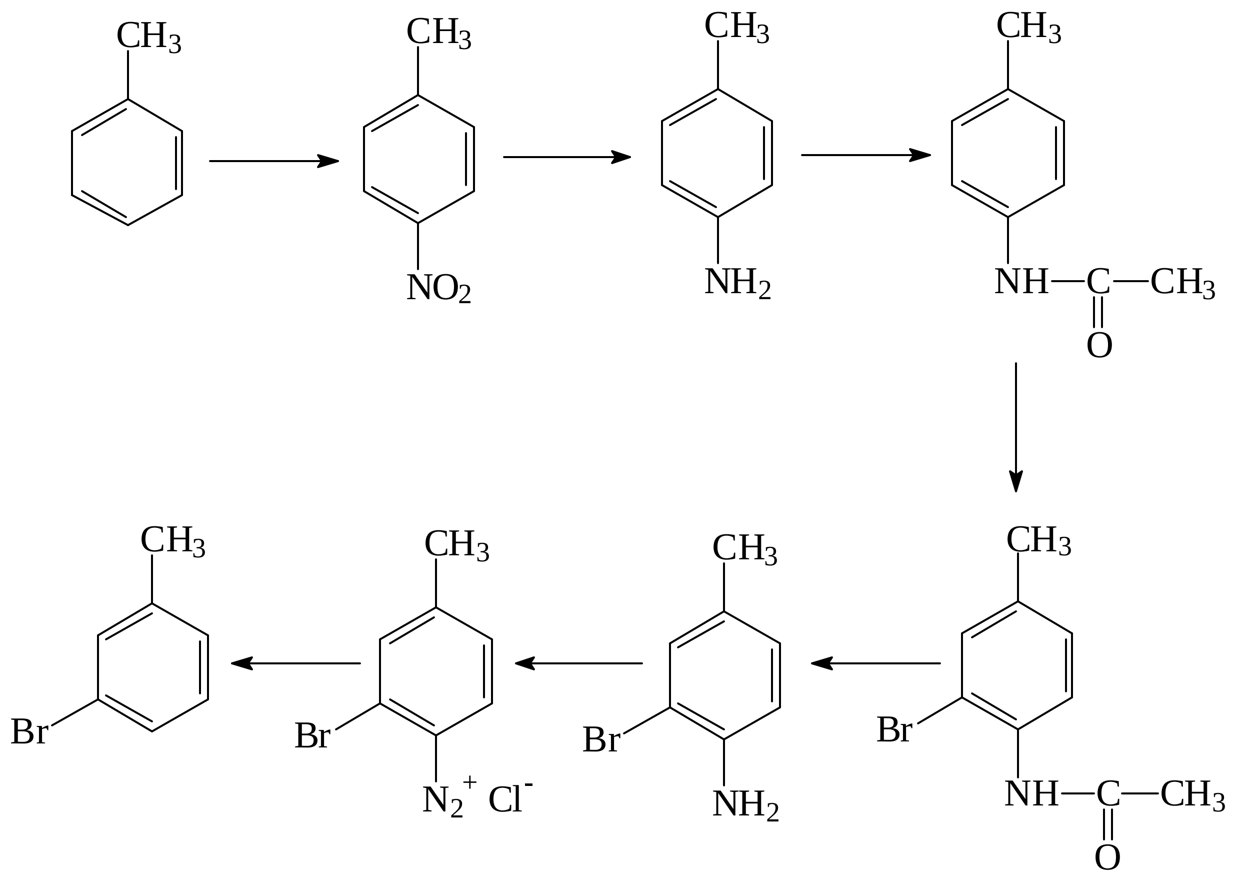


$$Ar\text{-}\overset{\oplus}{N_2}\ \overset{\ominus}{X} + H_3PO_2 + H_2O \longrightarrow ArH + N_2 + H_3PO_3 + HX$$

Overall:

$$Ar\text{-}H \xrightarrow[H_2SO_4]{HNO_3} Ar\text{-}NO_2 \xrightarrow[HCl]{Sn} Ar\text{-}NH_2 \xrightarrow{HONO} Ar\text{-}\overset{\oplus}{N_2} \xrightarrow{H_3PO_2} Ar\text{-}H\ !$$

However, the $-NO_2$ and $-NH_2$ groups can be used for directing purposes, *eg* prepare *m*-bromotoluene —

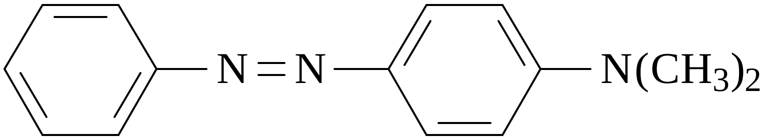


Coupling — The Synthesis of Azo Compounds —

$Ar\text{-}N_2^+ X^-$ + Ar'H -----> Ar-N=N-Ar' + HX

Usually Ar'H must contain a powerful electron releasing group *eg* -OH or $-NR_2$.

Azo compounds are often used as dyes. They are colored owing to extensive conjugation. For example, butter yellow was at one time used to color margarine yellow. It has been found to be carcinogenic and is no longer used for this purpose.



butter yellow