AMINES

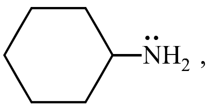
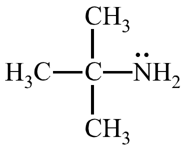
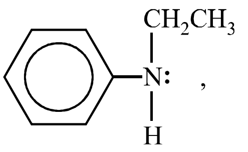
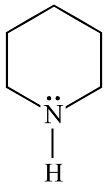
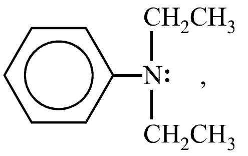
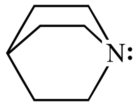
1. INTRODUCTION

Amines are organic derivatives of ammonia with one or more alkyl or aryl groups bonded to the nitrogen atom. Amines serve many functions in living organisms, such as bioregulation, neurotransmission, and defense against predators. Because of their high degree of biological activity, many amines are used as drugs and medicines.

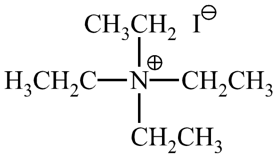
The alkaloids are an important group of biologically active amines, mostly synthesized by plants to protect them from being eaten by insects and other animals. Although some alkaloids are used medicinally (chiefly as painkillers), all alkaloids are toxic and cause death if taken in large quantities.

2. CLASSIFICATION

Amines are classified as **primary** (1°), **secondary** (2°), or **tertiary** (3°), corresponding to one, two or three alkyl or aryl groups bonded to nitrogen.

Type	Examples
Primary (1°) $R-NH_2$	 Cyclohexylamine (1°)  Tert-Butylamine (1°)
Secondary (2°) R_2NH	 N-Ethylaniline (2°)  Piperidine (2°)
Tertiary (3°) R_3N	 N, N-Diethylaniline (3°)  Quinuclidine (3°)

Quaternary ammonium salts have four alkyl or aryl bonds to a nitrogen atom. The nitrogen atom bears a positive charge, just as it does in simple ammonium salts such as ammonium chloride. The following are examples of quaternary (4°) ammonium salts.

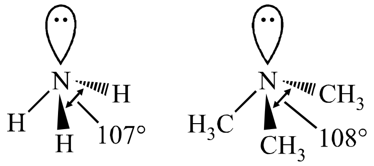


$$H_3CH_2C-\overset{CH_3CH_2\ I^{\ominus}}{\underset{CH_2CH_3}{N^{\oplus}}}-CH_2CH_3$$

Tetraethylammonium Iodide

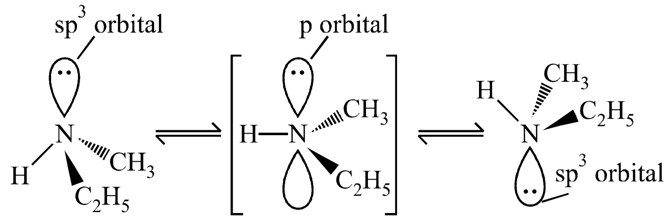
3. STRUCTURE OF AMINES

Ammonia has a slightly distorted tetrahedral shape. A lone pair of nonbonding electrons occupies one of the tetrahedral positions. This geometry is represented by sp^3 hybridization of nitrogen, with the bulky lone pair compressing the H—N—H bond angles to 107° from the "ideal" sp^3 bond angle of 109.5°. Trimethylamine shows less angle compression because the bulky methyl groups open the angle slightly.



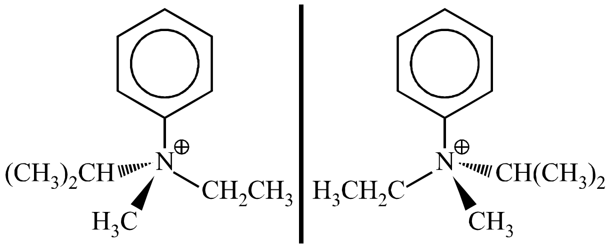
Ammonia Trimethylamine

A tetrahedral amine with three different substituents (and a lone pair) is non-superimposable on its mirror image. In most cases, we cannot resolve such an amine into two enantiomers, however, because the enantiomers interconvert rapidly. This interconversion takes place by **nitrogen inversion**, in which the lone pair moves from one face of the molecule to the other.



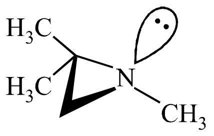
(R)-ethylmethylamine [Transition State] (S)-ethylmethylamine

In case of quaternary ammonium salts with asymmetic nitrogen atoms, inversion of configuration is not possible because there is no lone pair to undergo nitrogen inversion.

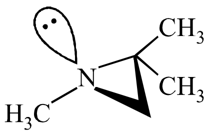


(R) (S)

Amines that cannot attain the sp^2-hybrid transition state for nitrogen inversion also show chirality. If the nitrogen atom is contained in a small ring, for example, it is prevented from attaining the 120° bond angles that facilitate inversion



(R)-1,2,2-Trimethylaziridine



(S)-1,2,2-Trimethylaziridine

4. PHYSICAL PROPERTIES

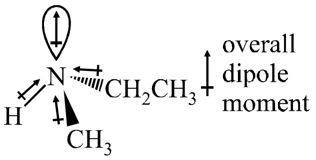
4.1 State

The lower aliphatic amines are gases with fishy odour. Primary amines with three or more carbon atoms are liquid and higher ones are solid.

Aniline and other aryl amines are usually colourless but gets coloured on storage due to atmospheric oxidation.

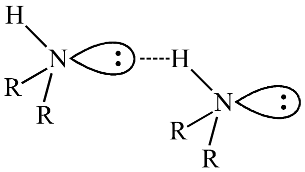
4.2 Dipole Moment

Amines are strongly polar because the large dipole moment of the lone pair of electrons adds to the dipole moments of the C←H and H→N bonds.

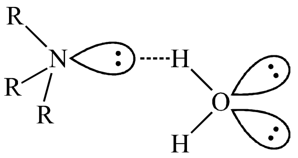


4.3 Solubility

Primary and secondary amines have N—H bonds, allowing them to form hydrogen bonds. Having no N—H bonds, pure tertiary amines cannot engage in hydrogen bonding. They can, however, accept hydrogen bonds from molecules having O—H or N—H bonds.



1° or 2° Amine:
Hydrogen Bond Donor and Acceptor



3° Amine:
Hydrogen Bond Acceptor only

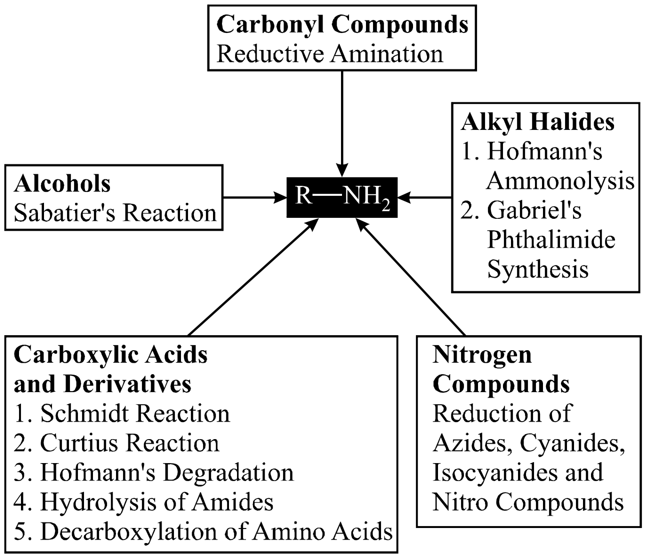
Therefore, lower aliphatic amines are soluble in water because they can form hydrogen bonds with water. However, solubility decreases with increase in molar mass of amines due to increase in size of the hydrophobic alkyl part. Higher amines are essentially insoluble in water.

4.4 Boiling Point

Because nitrogen is less electronegative than oxygen, the N—H bond is less polar than O—H bond. Therefore, amines form weaker hydrogen bonds than do alcohols of similar molecular weights. Primary and secondary amines have boiling points that are lower than those of alcohols, yet higher than those of ethers of similar molecular weights. With no hydrogen bonding, tertiary amines have lower boiling points than primary and secondary amines of similar molecular weights.

Compound	BP(°C)	Type	Molecular Weight
$(CH_3)_3N$:	3	Tertiary Amine	59
$CH_3—O—CH_2—CH_3$	8	Ether	60
$CH_3—NH—CH_2—CH_3$	37	Secondary Amine	59
$CH_3CH_2CH_2—NH_2$	48	Primary Amine	59
$CH_3CH_2CH_2—OH$	97	Alcohol	60

5. PREPARATION OF AMINES



AMINES

5.1 Alkyl Halides

5.1.1 Hofmann's Ammonolysis Method

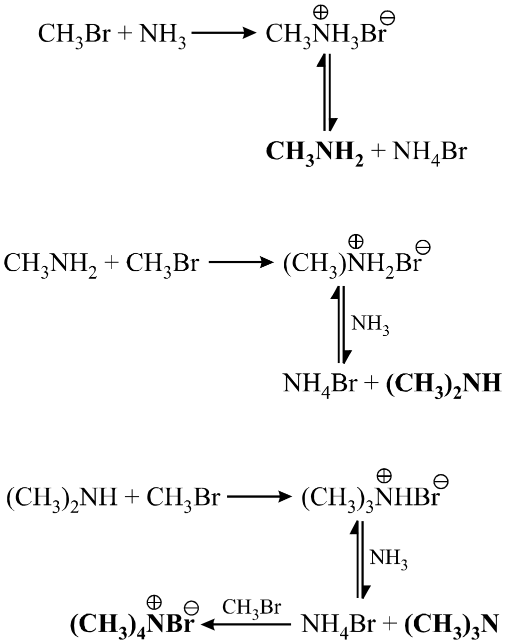
It is an **ammonolysis**. An alkyl halide and an ethanolic solution of ammonia are heated in a sealed tube at 100°C.

(a) The process gives a mixture of products.

(b) Tertiary alkyl halide is not suitable as it gives an alkene.

(c) Reaction follows bimolecular substitution (S_N2).

Example - 1



$$CH_3Br + NH_3 \longrightarrow CH_3\overset{\oplus}{N}H_3\overset{\ominus}{Br} \rightleftharpoons \mathbf{CH_3NH_2} + NH_4Br$$

$$CH_3NH_2 + CH_3Br \longrightarrow (CH_3)\overset{\oplus}{N}H_2\overset{\ominus}{Br} \xrightleftharpoons{NH_3} NH_4Br + \mathbf{(CH_3)_2NH}$$

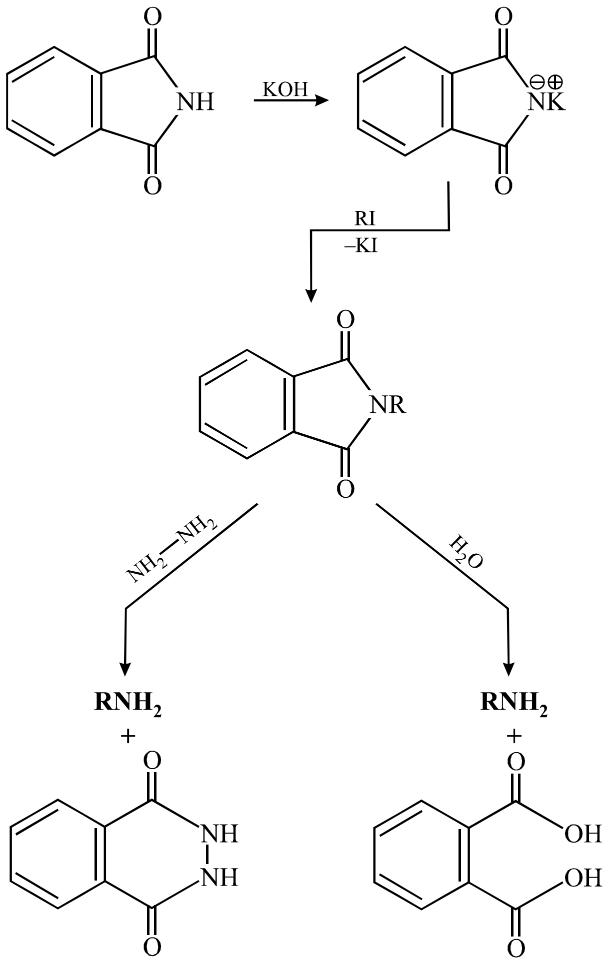
$$(CH_3)_2NH + CH_3Br \longrightarrow (CH_3)_3\overset{\oplus}{N}H\overset{\ominus}{Br} \xrightleftharpoons{NH_3} NH_4Br + \mathbf{(CH_3)_3N} \xrightarrow{CH_3Br} \mathbf{(CH_3)_4\overset{\oplus}{N}\overset{\ominus}{Br}}$$

5.1.2 Gabriel's Phthalimide Synthesis

Phthalamide is treated with KOH first and then potassium phthalamide is heated with alkyl halide to yield alkyl phthalamide. The subsequent hydrolysis produces exclusively 1° amine.

Alkyl phthalamide is also treated with hydrazine to get a better yield of 1° amine.

Example - 2



5.1.3 Grignard Reagent

Grignard reagent or a trialkyl borane on treatment with chloramine gives the primary amine.

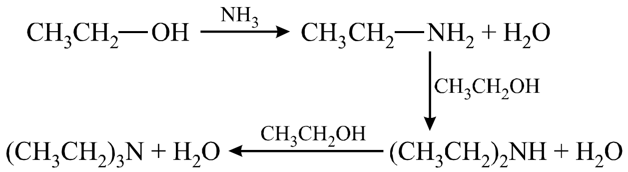
$$RMgX + ClNH_2 \longrightarrow R—NH_2 + MgXCl$$

5.2 Alcohols

5.2.1 Sabatier Reaction

Alcohols and ammonia are heated underpressure in the presence of a catalyst e.g., **copper chromite or alumina**. A mixture of products is obtained.

Example - 3



$$CH_3CH_2{-}OH \xrightarrow{NH_3} CH_3CH_2{-}NH_2 + H_2O$$

$$\xrightarrow{CH_3CH_2OH} (CH_3CH_2)_2NH + H_2O \xrightarrow{CH_3CH_2OH} (CH_3CH_2)_3N + H_2O$$

5.3 Carbonyl Compounds

5.3.1 Reductive Amination

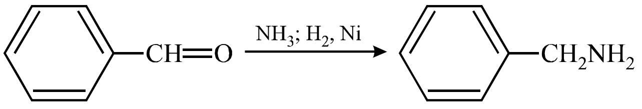
Several aldehydes and ketones are converted into amines by reduction in the presence of ammonia.

Reduction can be accomplished catalytically, **(hydrogen (20-150 atm) over Raney nickel at 40-150°C or by use of sodium cyanohydridoborate, $NaBH_3CN$).**

Example - 4

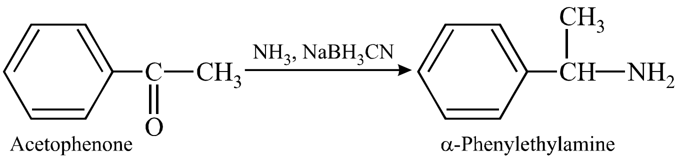
$$\underset{\text{Heptanal}}{CH_3(CH_2)_5CHO} \xrightarrow{NH_3;\ H_2,\ Ni} \underset{\text{1-Aminoheptane}}{CH_3(CH_2)_5CH_2NH_2}$$

Example - 5



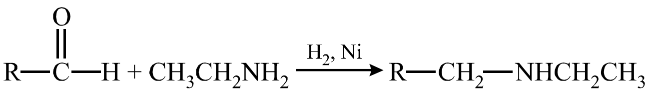
Benzaldehyde Benzylamine

Example - 6



Acetophenone α-Phenylethylamine

Example - 7



$$R{-}\overset{O}{\overset{\|}{C}}{-}H + CH_3CH_2NH_2 \xrightarrow{H_2,\ Ni} R{-}CH_2{-}NHCH_2CH_3$$

2° Amine

5.4 Carboxylic Acids & Derivatives

5.4.1 Schmidt Reaction

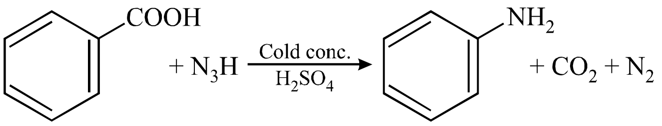
A treatment of cold conc. H_2SO_4 to the mixture of carboxylic acid and hydrazoic acid gives 1° amine.

$$RCOOH + N_3H \xrightarrow[H_2SO_4]{\text{Cold conc.}} RNH_2 + CO_2 + N_2$$

Note...

1. The product molecule contains one carbon atom less than that in acid.
2. Isocyanate is formed as an intermediate in the reaction.

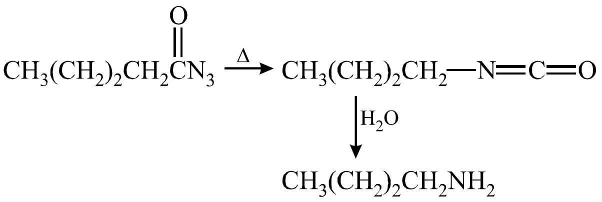
Example - 8



5.4.2 Curtius Reaction

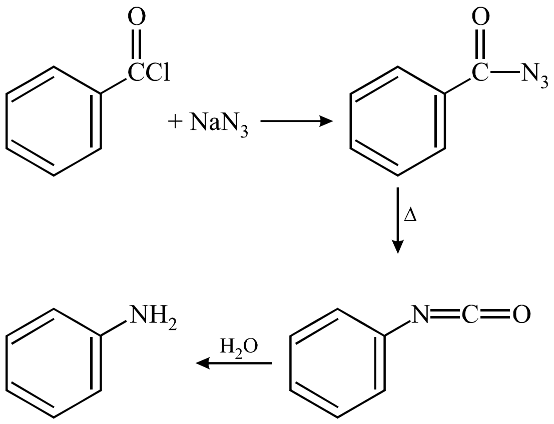
The reaction involves the pyrolysis of acyl azide to produce isocyanates. The subsequent hydrolysis gives amine.

Example - 9



$$CH_3(CH_2)_2CH_2\overset{O}{\overset{\|}{C}}N_3 \xrightarrow{\Delta} CH_3(CH_2)_2CH_2{-}N{=}C{=}O \xrightarrow{H_2O} CH_3(CH_2)_2CH_2NH_2$$

Example - 10



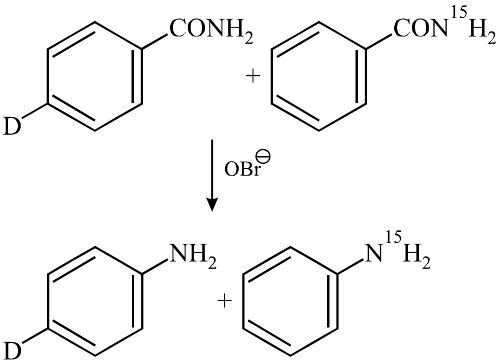
5.4.3 Hofmann's Degradation of Amides

Amide is warmed with bromine and concentrated aqueous KOH or NaOH solution.

(a) Product is 1° amine having one carbon less than amide.

(b) Alkyl isocyanate is the intermediate and rearrangement is intramolecular.

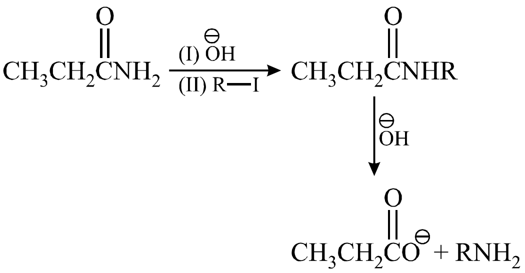
Example - 11



5.4.4 Hydrolysis of Amides & Isocyanides

N-substituted amide and isocyanide on hydrolysis give 1° amine.

Example - 12



$$CH_3CH_2\overset{O}{\overset{||}{C}}NH_2 \xrightarrow[\text{(II) R—I}]{\text{(I)}\ \overset{\ominus}{O}H} CH_3CH_2\overset{O}{\overset{||}{C}}NHR \xrightarrow{\overset{\ominus}{O}H} CH_3CH_2\overset{O}{\overset{||}{C}}O^{\ominus} + RNH_2$$

Example - 13

$$R—NC \xrightarrow[\Delta]{KOH,\ H_2O} R—NH_2 + HCOOK$$

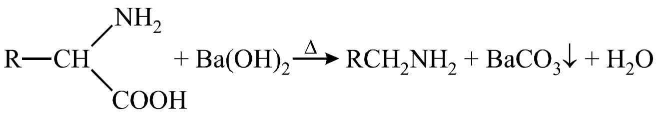
Hydrolysis of Isocyanates also yields amines.

$$\underset{\text{Alkyl Isocyanate}}{R—N{=}C{=}O} \xrightarrow[\Delta]{H_3O^{\oplus}} R—NH_2$$

5.4.5 Decarboxylation of Amino Acids

Amino acids on heating with barium hydroxide gives 1° amine.

Quaternary ammonium hydroxide on heating gets decomposed into alcohol if β-hydrogen is not present in the alkyl group but if there is β-hydrogen, **Hofmann elimination** proceeds.



$$R—CH\begin{matrix}NH_2\\ COOH\end{matrix} + Ba(OH)_2 \xrightarrow{\Delta} RCH_2NH_2 + BaCO_3\downarrow + H_2O$$

5.5 Nitrogen Compounds

5.5.1 Reduction of Cyanides, Isocyanides, Oximes, Imines

Nitrile (—CN), oxime (=NOH), imine (=NH), enamine etc. on catalytic reduction with H_2, Ni give the corresponding amine.

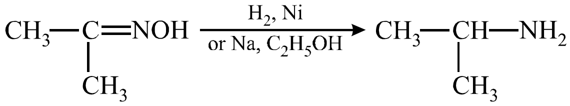
Note...

1. The reduction of nitrile by Na/C_2H_5OH is known as **Mendius reaction**.
2. In most of the cases $LiAlH_4$ is also effective for reduction.
3. Reduction of alkyl isocyanides with Na/C_2H_5OH or H_2/Pt gives 2° amine.

Example - 14

$$CH_3CH_2C{\equiv}N \xrightarrow[\text{Na, }C_2H_5OH]{H_2,\ Ni,\ \Delta \\ \text{OR}} CH_3CH_2CH_2NH_2$$

Example - 15



$$\underset{\text{Acetonoxime}}{CH_3—\underset{CH_3}{\underset{|}{C}}{=}NOH} \xrightarrow[\text{or Na, }C_2H_5OH]{H_2,\ Ni} CH_3—\underset{CH_3}{\underset{|}{CH}}—NH_2$$

Example - 16

$$\underset{\text{Imine}}{Ph—CH{=}NH} \xrightarrow[\Delta]{H_2,\ Ni} PhCH_2—NH_2$$

Example - 17

$$CH_3CH_2—\overset{\oplus}{N}{\equiv}\overset{\ddot{\ominus}}{C} \xrightarrow{4[H]} \underset{\text{2° Amine}}{CH_3CH_2NHCH_3}$$

Example - 18

$$CH_3—CH_2—\overset{\oplus}{N}{\equiv}\overset{\ddot{\ominus}}{C} \xrightarrow{H_2,\ Pt} CH_3CH_2—NH—CH_3$$

5.5.2 Reduction of Nitro Compounds

Nitroalkanes are usually reduced by tin and hydrochloric acid or lithium aluminium hydride into corresponding amine. H_2 and catalyst is also used for such a reduction.

Note...

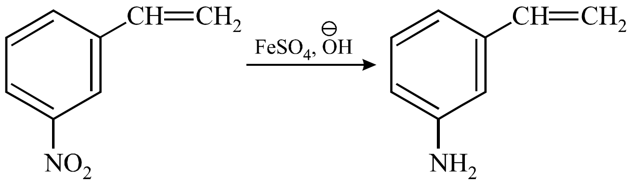
1. 1° aromatic amines are usually prepared by the reduction of corresponding nitro compounds by **tin, iron or zinc with HCl or CH_3COOH**.
2. Aqueous ethanolic ammonium hydrogen sulphide, aqueous sodium sulphide or methanoic sodium hydrogen sulphide selectively reduce one nitro group into a polynitro compound.

Example - 19

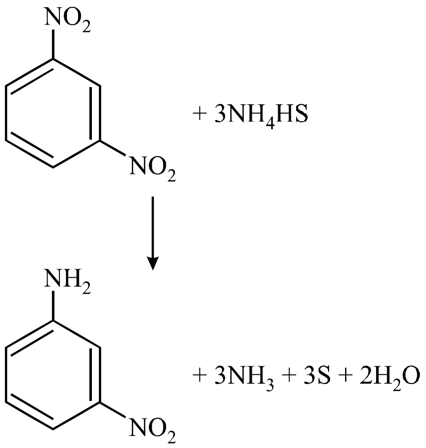
$$CH_3CH_2NO_2 + 6[H] \xrightarrow{Sn,\ HCl} CH_3CH_2NH_2$$

$$CH_3CH_2NO_2 + 3H_2 \xrightarrow{Pt} CH_3CH_2NH_2$$

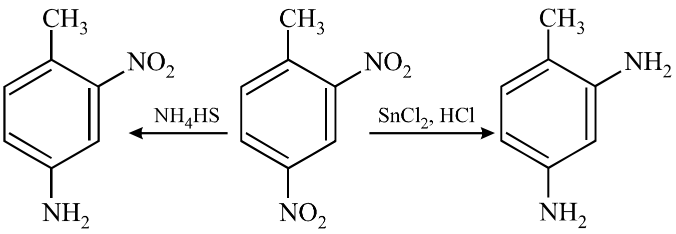
Example - 20



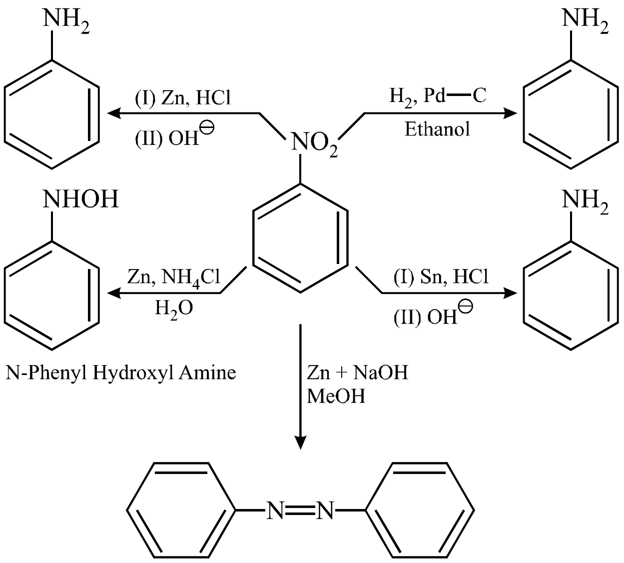
Example - 21



Example - 22



Example - 23



Azobenzene

6. REACTIONS OF AMINES

6.1 Sulphonylation – Hinsberg Test

Treatment with benzene sulphonyl chloride **(Hinsberg reagent)** or p-toluene sulphonyl chloride.

(a) The reaction is used to separate the amine mixture.

(b) 1° and 2° amine, due to the presence of active hydrogen react and give corresponding sulphonamide while 3° amine does not react.

(c) 1° amine product N-alkyl benzene sulphonamide is soluble in KOH forming a water-soluble salt.

$$C_6H_5SO_2Cl + \underset{1^\circ\text{ Amine}}{RNH_2} \longrightarrow \underset{\text{N-Alkylbenzene Sulphonamide}}{C_6H_5SO_2NHR} + HCl$$

$$\downarrow KOH$$

$$\underset{\text{Water Soluble Salt}}{C_6H_5SO_2\overset{\ominus}{N}R\overset{\oplus}{K}}$$

$$C_6H_5SO_2Cl + \underset{2^\circ\text{ Amine}}{R_2NH} \longrightarrow \underset{\text{N,N-Dialkylbenzene Sulphonamide}}{C_6H_5SO_2NR_2} + HCl$$

$$\downarrow KOH$$

Not soluble

$$C_6H_5SO_2Cl + \underset{3^\circ\text{ Amine}}{R_3N} \longrightarrow \text{No Reaction}$$

6.2 Nitrous Acid Test

(a) 1° amine on reaction with HNO_2 gives usually an alcohol. The reaction involves the formation of diazonium salt as an intermediate.

(b) 2° amine gives nitrosoamine which is a yellow oily liquid.

(c) 3° amine dissolves in cold HNO_2 to form an unstable salt which on heating decomposes to give nitrosoamine and an alcohol.

Example - 24

$$CH_3CH_2NH_2 \xrightarrow{HNO_2} CH_3CH_2OH + N_2 + H_2O$$

Example - 25

$$(CH_3)_2NH \xrightarrow{HNO_2} (CH_3)_2N{-}N{=}O + H_2O$$

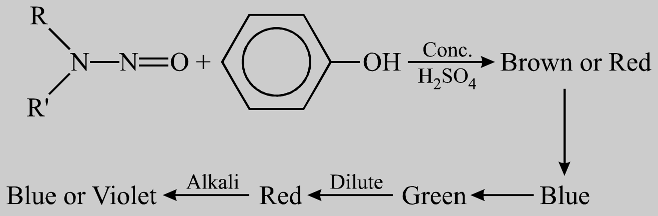
Example - 26

$$(CH_3CH_2)_3N \xrightarrow{HNO_2} (CH_3CH_2)_3N{\cdot}HNO_2$$

$$\big\downarrow \Delta$$

$$(CH_3CH_2)_2N{-}N{=}O + CH_3CH_2OH$$

Note... **Liebermann's Nitroso Test -** Test for 2° amines (nitroso amines) and phenols.

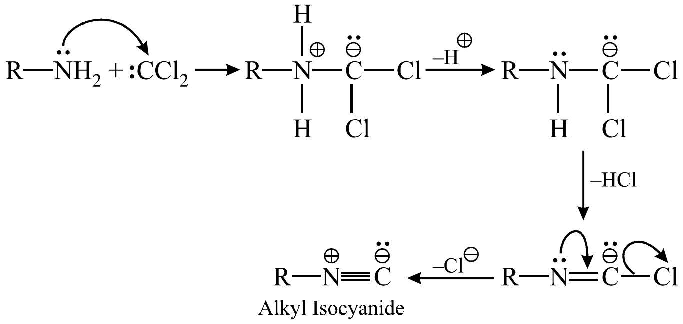


6.3 Carbylamine Reaction

1° amine on treatment with chloroform and alcoholic KOH gives out unpleasant or pungent vapours of alkyl carbylamine (isocyanide).

The reaction is known as a test for 1° amine.

$$CHCl_3 + OH^{\ominus} \longrightarrow :CCl_2 + H_2O$$

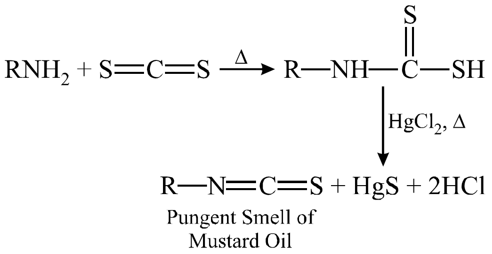


6.4 Treatment with $CS_2/HgCl_2$

(a) 1° amine on warming with CS_2 produces dithiocarbamic acid, which is decomposed by mercuric chloride to alkyl isothiocyanate. It is called as **Hofmann's Mustard Oil Reaction.**

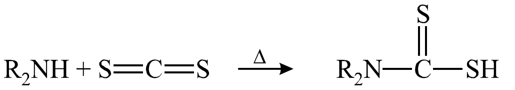
(b) Although 2° amine gives dithiocarbamic acid but is not decomposed by mercuric chloride.

(c) 3° amine don't react with CS_2.



$$RNH_2 + S{=}C{=}S \xrightarrow{\Delta} R{-}NH{-}\overset{\overset{\displaystyle S}{\|}}{C}{-}SH \xrightarrow{HgCl_2,\ \Delta} R{-}N{=}C{=}S + HgS + 2HCl$$

Pungent Smell of Mustard Oil



$$R_2NH + S{=}C{=}S \xrightarrow{\Delta} R_2N{-}\overset{\overset{\displaystyle S}{\|}}{C}{-}SH$$

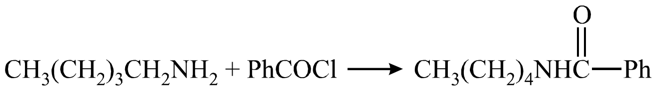
Dialkyl Dithiocarbamic Acid

6.5 Acylation

1° and 2° amines react with acid halide or anhydride to give N-substituted amides.

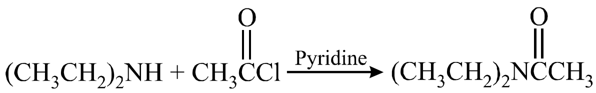
For aniline, the reaction is used to protect the ring.

Example - 27



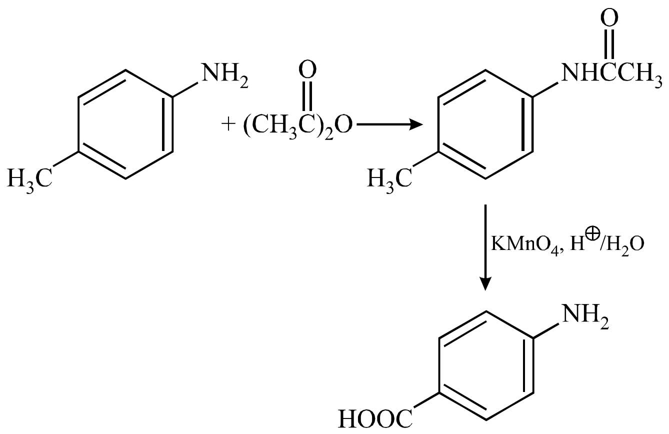
$$CH_3(CH_2)_3CH_2NH_2 + PhCOCl \longrightarrow CH_3(CH_2)_4NH\overset{\overset{\displaystyle O}{\|}}{C}{-}Ph$$

Example - 28

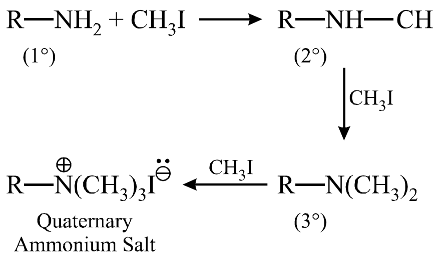


$$(CH_3CH_2)_2NH + CH_3\overset{O}{\overset{\|}{C}}Cl \xrightarrow{\text{Pyridine}} (CH_3CH_2)_2N\overset{O}{\overset{\|}{C}}CH_3$$

Example - 29

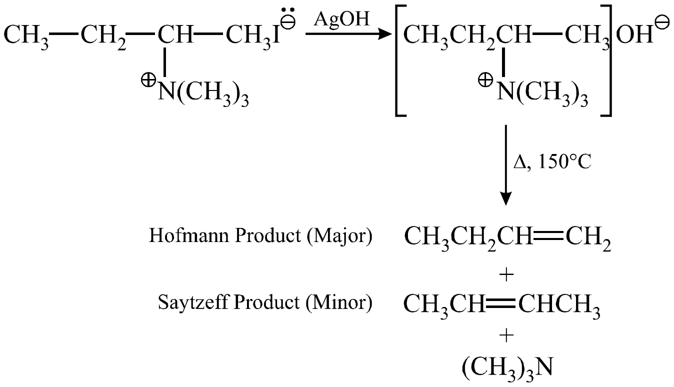


6.6 Hofmann's Exhaustive Methylation and Elimination

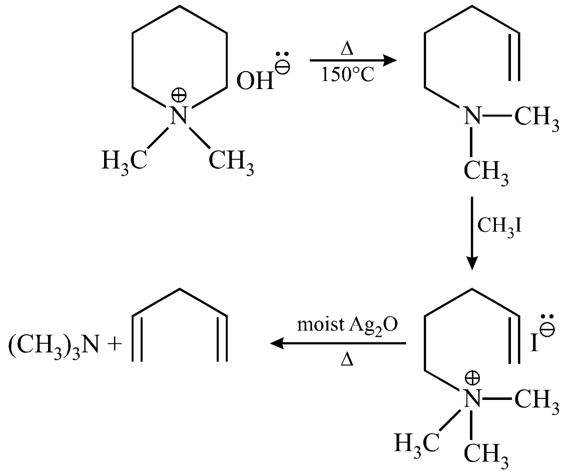


Quarternary Ammonium Iodides are converted to hydroxides with moist Ag_2O. The hydroxide on heating undergo elimination to give 3° amines and alkenes. The important aspect of this elimination is that the least substituted alkene is the major product (**Hofmann Rule**). This is known as **Hofmann's Elimination**.

Example - 30



Example - 31



6.7 Metal Ions

Amines form coordination compounds with metal ions.

Example - 32

$$AgCl \longrightarrow [Ag(CH_3NH_2)_2]^{\oplus}Cl^{\ominus}$$

Soluble Complex

$$Cu^{2\oplus} \longrightarrow [Cu(CH_3NH_2)_2]^{2\oplus}$$

Deep Blue Complex

7. PREPARATION OF AROMATIC AMINES

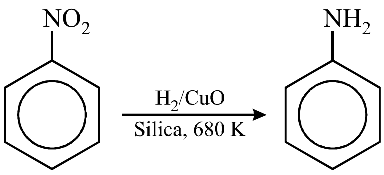
Besides the methods in the preparation of aliphatic amines, following methods can also be used.

7.1 Reduction of Nitro Compounds

7.1.1 Vapour-Phase Reduction

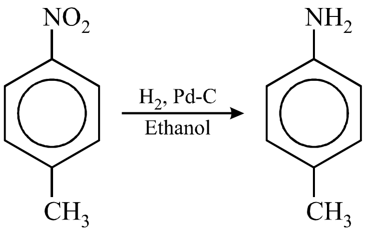
Reducing Agents : CuO on SiO_2 or V–Pt Catalyst.

Example - 33

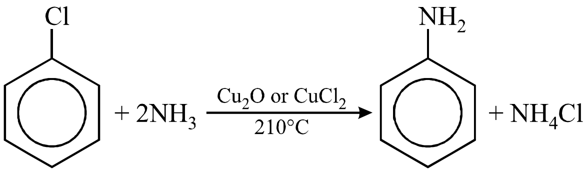


7.1.2 Catalytic Hydrogenation

Reducing Agents : H_2, Pd–C/Et–OH.

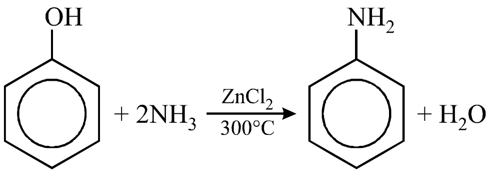


7.2 Ammonolysis of Aryl Halides

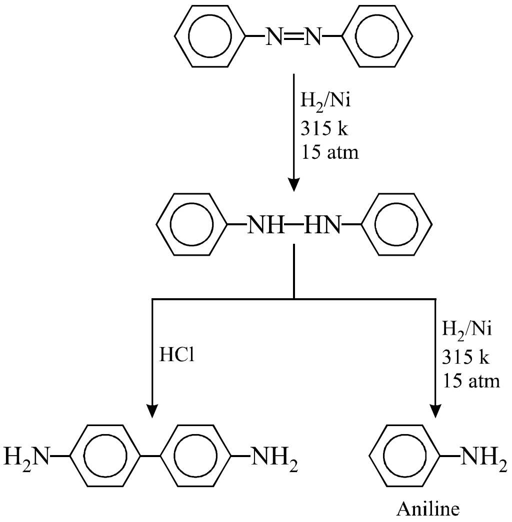


Note... If deactivating groups ($–NO_2$ etc.) are at *ortho* or *para* position, reaction becomes quite easy to carryout.

7.3 Phenol and Ammonia

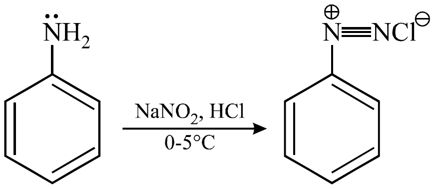


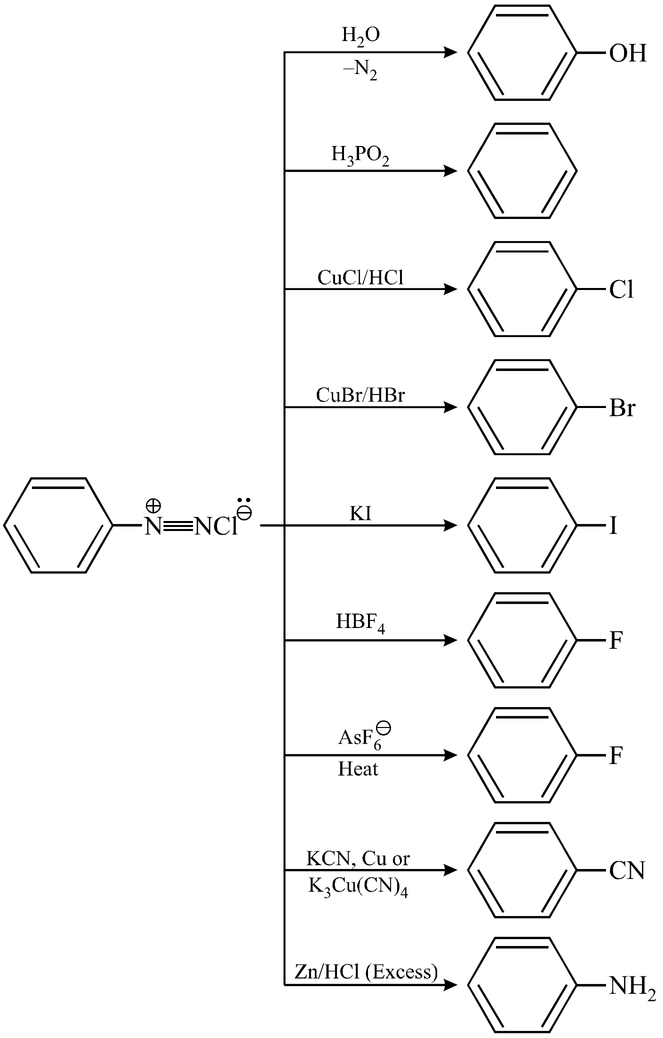
7.4 Reduction of Azo Compounds

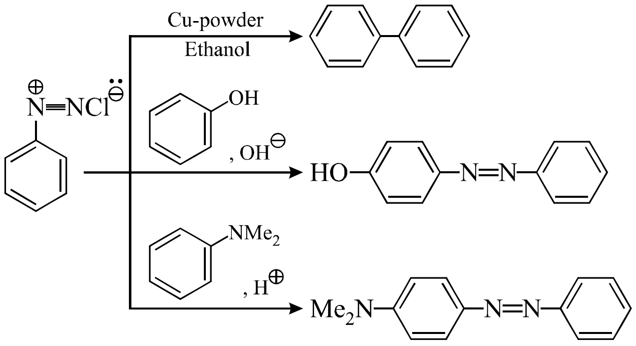


8. REACTIONS OF AROMATIC AMINES

8.1 Diazonium Salt and Reactions



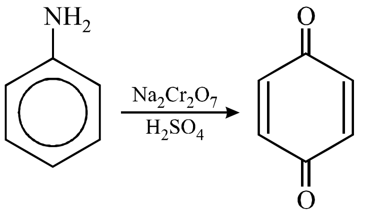




8.2 Oxidation

Aromatic amines are readily oxidised to various products depending on conditions. Under controlled oxidation using $Na_2Cr_2O_7$ and H_2SO_4, aniline is oxidised to p-benzoquinone. In fact, on standing in air, p-benzoquinone is formed.

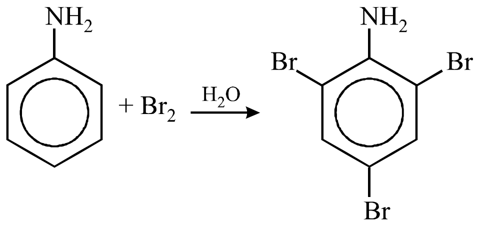
If oxidation is not controlled, a black dye, aniline black is formed.



(Brown Colour)

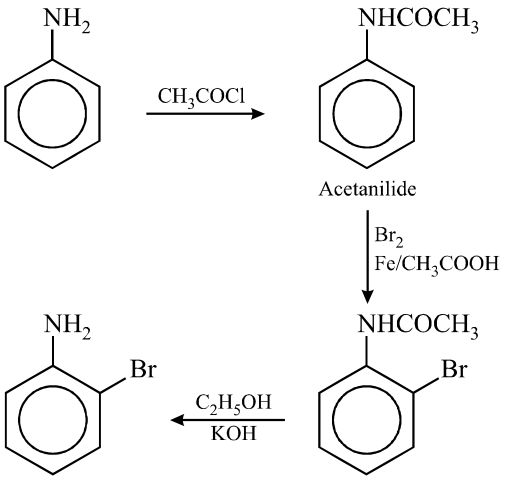
8.3 Halogenation

Amine group (NH_2) is a very strong activating group and an ortho/para director. It forms 2, 4, 6-tribromo aniline on normal bromination in H_2O.



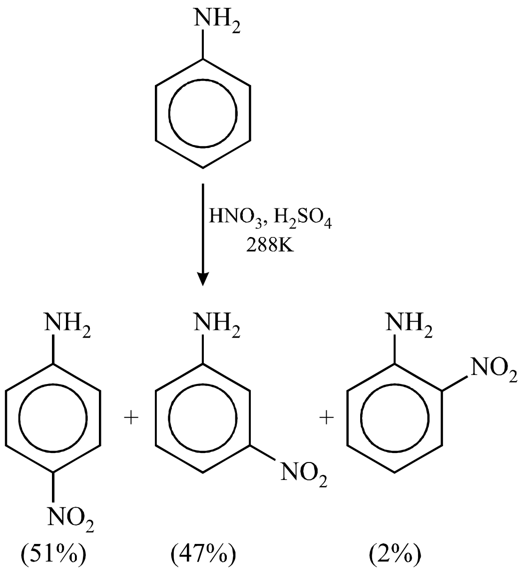
ortho and *para* derivatives can be made by decreasing the activating power of amino group by acetylation of aniline. $-NHCOCH_3$ group is a mild *ortho* and *para* director.

Example - 34

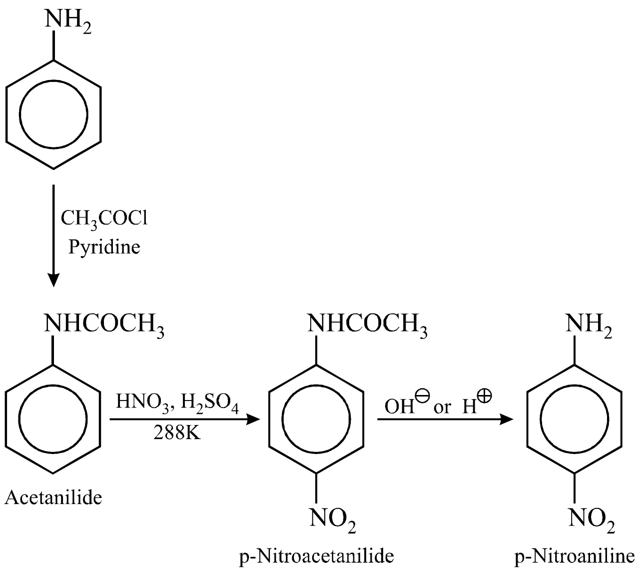


8.4 Nitration

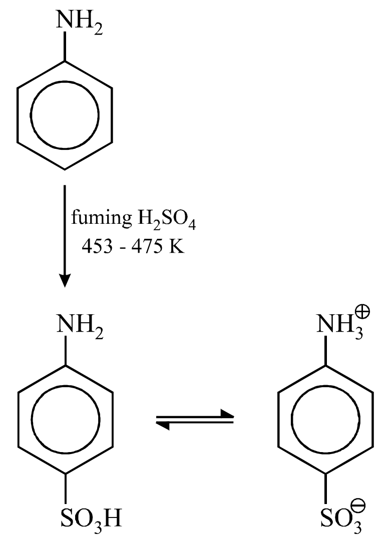
The normal nitration of aniline is not done as nitrating mixture is oxidising and NH_2 is a strong activating group. Moreover, at 288 K aniline is protonated to form the anilinium ion which is meta directing. That is why besides the ortho and para derivatives, a significant amount of meta derivative is also formed.



However, by protecting the $-NH_2$ group by acetylation reaction with acetic anhydride, the nitration reaction can be controlled and the p-nitro derivative can be obtained as the major product.



8.5 Sulphonation



Sulphanilic Acid

Zwitter Ion
(Dipolar Ion)

Note... Usually $-NH_2$ group attached to benzene is unable to form zwitter ion but here $-SO_3H$ is very strongly acidic. Hence sulphanilic acid forms zwitter ion. For example when $-NH_2$ group is attached to benzoic acid in any position, zwitter ion is not formed.

9. ANALYSIS OF AMINES

Amines are characterized chiefly through their basicity. A water-insoluble compound that dissolves in cold dilute hydrochloric acid or a water-soluble compound whose aqueous solution turns litmus blue - must almost certainly be an amine.

Whether an amine is primary, secondary, or tertiary is best shown by the **Hinsberg test**. The amine is shaken with benzenesulfonyl chloride in the presence of aqueous potassium hydroxide. Primary and secondary amines form substituted sulfonamides; tertiary amines do not.

The monosubstituted sulfonamide from a primary amine has an acidic hydrogen attached to nitrogen. Reaction with potassium hydroxide converts this amide into a soluble salt.

The disubstituted sulfonamide from a secondary amine has no acidic hydrogen and remains insoluble in the alkaline reaction mixture.

Behaviour toward nitrous acid is of some use in determining the class of an amine. In particular, the behaviour of primary aromatic amines is quite characteristic: treatment with nitrous acid converts them into diazonium salts, which yield highly colored azo compounds upon treatment with β-naphthol.

Hinsberg test is also used for the separation of amines.