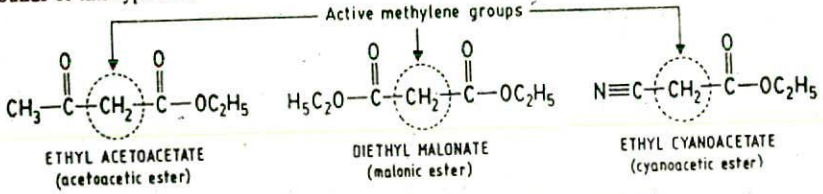
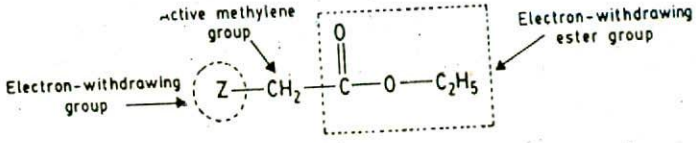
Chapter **26**

Active Methylene Compounds

When a methylene group, $-CH_2-$, is flanked by two electron-withdrawing groups, the hydrogen atoms bonded to carbon become acidic and reactive. The compounds containing such methylene groups are referred to as **Active Methylene Compounds.** Some important compounds of this type are :



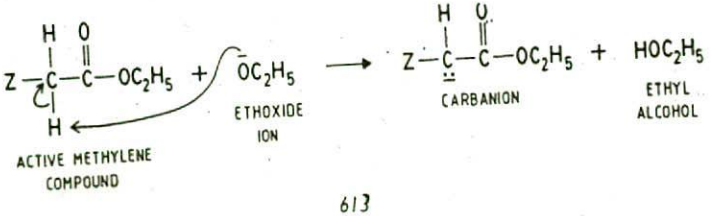
All the above active methylene compounds can be represented by the formula



where the ester group ($-CO-OC_2H_5$) is a common electron-withdrawing group, the second electron-withdrawing group being

either $CH_3-\overset{O}{\overset{\|}{C}}-$ (acetyl) or $H_5C_2O-\overset{O}{\overset{\|}{C}}-$ (ester) or $N\equiv C-$ (cyanide)

The enhanced activity of the active methylene groups is attributed to the influence of the adjacent electron-withdrawing groups and the formation of the resonance-stabilised carbanion. The carbon-hydrogen bonds of the methylene group are thus weakened so as to make its H atoms acidic and reactive. In the presence of a base such as ethoxide ion, carbanion is formed as follows.

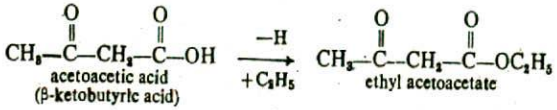


The carbanion so generated acts as a strong nucleophilic agent and participates in quite a number of S_N2 reactions.

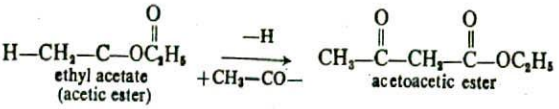
The active methylene compounds are valuable synthetic reagents in organic chemistry. A number of compounds which cannot be easily obtained by other conventional methods can be synthesised through the application of the active methylene compounds.

ETHYL ACETOACETATE, *Acetoacetic Ester,* $CH_3—CO—CH_2—COOC_2H_5$

It is the ethyl ester of acetoacetic acid (β-ketobutyric acid) and hence its name *Ethyl Acetoacetate,*

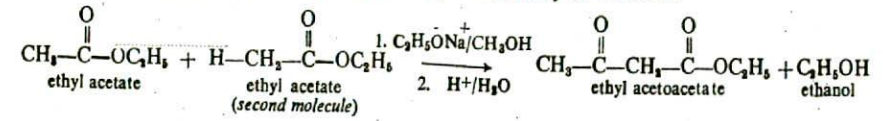


It is some times referred to as simply *Acetoacetic Ester* since it could be regarded as acetyl derivative of acetic ester *i.e.*, ethyl acetate.



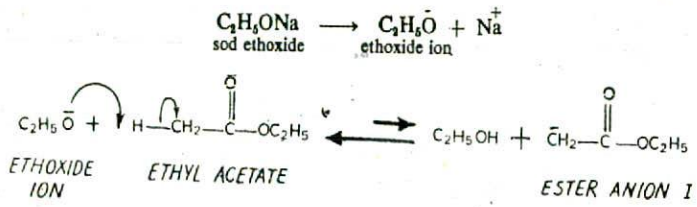
Ethyl acetoacetate is easily the best known active methylene compound and will be discussed in detail.

Preparation. Ethyl acetoacetate is prepared by refluxing ethyl acetate in presence of sodium ethoxide ($C_2H_5—O^-Na^+$) in ethanol, followed by acidification. The overall reaction which is the self-condensation of two molecules of ethyl acetate may be written as

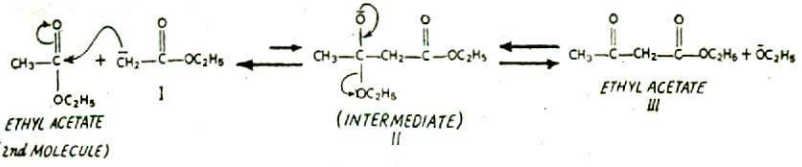


MECHANISM. The above reaction, often referred to as *Claisen Condensation,* occurs by the following steps.

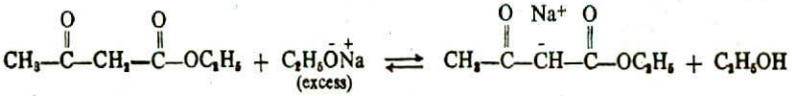
(*i*) The hydrogen atoms of methyl group of an ethyl acetate molecule are weakly acid because of the adjacent electron-withdrawing ester group. Therefore they form the corresponding ester anion (I) in presence of strongly basic ethoxide ions.

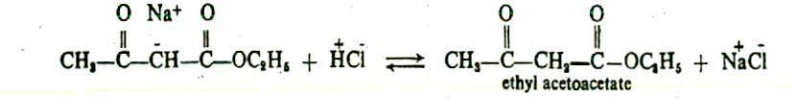


(*ii*) The nucleophilic attack of the ester anion (I) takes place on the carbonyl group of the second molecule of ethyl acetate. The intermediate which is formed eliminates ethoxide ion to produce ethyl acetoacetate (III).

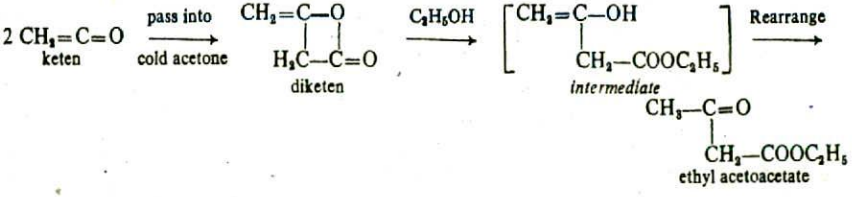


(*iii*) Since the three reactions described above in steps (*i*) and (*ii*) are reversible, to drive the formation of ethyl acetoacetate to completion, excess of sodium ethoxide has to be taken in step (*i*). The excess of sodium ethoxide, however, converts ethyl acetoacetate into its sodium salt. Ethyl acetoacetate is regenerated from its salt upon acidification.

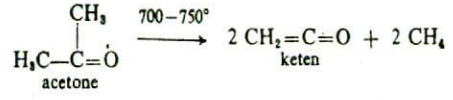




Industrial Method. Ethyl acetoacetate is produced industrially by passing ketene into cold acetone when it dimerises to form diketen. The diketen on subsequent treatment with ethanol produces ethyl acetoacetate.

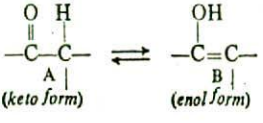


The keten required as starting material is obtained by the pyrolysis of acetone at 700—750°C.



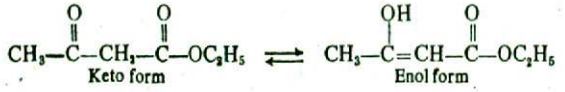
Tautomerism of Ethyl acetoacetate

In the early days of Organic Chemistry, there was noted a phenomenon whereby the same compound reacted as if it was made of two structural components. This was referred to as *Tautomerism* (Gr, *tauto*=same ; *meros*=parts). Later studies led to the modern definition of **Tautomerism** as *the phenomenon in which two isomeric forms having different functional groups are spontaneously interconvertible and can exist in dynamic equilibrium.* The two forms in tautomeric equilibrium are called **Tautomers** of each other. All carbonyl compounds : aldehydes, ketones and esters exhibit tautomerism.



Here the two forms in tautomeric equilibrium are A and B. The form A contains a keto group (C—CO—C) and is called the **Keto form**. The form B which contains the functional group >C=C—OH is called the **Enol form** (IUPAC, *en*=double bond ; *ol*=alcohol). *This particular type of tautomerism which involves a dynamic equilibrium between keto form and enol form of a compound is termed* **Keto-Enol Tautomerism.**

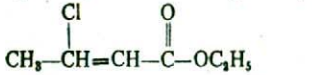
Ethyl acetoacetate is the best studied classical example of keto-enol tautomerism.



Geuther (1863) suggested the keto structure, while Frankland and Duppa (1865) independently proposed the enol structure of ethyl acetoacetate. The presence of each of the enol and keto forms in ethyl acetoacetate was supported by two sets of reactions listed below.

Reactions Supporting the Enol Structure. (1) Ethyl acetoacetate reacts with sodium to form its corresponding sodium salts. This reaction is typical of alcohols and indicates the presence of a the hydroxy group.

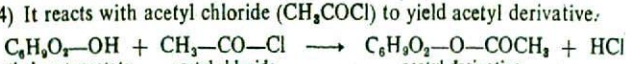
(2) It reacts with phosphorus pentachloride to give ethyl β-chlorocrotonate,



In this reaction one OH group is replaced by Cl atom, a behaviour typical of hydroxy compounds.

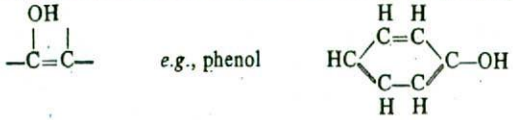
(3) When treated with ethanolic solution of bromine, ethyl acetoacetate discharges the brown colour of bromine rapidly. This indicates the presence of carbon-carbon double bond (C=C).

(4) It reacts with acetyl chloride (CH_3COCl) to yield acetyl derivative.



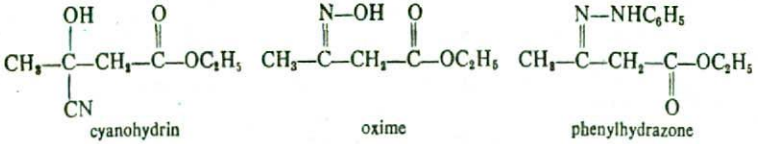
This also proves the presence of hydroxy group in ethyl acetoacetate.

(5) Ethyl acetoacetate produces a reddish violet colouration when a *little* ferric chloride is added to it. This is characteristic of compounds containing the grouping :



(6) Although neutral to litmus, it dissolves in alkalis showing its feeble acidic character.

Reactions Supporting the Keto Structure. (1) The presence of a ketonic carbonyl group in ethyl acetoacetate is indicated as it reacts with : (*i*) sodium bisulphite solution to form a crystalline bisulphite compound ; (*ii*) hydrogen cyanide to form a cyanohydrin ; (*iii*) hydroxylamine to form an oxime ; and (*iv*) phenylhydrazine to form phenylhydrazone.



(2) When reduced with sodium amalgam, it produces a secondary alcohol group which must have been obtained as a result of the reduction of a keto group.

(3) Ethyl acetoacetate upon hydrolysis with aqueous or ethanolic potassium hydroxide, followed by acidification and subsequent heating at 200° yields acetone ($CH_3—CO—CH_3$). This proves the presence of a ketonic group.

Evidence for the Existence of Dynamic Equilibrium. From the above reactions it is clear that both the keto form and enol form are simultaneously present in ethyl acetoacetate. Further, since with a particular reagent the whole substance behaved as keto or enol form, it stands to reason that there existed dynamic equilibrium between the two forms. Thus when a reagent reacts with say keto form, the equilibrium is shifted so as to produce more of it instantaneously from the enol form. This process continues till the enol form is exhausted and in this way the whole substance behaves as if it were keto ethyl acetoacetate.

Separation of Keto and Enol Forms. The theory of the existence of dynamic equilibrium in ethyl acetoacetate was confirmed by Ludwig Knorr (1911). He succeeded in separating the two tautomeric forms (keto and enol) and demonstrated their reconversion to the tautomeric mixture which is ordinary ethyl acetoacetate.

Knorr cooled a solution of ordinary ethyl acetoacetate in petroleum ether to −78°. The colourless crystalline substance thus separated had *mp* −39°. It produced no coloration with ferric chloride and did not decolourise ethanolic bromine solution. It was therefore pure keto form.

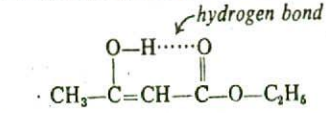
The enol form was isolated by Knorr by treating a suspension of the sodium salt of ethyl acetoacetate in petroleum ether and passing into it theoretical quantity of HCl gas to decompose the sodium salt. The resulting mixture was freed from sodium chloride by filtration and the filterate evaporated under reduced pressure at −78°. The oily substance thus obtained gave an intense colour with ferric chloride and immediately decolorised ethanolic bromine solution. It was therefore pure enol form.

Table. Characteristic Properties of Keto and Enol forms (Knorr)

Keto Form	*Enol Form*
(1) Long colourless needles, *mp* (−39°)	(1) Colourless oily liquid, at −78°
(2) Refractive Index, $n_D^{10} = 1{\cdot}4225$	(2) Refractive Index, $n_D^{10} = 1{\cdot}4430$
(3) Gives no colouration with ferric chloride	(3) Gives intense colour with ferric chloride
(4) Decolorises ethanolic bromine solution immediately.	(4) Does not decolourise ethanolic bromine solution.

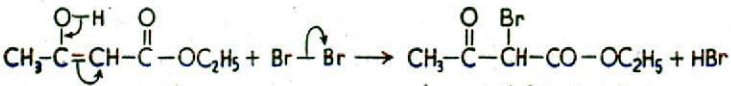
Knorr further showed that either the keto or the enol form separated by him, on standing for some time at room temperature became identical. Each form passed into the same equilibrium mixture of tautomers, giving ordinary ethyl acetoacetate. This confirmed the existence of dynamic equilibrium between keto and enol forms.

K.H. Meyer (1920) confirmed the findings of Knorr about the keto-enol tautomerism in ethyl acetoacetate. He also succeeded in separating practically pure keto and enol forms by fractionally distilling ethyl acetoacetate in quartz apparatus (enol, *bp* 41°; keto, *bp* 23°, both at 2 mm pressure). In quartz vessels the rate of attainment of tautomeric equilibrium is greatly reduced and, therefore, on slow distillation the enol being more volatile distils over first. The greater volatility of the enol form compared to keto form is due to intramolecular hydrogen bonding. This reduces intermolecular association and lowers the boiling point.



It may be noted that the interconversion of the keto and enol forms of ethyl acetoacetate is greatly catalysed by acids and bases, even in very small amounts. Thus the separation of the two forms cannot be effected in ordinary soda glass because even traces of alkali derived from glass lead to the rapid establishment of tautomeric equilibrium.

Composition of Keto-Enol Tautomeric Mixtures. K.H. Meyer observed that only the enol form of ethyl acetoacetate reacts rapidly with bromine in ethanolic solution, while the keto form does not.



bromo ethyl acetoacetrate

He made use of this fact to determine the proportion of enol form in the equilibrium mixture.

A weighed sample of ethyl acetoacetate is rapidly treated with a slight excess of bromine at 0°, and then immediately an ethanolic solution of β-naphthol is added to remove the excess of bromine.



β-naphthol

The reaction mixture is acidified with hydrochloric acid and potassium iodide added in excess. The hydrogen iodide formed reduces the bromo ester to the keto form of ethyl acetoacetate and liberates iodine. The liberated iodine is titrated against a standard solution of sodium thiosulphate. From the amount of iodine thus determined, the bromo ester can be estimated. This gives a measure of the enol content of the equilibrium mixture.

$$\underset{\text{bromo ester}}{CH_3{-}CO{-}CHBr{-}COOC_2H_5} + KI \longrightarrow \underset{\text{iodo ester}}{CH_3{-}CO{-}CHI{-}COOC_2H_5} + KBr$$

$$KI + HCl \longrightarrow KCl + HI$$

$$\underset{\text{iodo ester}}{CH_3{-}CO{-}CHI{-}COOC_2H_5} + HI \longrightarrow \underset{\text{ethyl acetoacetate}}{CH_3{-}CO{-}CH_2{-}COOC_2H_5} + I_2$$

By this procedure and other available methods it has been etablished that at room temperature the equilibrium mixture of ethyl acetoacetate contains 7·5% of the enol form and 92·5% of the keto form. The same results are also obtained from a study of the NMR spectrum of ethyl acetoacetate. The spectrum shows absorption peaks of the hydroxyl, vinyl and methyl protons in addition to those expected for the keto form. From a comparison of the areas under the absorption peaks for the various groups in the NMR Spectrum, one can calculate the percentage of keto and enol forms in the mixture.

Table. Composition of Ethyl Acetoacetate in different solvents at 18° (Meyer)

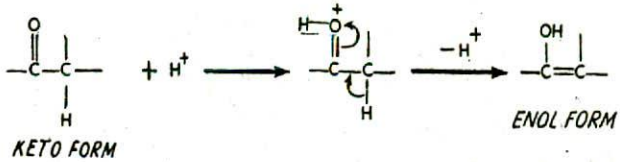
Solvent	*% Keto form*	*% Enol form*
Water	99·6	0·0
Ethanol	90	10
Ether	73	27
n-hexane	54	46

It is noteworthy that the enol content in a keto-enol tautomeric equilibrium mixture, is not fixed. The proportions of the two tautomeric forms depend on temperature, the nature of the solvent as also on the concentration of the solution.

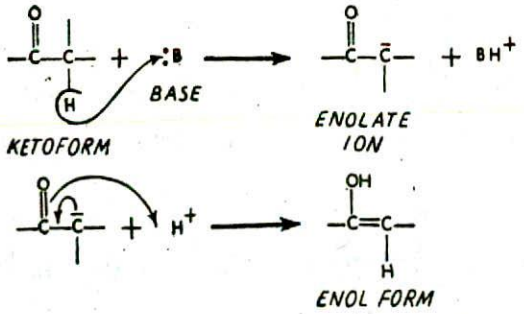
Mechanism of Keto-Enol Tautomerism. We have seen that in keto-enol tautomerism, the tautomers (keto and enol forms) differ only in respect of the position of hydrogen. It is believed that interconversion of tautomers involves the separation of a proton at one atom and addition of proton at the other. *The type of tautomerism which occurs due to change in the position of a proton is called* **Prototropy** (Gr. *trope*, a turning). All the cases of tautomerism commonly encountered in organic chemistry are examples of Prototropy.

MECHANISM. Keto-enol tautomerism is subject to catalysis by acid or base. Thus, the process of equilibration of a pure keto form or enol form is greatly speeded up by the addition of acid or base catalysis. The generally accepted mechanism of acid and base catalysis is as follow.

(1) *Catalysis by Acid* takes place in two steps : (*i*) Protonation of oxygen to give the conjugate acid ; (*ii*) abstraction of the proton on carbon.



(2) *Catalysis by Base.* (: B) also takes place in two steps : (*i*) removal of proton by base to give enolate ion ; and (*ii*) Protonation on oxygen to give the enol.



The addition of one proton and the removal of the other may take place simultaneously. However, it is generally not the same proton involved in the two steps.

TAUTOMERISM *VERSUS* RESONANCE

Tautomerism is entirely different from resonance and the two are not to be confused.

(1) In tautomerism the two forms of a compound in equilibrium, having different structures, actually exist and can be separated. For example, the enol and keto forms of ethyl acetoacetate, which exist as independent molecules, have been isolated.

Resonance contributing forms have no independent existence. They are drawn on paper just to meet the valence bond requirements of molecular structure of certain compounds to account for their stability.

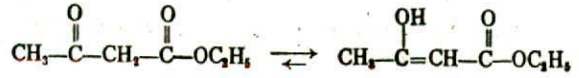
(2) In tautomerism the structures of tautomers differ principally in the position of at least one atom relative to the other atoms in the molecules. For example, in the enol form of ethyl acetoacetate the hydrogen is on the oxygen, while in keto form it is on the carbon.

In resonance the chief difference in the various canonical forms is in the position of electrons, all the atoms in each form having the same relative positions.

Properties of Ethyl Acetoacetate

(*Physical*). Ethyl acetoacetate is a colourless liquid with a fruity odour. It boils at 181° with slight decomposition. It is sparingly soluble in water but dissolves readily in ethanol, ether and most other organic solvents. It is neutral to litmus. Refractive index of ordinary ethyl acetoacetate is $n_D^{10} = 1{\cdot}4232$.

(*Chemical*). Ethyl acetoacetate is a tautomeric mixture of the keto and enol forms. Under ordinary conditions the equilibrium mixture contains about 7·5% of the enol form and 92·5% of the keto form.

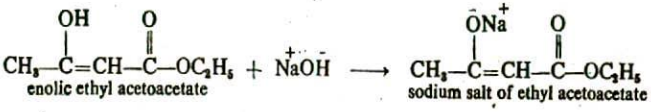


Therefore, the chemical reactions of ethyl acetoacetate are those of :

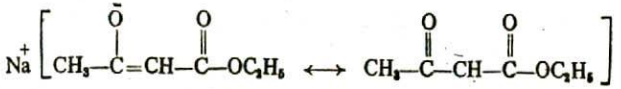
(*i*) *the Enol form* ; (*ii*) *the Keto form* ; *and* (*iii*) *the Active Methylene group.*

A. REACTIONS OF THE ENOL FORM

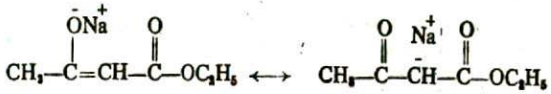
(1) **Formation of Sodium Salt.** The hydrogen of the hydroxy group of the enol form of ethyl acetoacetate is weakly acidic. Therefore, ethyl acetoacetate reacts with alkalis to form salts.



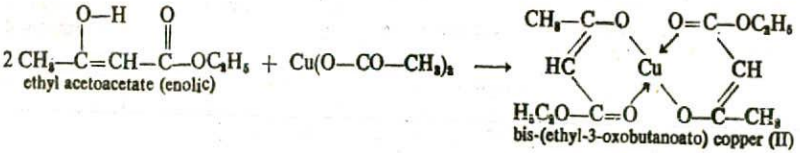
Actually the enolate ion is a resonance hybrid and the sodium salt of ethyl acetoacetate may be represented as



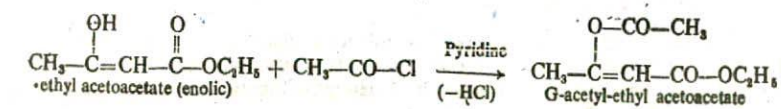
OR



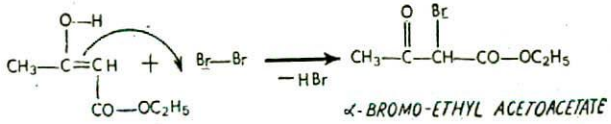
(2) **Formation of Copper Compound.** Ethyl acetoacetate when treated with a solution of copper acetate forms a green coloured compound. This is soluble in benzene and other organic solvents, indicating that it is not an ionic but a chelated compound.



(3) **Reaction with Acetyl Chloride.** Ethyl acetoacetate in benzene solution reacts with acetyl chloride to form the O-acetyl derivative of the enolic form.

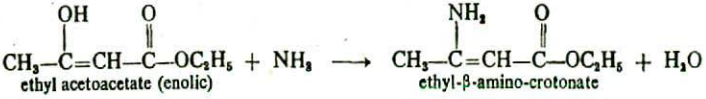


(4) **Reaction with Bromine.** It reacts with an ethanolic solution of bromine to form α-bromo-ethyl acetoacetate.



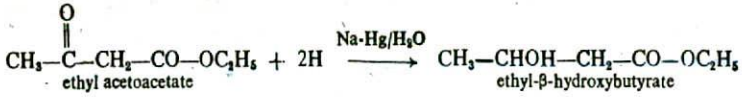
This reaction is used in the estimation of the enol in ethyl acetoacetate.

(5) **Reaction with Ammonia.** Ethyl acetoacetate reacts with ammonia to form ethyl-β-amino-ethyl crotonate.

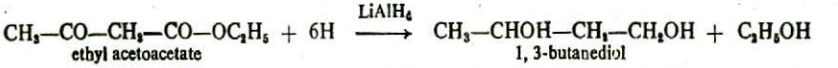


B. REACTIONS OF KETO FORM

(1) **Reduction.** Ethyl acetoacetate when reduced with sodium amalgam forms ethyl β-hydroxybutyrate.

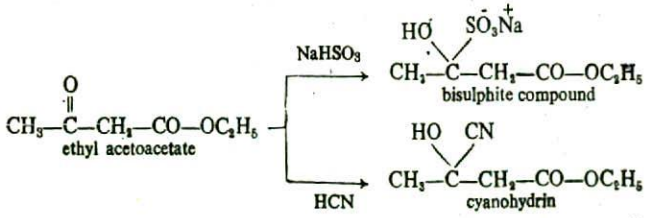


The same product is also obtained when ethyl acetoacetate is reduced with lithium-aluminium hydride in pyridine solution. If the reduction is carried with $LiAlH_4$ in absence of pyridine, 1, 3-butanediol is obtained.



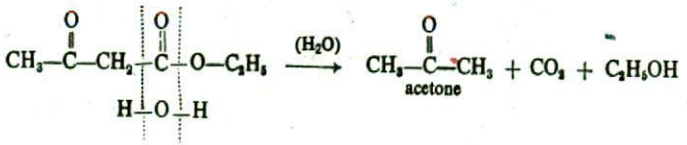
Kent *et al.* (1963) have shown that diol is also produced by sodium borofluoride in boiling ethanol.

(2) **Addition and Condensation Reactions of the Ketonic C=O group.** Ethyl acetoacetate reacts with sodium bisulphite and hydrogen cyanide to form the bisulphite compound and cyanohydrin respectively.

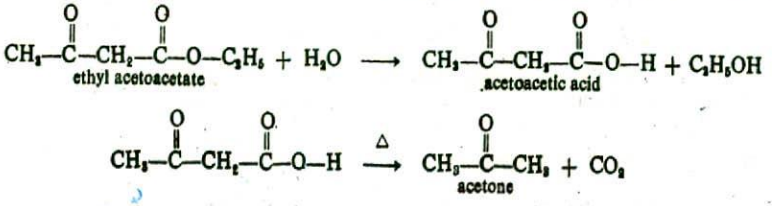


It condenses with hydroxylamine and phenylhydrazine to form the oxime and phenyl hydrazone respectively. These products being unstable finally undergo ring closure giving methyl isooxazolone and *N*-phenyl-methyl-pyrazolone (*See synthetic uses*).

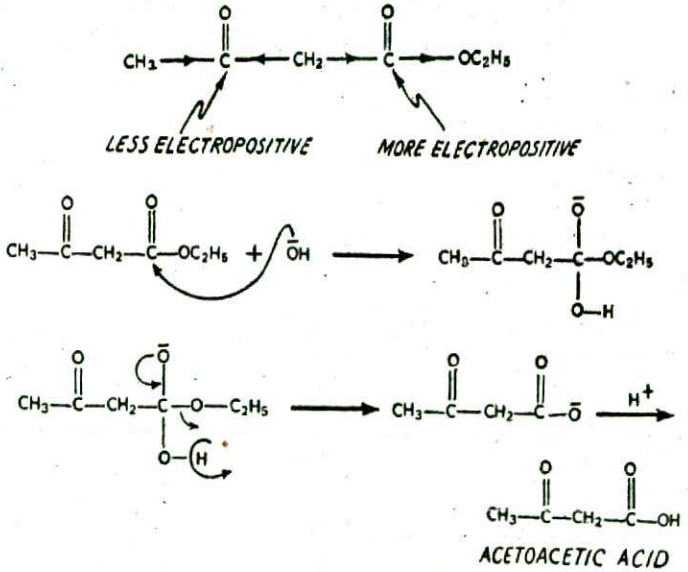
(3) **Hydrolysis.** (*a*) *Ketonic Hydrolysis.* When ethyl acetoacetate is heated with dil HCl, or heated with dil aqueous or ethanolic alkali, followed by acidification and heating, the net result is the formation of a ketone (acetone).



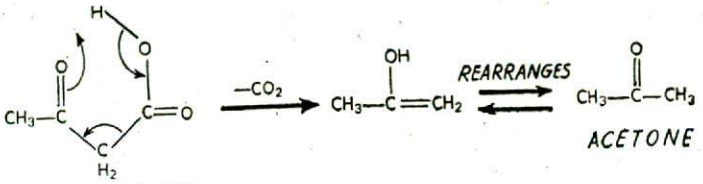
This type of hydrolysis which proceeds by cleavage of the molecule so as to produce a ketone, is called **Ketonic Hydrolysis** or **Ketone Cleavage.** Of course, the hydrolysis of the ester group first forms acetoacetic acid which decarboxylates rapidly upon heating to yield ketone.



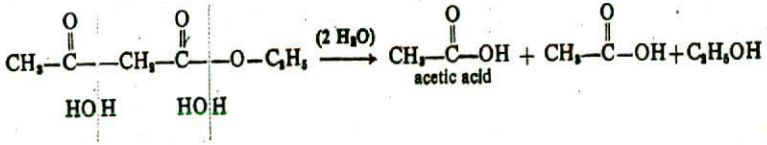
MECHANISM. Under these mild conditions, the nucleophile $\bar{O}H$ attacks only the more electropositive carbonyl carbon and the other carboxyl carbon remains practically unattacked.



The acetoacetic acid produced on acidification decarboxylates to give acetone. This is made easier because the H-atom of the O—H group of the acid being contiguous to the ketonic oxygen atom, a simple flow of electrons is facilitated. The initial product is an enol which then rearranges in the acid solution.

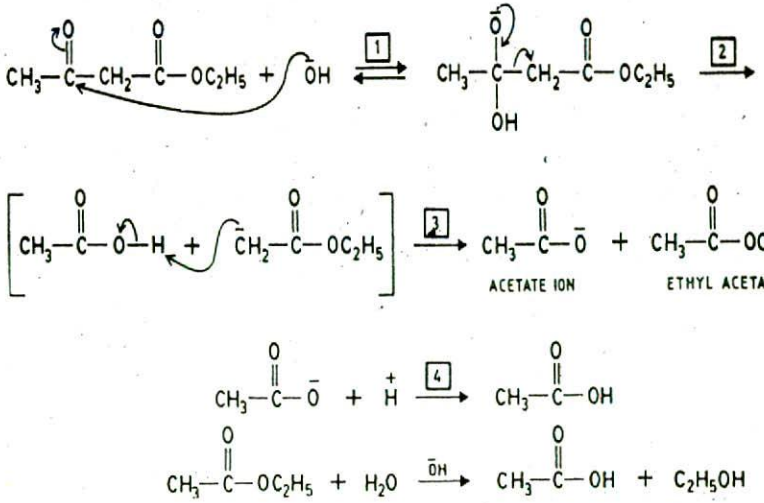


(*b*) *Acid Hydrolysis.* When the hydrolysis of ethyl acetoacetate is carried by boiling with concentrated aqueous or ethanolic solution of KOH, followed by acidification with dil HCl, the main product is an acid (acetic acid).

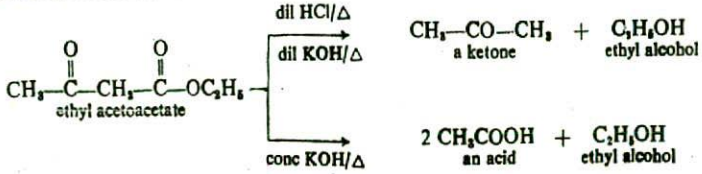


This type of hydrolysis since it results in the formation of acids by cleavage of the molecule as above, is referred to as **Acid Hydrolysis** or **Acid Cleavage.**

MECHANISM. The key step in acid hydrolysis of ethyl acetoacetate with a strong alkali is the reversal of the Claisen Condensation which leads to the formation of acetic acid.

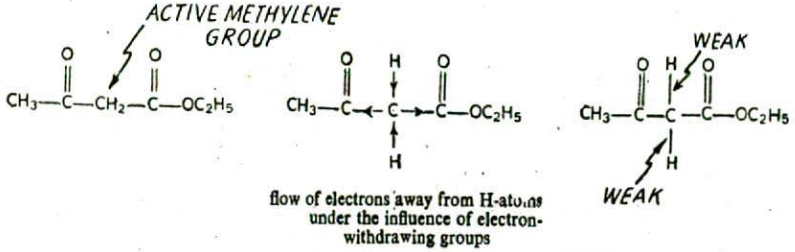


The Ketonic and Acid Hydrolysis are of great use in synthetic methods and may, therefore, be restated as follows.

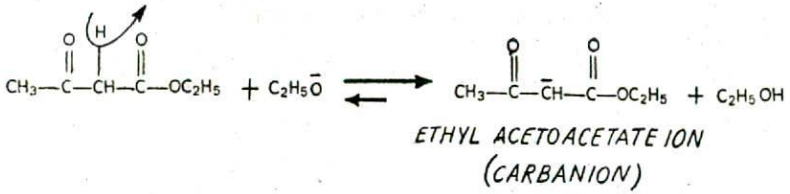


C. REACTIONS OF THE ACTIVE METHYLENE GROUP

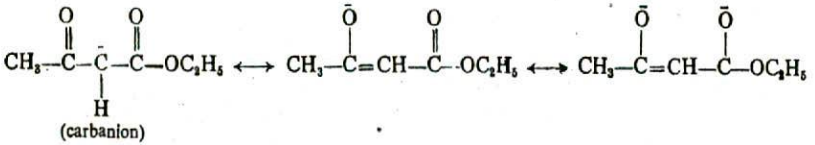
Ethyl acetoacetate molecule contains a methylene group which is very reactive. The H-atoms of this methylene group are rendered acidic on two accounts : (*i*) the C—H bonds of the methylene group are sufficiently weakened by the strong electron-withdrawing effect of the $CH_3—CO—$ and $—CO—OC_2H_5$ flanking it.



(*ii*) The ethyl acetoacetate anion left after the removal of a proton is resonance stabilised. Thus in the presence of a base such as ethoxide ion, the carbanion is formed as below.



The resulting anion exists in the following resonance forms.

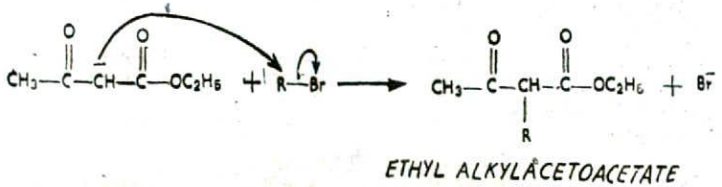


A few important reactions of the active methylene group are stated as follows.

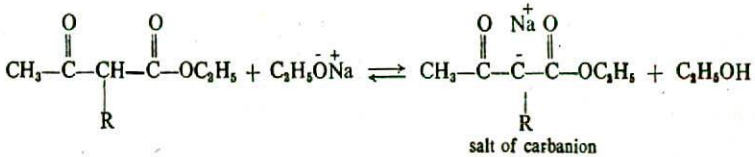
(1) **Alkylation.** In the presence of sodium ethoxide (a strong base) ethyl acetoacetate generates a nucleophilic carbanion.



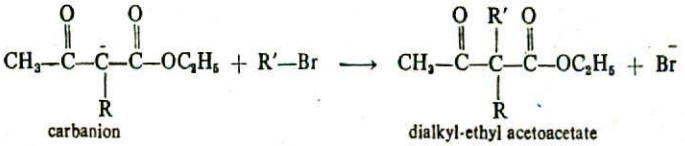
The sodium salt of ethyl acetoacetate is then reacted with alkyl bromide. The carbanion is alkylated in an S_N2 reaction



Since the monoalkyl derivative of ethyl acetoacetate still possesses an ionisable hydrogen (second H-atom of methylene), the above process may be repeated to produce the dialkyl derivative.

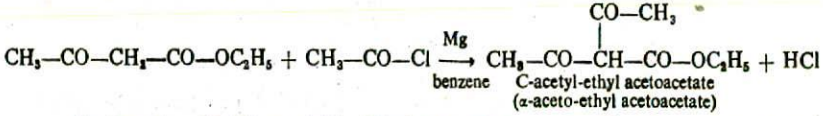


salt of carbanion



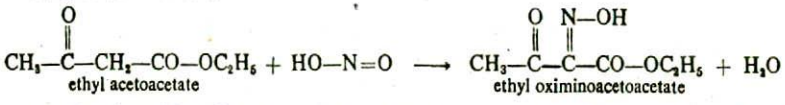
carbanion dialkyl-ethyl acetoacetate

(2) **Formation of C-Acetyl derivative.** We have already seen that O-acetyl-ethyl acetoacetate is obtained by the reaction of ethyl acetoacetate enol with acetyl chloride in pyridine solution. However, if a benzene solution of ethyl acetoacetate is treated with acetyl chloride in presence of Mg metal, the product is C-acetyl ethyl acetoacetate.



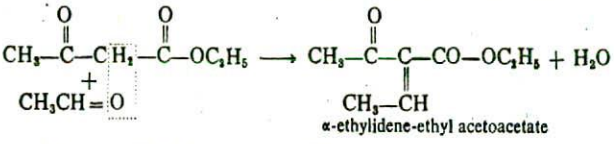
benzene C-acetyl-ethyl acetoacetate (α-aceto-ethyl acetoacetate)

(3) **Reaction with Nitrous Acid.** Ethyl acetoacetate reacts with nitrous acid to produce ethyl α-oximino-acetoacetate.



ethyl acetoacetate ethyl oximinoacetoacetate

(4) **Reaction with Aldehydes.** Ethyl acetoacetate undergoes Knoevenagel condensation in presence of a base such as pyridine to form α-ethylidene-ethyl acetoacetate.

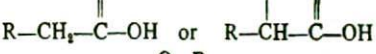


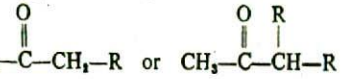
α-ethylidene-ethyl acetoacetate

SYNTHETIC USES OF ETHYL ACETOACETATE

By virtue of the presence of an active methylene group in its molecule as also its existence as keto and enol forms, ethyl acetoacetate is capable of reacting with a number of reagents to yield a variety of useful compounds which are not available from routine preparative methods. The compounds synthesised from ethyl acetoacetate include saturated monocarboxylic acids, unsaturated acids, dicarboxylic acids, keto acids, ketones, diketones, alicylic compounds and heterocyclic compounds. All syntheses accomplished with the help of ethyl acetoacetate (acetoacetic ester) are some times referred to as **Acetoacetic Ester Synthesis.**

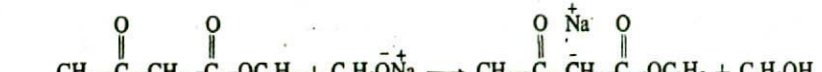
The most important uses of ethyl acetoacetate are for the synthesis of :

(*a*) Monocarboxylic acids of the type 

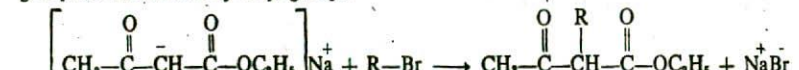
(*b*) Ketones of the type 

In the synthesis of these monocarboxylic acids and ketones particularly we make use of the following reactions of ethyl acetoacetate.

(*i*) *Formation of Sodium Salts.* In the presence of strong base as sodium ethoxide, the available H-atoms of the active methylene group are ionised and sodium salt of ethyl acetoacetate results.

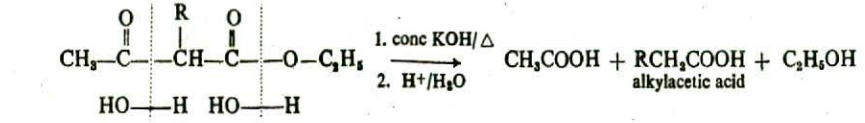


(*ii*) *Alkylation.* The carbanion produced from ethyl acetoacetate is an aggressive nucleophile and attacks many alkyl halides. As a result the available H-atom/s of the methylene group are substituted by alkyl groups.

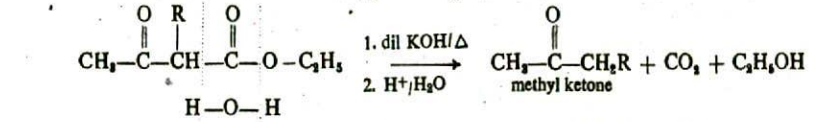


Similarly the second H-atom of methylene can be replaced by another alkyl group to yield dialkyl derivatives.

(*iii*) *Acid Hydrolysis* (*A. Hydrol*). Alkyl derivatives of ethyl acetoacetate when (*a*) boiled with conc KOH solution ; and (*b*) acidified, yield alkylacetic acids,

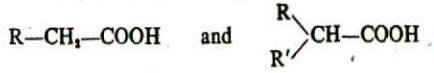


(*iv*) *Ketonic Hydrolysis* (*K. Hydrol*). Alkyl derivatives of ethyl acetoacetate when boiled with dilute KOH solution and acidified, give methyl ketones.

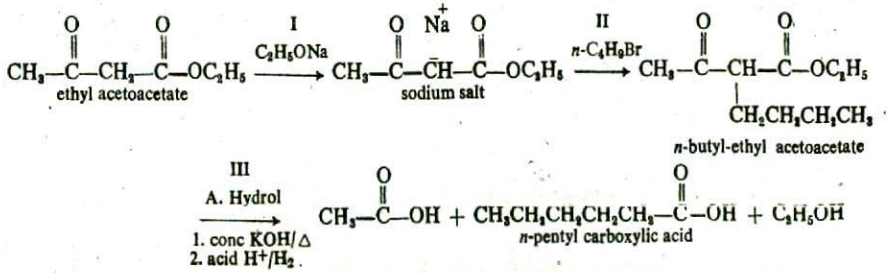


A few important synthetic uses of ethyl acetoacetate will be discussed here.

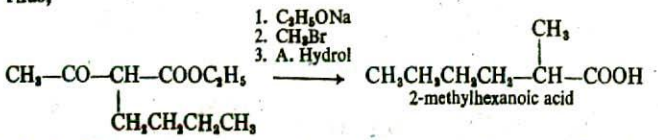
Synthesis of Alkylacetic acids. Acids of the general structures



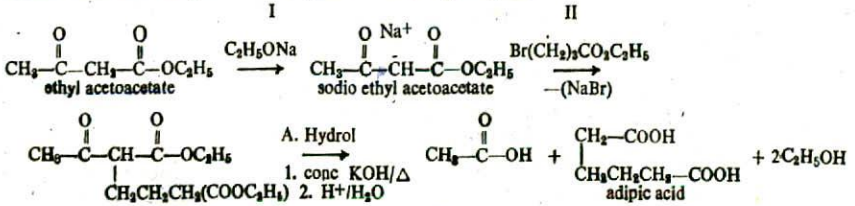
may be synthesised by the reaction of sodium salt of ethyl acetoacetate with an alkyl bromide followed by acid hydrolysis.



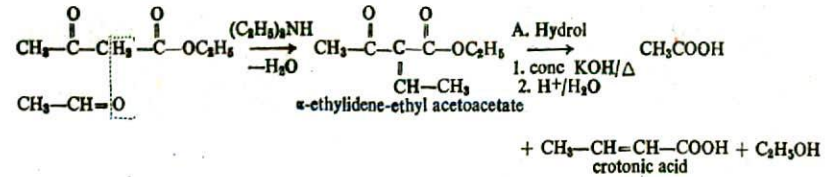
Starting from monoalkyl-ethyl acetoacetate, $CH_3COCHRCOOC_2H_5$, and repeating all the three steps (I, II, III) by taking a suitable alkyl halide in step II, a dialkylacetic acid can be synthesised. Thus,



(2) **Synthesis of Dicarboxylic acids.** Sodio ethyl acetoacetate is treated with appropriate bromo ester and the product is subjected to acid hydrolysis.



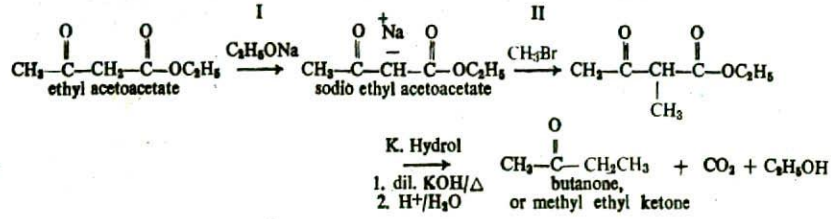
(3) **Synthesis of α, β-Unsaturated acids.** Ethyl acetoacetate undergoes Knoevenagel condensation with aldehydes in the presence of a base to produce alkylidene derivatives which upon acid hydrolysis yield α, β-unsaturated acids. For example, crotonic acid may be synthesised as follows.



Similarly, cinnamic acid, $C_6H_5CH=CHCOOH$, may be obtained by taking benzaldehyde in place of acetaldehyde.

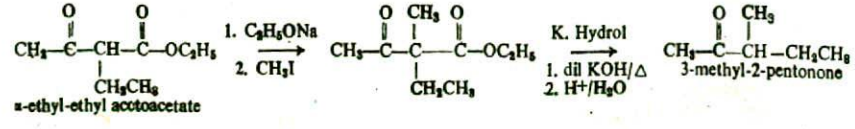
(4) **Synthesis of Ketones.** Mono and dialkyl derivatives of ethylacetoacetate on ketonic hydrolysis yield highe ketones. For example, butanone and 3-methyl-2-pentanone may be synthesised by the following steps.

(*a*) *Butanone*, $CH_3—CO—CH_2CH_3$

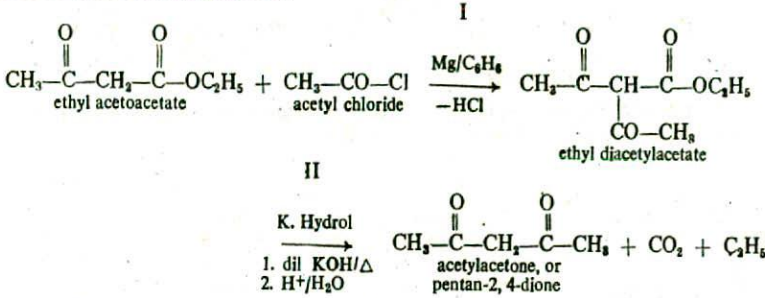


(*b*) *3-Methyl-2-pentanone*, $CH_3—CO—CH(CH_3)CH_2CH_3$

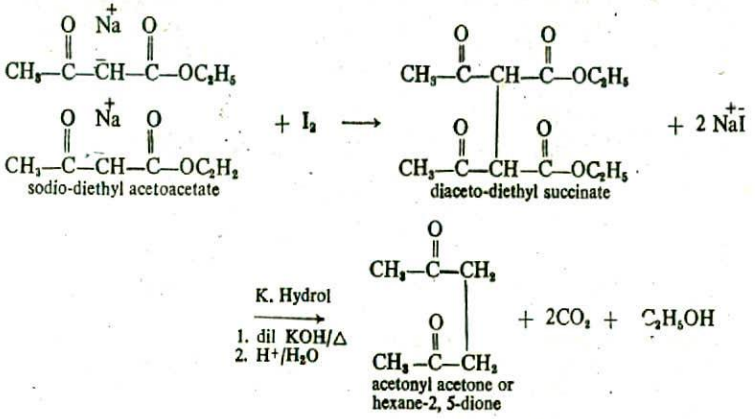
The product of step II in (*a*) is reacted with methyl iodide as follows and subjected to ketonic hydrolysis.



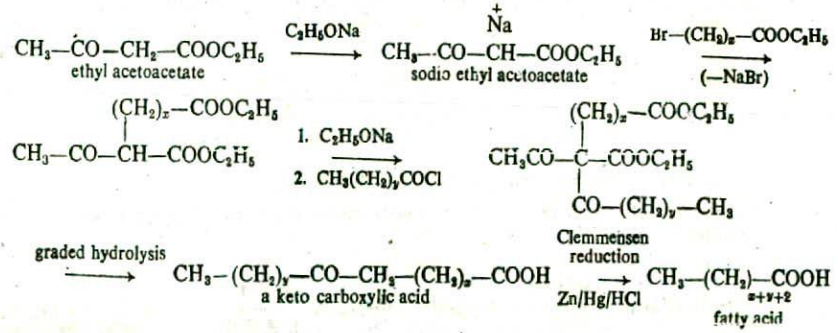
(5) **Synthesis of 1, 3-Diketones.** Ethyl acetoacetate in benzene solution is treated with an acid chloride (RCOCl) in presence of magnesium and the resultant product is subjected to ketonic hydrolysis, when 1, 3-diketone is obtained. For example, acetylacetone may be synthesised in the following manner.



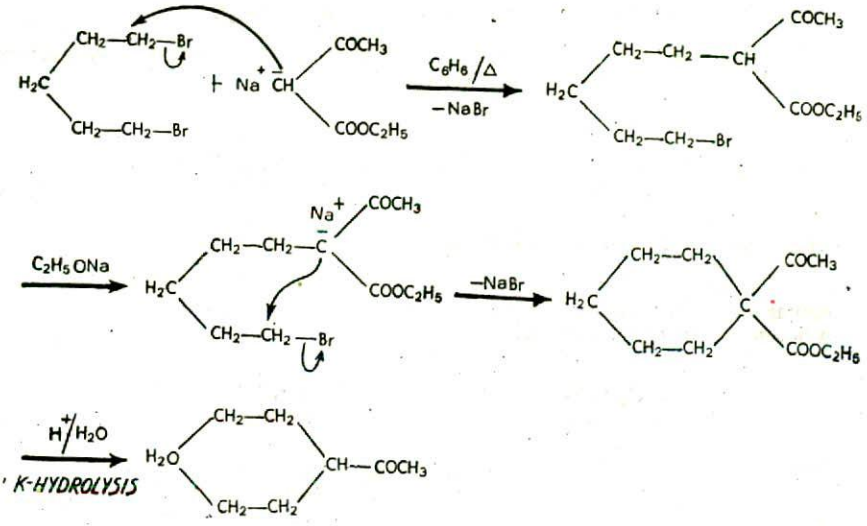
(6) **Synthesis of 1, 4-Diketones.** When an excess of sodioacetic ester (2 moles) treated with iodine and the product subjected to ketonic hydrolysis, 1, 4-diketone is obtained



(7) **Synthesis of Long-chain Fatty acids.** It involves a combination of methods (2) and (5).



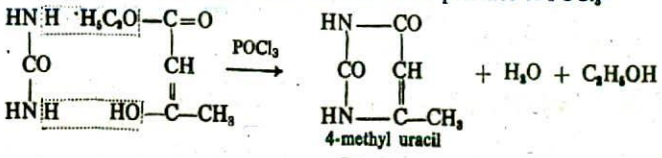
(8) **Synthesis of Alicyclic Compounds.** Alicylic compounds of ring size (5 to 7 carbons) can be synthesised by the reaction of ethyl acetoacetate with dihalogen compounds. For example,



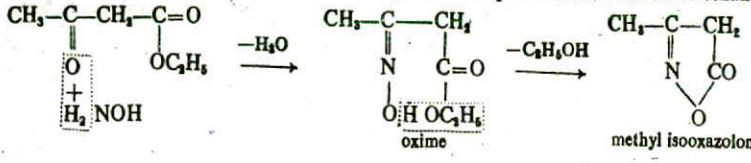
ACETYLCYCLOHEXANE

(9) **Heterocyclic Compounds.** A variety of heterocyclic compounds can be synthesised from ethyl acetoacetate. For example,

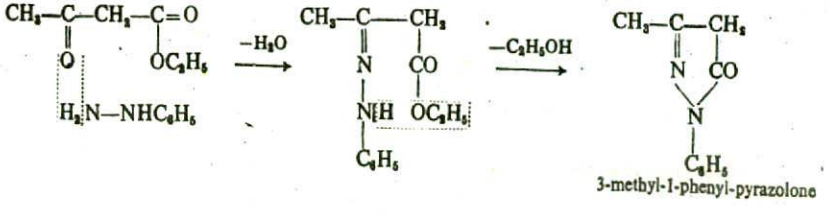
(*i*) *4-Methyl Uracil*, an important starting material in the synthesis of uric acid, may be obtained by the action of ethyl acetoacetate with urea in the presence of $POCl_3$-



(*ii*) *Methyl Isooxazolone* can be synthesised by the action of ethyl acetoacetate with hydroxylamine to form the oxime which being unstable splits out a molecule of ethanol.



(*iii*) *3-Methyl-1-phenyl-pyrazolone* is obtained by treating ethyl acetoacetate with phenylhydrazine. The phenylhydrazone produced splits out a molecule of ethanol to yield the desired product.



DIETHYL MALONATE, *Malonic Ester,* $H_5C_2OOC-CH_2-COOC_2H_5$

This is diethyl ester of malonic acid and is thus properly named as diethyl malonate, although it is commonly referred to as **Malonic Ester.**

$$\underset{\text{malonic acid}}{HO-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OH} \xrightarrow[+C_2H_5]{-2H} \underset{\substack{\text{diethyl malonate}\\ \textit{(malonic ester)}}}{H_5C_2O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5}$$

Diethyl malonate is a very useful reagent for synthesising a variety of organic acids.

Preparation. (1) Diethyl malonate is readily prepared from sodium chloroacetate by heating with sodium cyanide. Sodium cyanoacetate so obtained is boiled in absolute ethanol with concentrated hydrochloric acid.

$$\underset{\text{sod chloroocetate}}{Cl-CH_2COO^-Na^+} + Na^+CN^- \longrightarrow \underset{\text{sod cyanoacetate}}{N\equiv C-CH_2COO^-Na^+} + Na^+Cl^-$$

$$N\equiv C-CH_2COO^-Na^+ + 2C_2H_5OH + 2H^+Cl^- \longrightarrow \underset{\text{diethyl malonate}}{C_2H_5OOC-CH_2-COOC_2H_5} + NH_4^+Cl^- + Na^+Cl^-$$

It may be noted that hydrolysis of the cyanide group and esterification take place simultaneously in one operation.

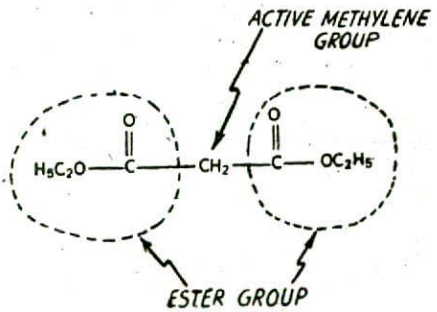
Malonic ester may also be obtained by first converting methylene chloride into methylene cyanide, followed by simultanous hydrolysis and esterification with absolute ethanol and concentrated hydrochloric acid.

$$\underset{\text{methylene chloride}}{Cl-CH_2-Cl} + 2Na^+CN^- \xrightarrow{\Delta} N\equiv C-CH_2-C\equiv N + 2Na^+Cl^-$$

$$N\equiv C-CH_2-C\equiv N + 2C_2H_5OH + 2HCl + 2H_2O \longrightarrow \underset{\text{diethyl malonate}}{H_5C_2OOC-CH_2-COOC_2H_5} + 2NH_4^+Cl^-$$

Properties. (*Physical*). Diethyl malonate is a colourless liquid having a fruity odour. It boils at 198° and is sparingly soluble in water.

(*Chemical*). Diethyl malonate molecule is made of an active methylene group bonded directly to two ester groups, one on either side.

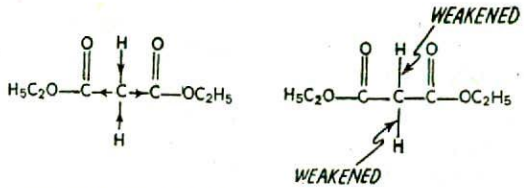


Thus the reactions of diethyl malonate are those of the active methylene group and two ester groups.

A. REACTIONS OF THE ACTIVE METHYLENE GROUP

Like ethyl acetoacetate, diethyl malonate contains an active methylene group. The methylene group is flanked on both sides by electron-withdrawing carbonyl groups. The H-atoms of the methylene group are rendered considerably acidic or mobile due to two reasons.

(*a*) The C—H bonds of methylene group are considerably weakened by the powerful electron-withdrawing effect of the ester group in duplicate.



Electron-withdrawing effect of the ester group doubled, causing flow of electrons away from H-atoms.

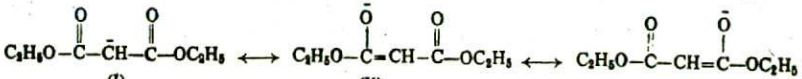
C—H bonds of methylene group greatly weakened, making H atoms acidic.

(*b*) The diethyl malonate anion left after the removal of a proton from methylene carbon is resonance stabilished.



DIETHYLMALONATE ANION (I)

The stability is conferred on the anion as it exists in the following resonance forms.



(I) (II) (III)

In terms of the Molecular Orbital theory, the diethyl malonate anion has an extended π orbital enveloping the five atomic nuclei (*See* Fig. 26·1). The electron giving negative charge to the anion is delocalized and thus the negative charge is distributed over both the ester carbonyl oxygens as also on the central carbon. This makes the diethyl malonate anion considerably stable

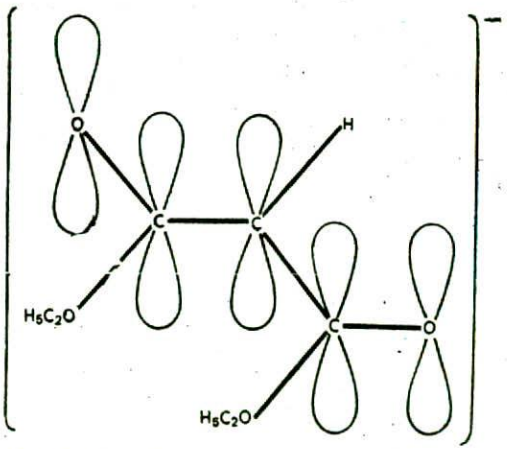
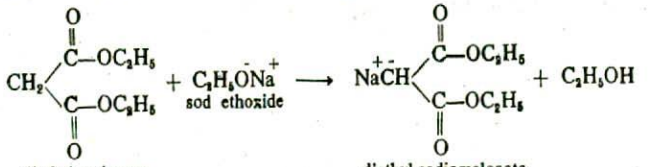


Fig. 26·1. Molecular Orbital Model of diethyl malonate anion.

For the above considerations, diethyl malonate is as strong an acid ($K_a = 10^{-13}$) as phenol ($K_a = 10^{-10}$). However, it may be pointed out here that unlike ethyl acetoacetate, diethyl malonate contains only a minute quantity of the enol form in the equilibrium mixture.

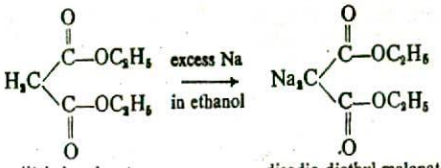
The reactions of diethyl malonate due to the active methylene group are given below.

(1) **Formation of Sodium Salt.** Since diethyl malonate is fairly acidic, it reacts with a strong base such as sodium ethoxide to form diethyl sodiomalonate.



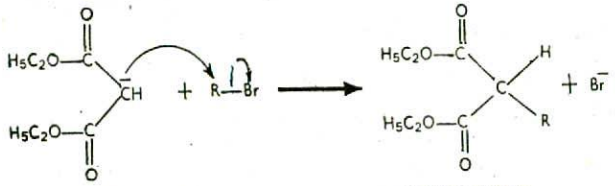
diethyl malonate — diethyl sodiomalonate

With an excess of sodium in ethanol, diethyl malonate forms disodium derivative straight-away.



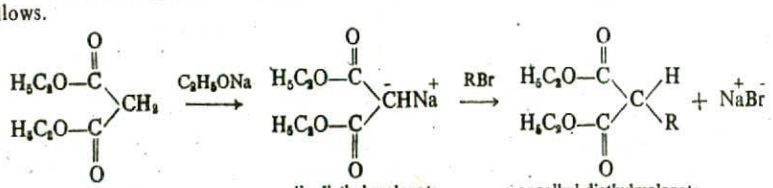
diethyl malonate — disodio diethyl malonate

(2) **Alkylation.** Diethyl malonate ion is an agressive nucleophile and as such attacks alky halides to form alkyl derivatives.



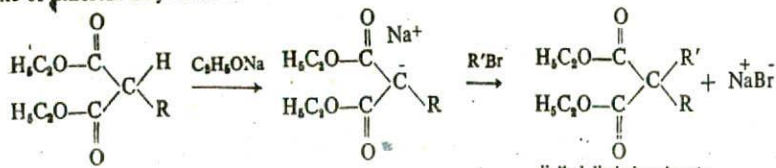
DIETHYLMALONATE ANION — MONOALKYL DIETHYLMALONATE

Thus starting from diethyl malonate monoalkyl diethyl malonate can be synthesised as follows.



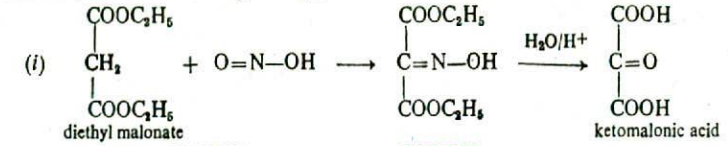
diethylmalonate — sodio diethyl malonate — monoalkyl diethylmalonate

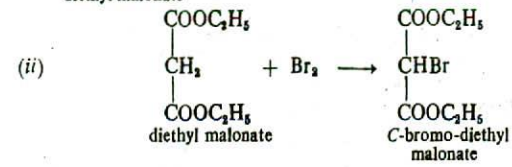
Since monoalkyl malonate still has one acidic H-atom, it can be alkylated again using the same or different alkyl halides.



dialkyl diethyl malonate

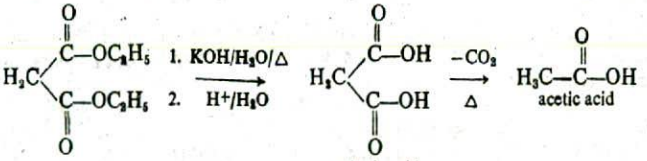
(3) **Action with Nitrous acid and Bromine.** The active methylene group of diethyl malonate also reacts with a number of reagents *e.g.*, nitrous acid or bromine.



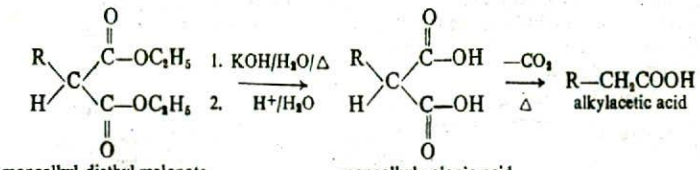


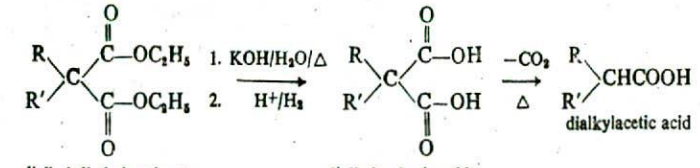
B. REACTIONS OF TWO ESTER GROUPS

(3) **Hydrolysis.** Diethyl malonate and its C-alkyl derivatives when hydrolysed with KOH solution and acidified give the corresponding dicarboxylic acid. The dicarboxylic acids in which the two carboxyl groups are bonded to the same carbon when heated just above the melting point (150—200°), easily undergo decarboxylation to furnish monoalkyl and dialkyl acetic acids.



Similarly,

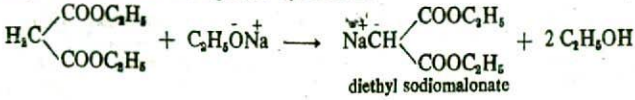




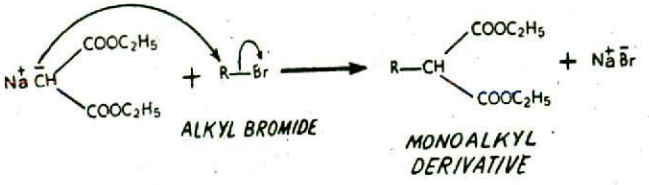
SYNTHETIC USES OF DIETHYL MALONATE

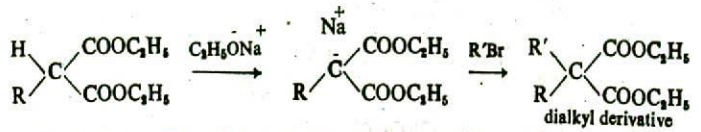
The synthesis of a wide variety of organic acids starting from diethyl malonate involving formation of diethyl sodiomalonate, alkylation, hydrolysis and decarboxylation of the product is often referred to as the **Malonic Ester Synthesis.**

(*a*) *Formation of Diethyl sodiomalonate.* The acidic H-atoms of the active methylene group of diethyl malonate can be replaced by sodium.

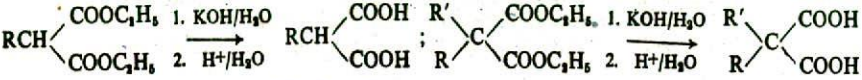


(*b*) *Alkylation.* The diethyl sodiomalonate produced in step (*a*) can be reacted with alkyl halide to get alkyl derivatives of diethyl malonate.

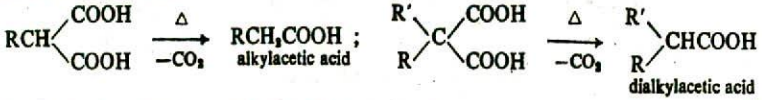




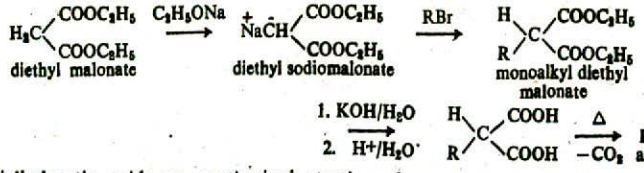
(*c*) *Hydrolysis.* The alkyl derivatives from step (*b*) are hydrolysed with dilute KOH solution and the reaction mixture is acidified to produce the parent free dicarboxylic acid.



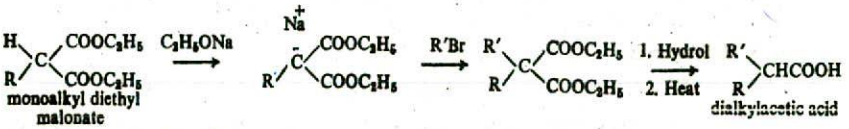
(*d*) *Decarboxylation.* The free alkyl dicarboxylic acids obtained from step (*c*) when are heated above their melting point, one of the COOH groups splits out a molecule of CO_2 to give monocarboxylic acids.



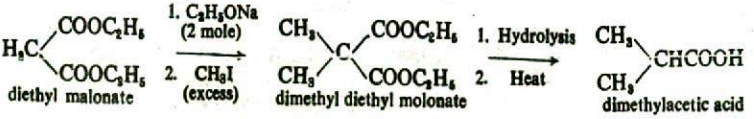
(1) **Synthesis of Monocarboxylic acids.** Diethyl malonate upon reaction with sodium ethoxide in ethanol gives diethyl sodiomalonate which is treated with alkyl halide to produce monoalkyl derivative of diethyl malonate. This upon hydrolysis and heating the product above its melting point yields alkylacetic acid.



Dialkylacetic acids are synthesised starting from monoalkyl diethyl malonate and repeating the procedure cited above.



In case R′ and R are same, the dialkyl derivative is obtained in one operation by taking two moles of sodium ethoxide per mole of diethyl malonate and treating the mixture with excess of alkyl halide. For Example,



(2) **Synthesis of Dicarboxylic acids.** (*a*) ALKYLMALONIC ACIDS can be obtained as shown above by the hydrolysis of alkylmalonic ester.

(*b*) STRAIGHT CHAIN α, ω-DICARBOXYLIC ACIDS can also be synthesised from diethyl malonate. Two moles of diethyl sodiomalonate are treated with one mole of α, ω-dihalide. The resulting tetracarboxylic ester is hydrolysed and decarboxylated to produce dicarboxylic acids.

$$(H_5C_2OOC)_2\overset{+}{C}H\overset{+}{N}a + Br-(CH_2)_n-Br + \overset{+}{N}a\bar{C}H(COOC_2H_5)_2 \xrightarrow{-2\overset{+}{N}a\bar{B}r}$$

diethyl sodiomalonate; α, ω-dihalide

$$(H_5C_2OOC)_2CH-(CH_2)_n-CH(COOC_2H_5)_2 \xrightarrow[2.\ H^+/H_2O]{1.\ KOH/H_2O} (HOOC)_2CH-(CH_2)_n-CH(COOH)$$

tetraester; tetracarboxylic acid

$$\xrightarrow[-2\ CO_2]{\Delta} HOOCCH_2-(CH_2)_n-CH_2COOH$$

dicarboxylic acid

For example, adipic acid may be prepared by treating diethyl sodiomalonate with ethylene bromide followed by hydrolysis and decarboxylation.

$$\begin{matrix}CH_2Br\\|\\CH_2Br\end{matrix} + \begin{matrix}\overset{+}{N}a\bar{C}H(COOC_2H_5)_2\\\overset{+}{N}a\bar{C}H(COOC_2H_5)_2\end{matrix} \longrightarrow \begin{matrix}CH_2-CH(COOC_2H_5)_2\\|\\CH_2-CH(COOC_2H_5)_2\end{matrix} \xrightarrow[2.\ \Delta]{1.\ Hydrol} \begin{matrix}CH_2-CH_2-COOH\\|\\CH_2-CH_2-COOH\end{matrix}$$

ethylene dibromide; diethyl sodiomalonate; tetracarboxylic ester; adipic acid

Alternatively, dicarboxylic acids may be prepared by treating diethyl malonate with appropriate chloro esters. For examples, succinic acid is produced by the interaction of diethyl sodiomalonate with ethyl chloroacetate followed by hydrolysis and decarboxylation.

$$(H_5C_2OOC)_2\overset{+}{C}H\overset{+}{N}a + Cl-CH_2COOC_2H_5 \xrightarrow{Na^+Cl^-} (H_5C_2OOC)_2CH-CH_2COOC_2H_5$$

diethyl sodiomalonate

$$\xrightarrow[2.\ H^+/H_2O]{1.\ KOH/H_2O} (HOOC)_2CH-CH_2COOH \xrightarrow[-CO_2]{\Delta} HOOCCH_2-CH_2COOH$$

succinic acid

(3) **Synthesis of α, β-Unsaturated acids.** Like ethyl acetoacetate, diethyl malonate also undergoes Knoevenagel condensation with aldehydes in the presence of organic bases such as pyridine or diethylamine to produce alkylidene diethylmalonate. This upon hydrolysis and decarboxylation gives α, β-unsaturated acids. For example, crotonic acid may be obtained as follows.

$$CH_3-CH=O + H_2C\begin{matrix}COOC_2H_5\\COOC_2H_5\end{matrix} \xrightarrow[-H_2O]{(C_2H_5)_2NH} CH_3-CH=C\begin{matrix}COOC_2H_5\\COOC_2H_5\end{matrix} \xrightarrow[2.\ H^+/H_2O]{1.\ KOH/H_2O}$$

acetaldehyde; diethyl malonate; ethylidene diethyl malonate

$$CH_3-CH=C\begin{matrix}COOH\\COOH\end{matrix} \xrightarrow[-CO_2]{\Delta} CH_3-CH=CH-COOH$$

crotonic acid

Similarly, cinnamic acid, $C_6H_5CH=CHCOOH$, can be synthesised by taking benzaldehyde in place of acetaldehyde.

(4) **Synthesis of Higher Ketonic acids.** Diethyl sodiomalonate when treated with acid chloride ester of a dicarboxylic acid followed by hydrolysis and decarboxylation gives a β-dicarboxylic acid. This being unstable eliminates a molecule of carbon dioxide to form a higher ketonic acid. For example, laevulinic acid may be synthesised as follows.

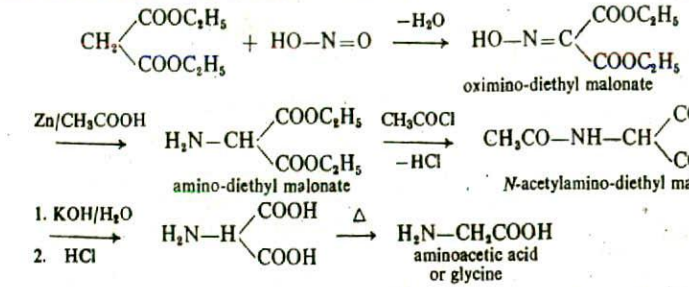
$$H_5C_2OOCCH_2-CH_2COCl + \overset{+}{N}a\bar{C}H(COOC_2H_5)_2 \xrightarrow{-\overset{+}{N}a\bar{C}l} H_5C_2OOC-CH_2CH_2COCH(COOC_2H_5)_2$$

succinic ester-acid chloride; diethyl sodiomalonate

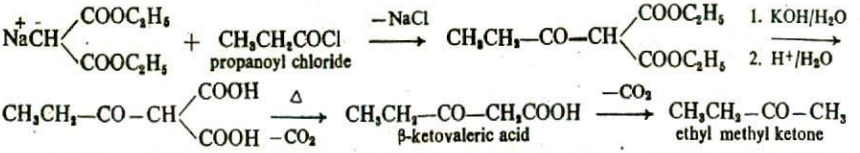
$$\xrightarrow[2.\ H^+/H_2O]{1.\ KOH/H_2O} HOOCCH_2CH_2-CO-CH(COOH)_2 \xrightarrow{\Delta} HOOCCH_2CH_2-CO-CH_2COOH$$

β-ketoadipic acid

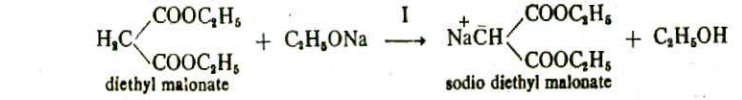
(5) **Synthesis of Amino acids.** Diethyl malonate is first treated with nitrous acid and α-oximino-diethyl malonate so obtained is reduced to give aminomalonic ester. The amino group is subsequently acetylated and the acetylamino-diethyl malonate thus produced can be converted into aminoacetic acid.

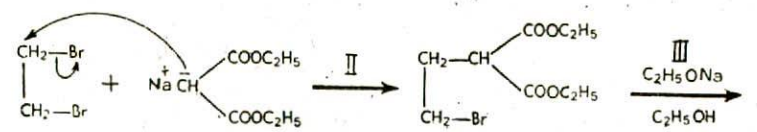


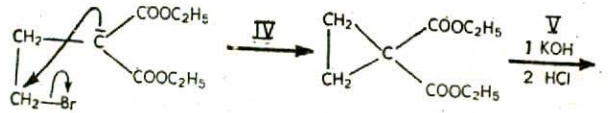
(6) **Synthesis of Ketones.** Ketones may be prepared from diethyl malonate by treating diethyl sodiomalonate with an acid chloride, followed by hydrolysis and decarboxylation. For example, ethyl methyl ketone may be synthesised by the procedure sketched below.

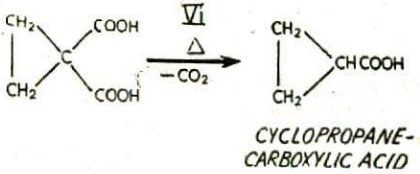


(7) **Synthesis of Alicyclic Compounds.** (*a*) CYCLOALKANECARBOXYLIC ACIDS. α, ω-dihalides (1 mole) react with 1 mole of diethyl malonate in the presence of 2 moles of sodium ethoxide to form three to six-membered cycloalkane-1, 1-dicarboxylic esters. These upon hydrolysis and decarboxylation yield cycloalkanecarboxylic acids.



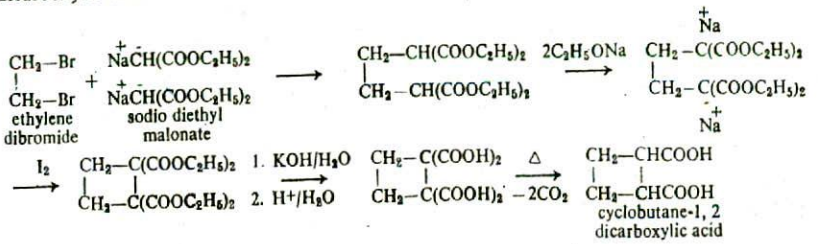




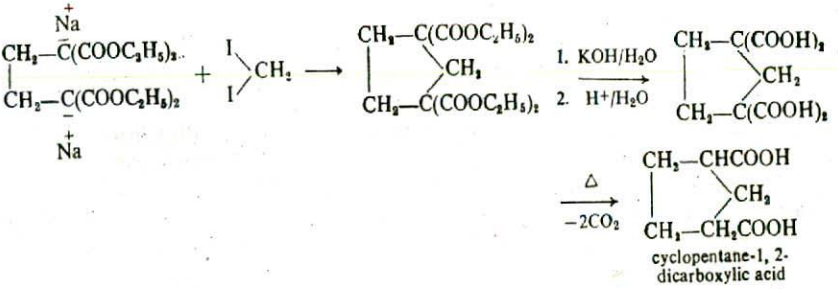


CYCLOPROPANE-CARBOXYLIC ACID

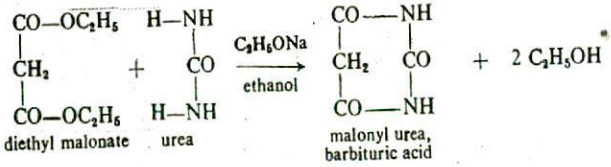
(*b*) CYCLOALKANEDICARBOXYLIC ACIDS. α, ω-dibromides can be made to react with sodio diethyl malonate (2 moles) to form a tetracarboxylic ester. This upon treatment with sodium ethoxide (2 moles) gives the corresponding disodio derivative which when treated with iodine (1 mole) followed by hydrolysis and decarboxylation, gives cycloalkane-1, 2-dicarboxylic acid.



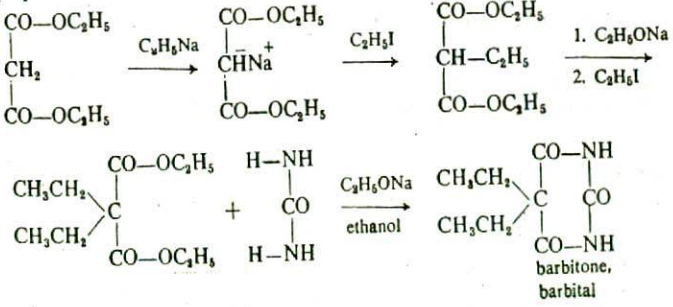
If methylene iodide is used instead of iodine, cyclopentane-1, 3-dicarboxylic acid is obtained.



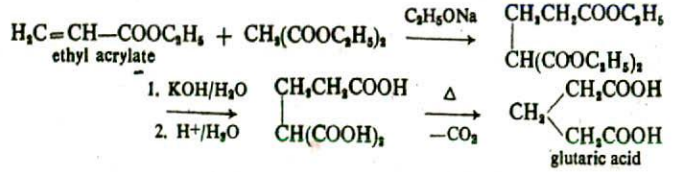
(8) **Heterocyclic Compounds.** Diethyl malonate condenses with urea to form malonyl urea or barbituric acid.



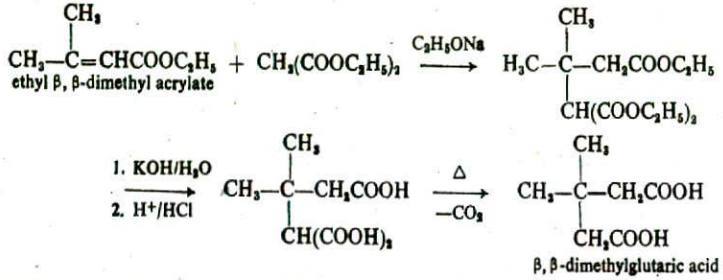
Barbituric acid derivatives are used in medicine as hypnotics and sedatives. Thus barbitone or barbital is prepared as follows.



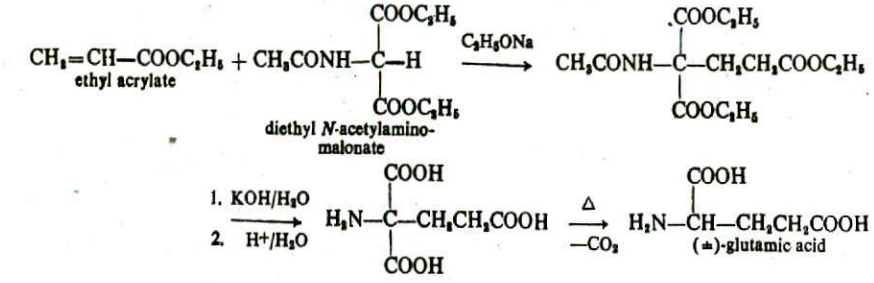
(9) **Synthesis of Glutaric acid and β, β-Dimethylglutaric acid.** As already discussed, dimethyl malonate anion is a potent nucleophile and undergoes *Michael Condensation* with esters of α, β-unsaturated acids in the presence of C_2H_5ONa as base, For example, we can get glutaric acid starting from diethyl malonate and ethyl acrylate by the following procedure.



Similarly starting from ethyl β, β-dimethyl acrylate and diethyl malonate, we can get β, β-dimethyl glutaric acid.



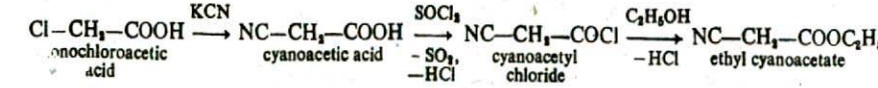
(10) **Synthesis of Glutamic acid.** Diethyl *N*-acetylaminomalonate obtained in the synthesis of amino acids still contains an active H-atom. The Michael Condensation between this and ethyl acrylate followed by hydrolysis and decarboxylation yields (±)-glutamic acid.



ETHYL CYNOACETATE, $N\equiv C—CH_2—COOC_2H_5$

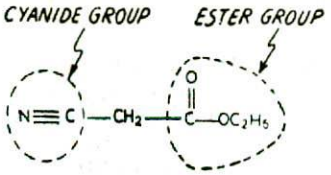
It is the ethyl ester of cyanoacetic acid $NC—CH_2COOH$, and is frequently referred to as **Cyanoacetic ester.**

Preparation. Ethyl cyanoacetate is made from monochloroacetic acid which upon treatment with potassium cyanide gives cyanoacetic acid. This on esterification produces ethyl cyanoacetate.

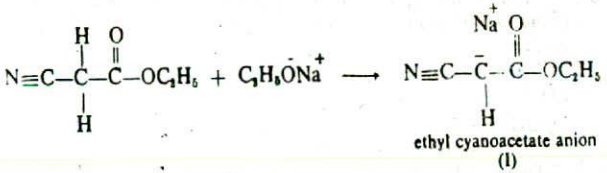


It may be noted that ethyl cyanoacetic acid cannot be esterified with ethyl alcohol and hydrochloric acid. In that case the cyano group would also suffer simultaneous hydrolysis and esterification, and consequently the product would be diethyl malonate.

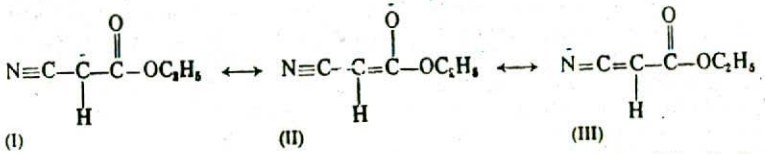
Properties. Ethyl cyanoacetate is a colourless liquid, bp 207°. Like ethyl acetoacetate and diethyl malonate it contains an active methylene group flanked by one cyano group, $C\equiv N$, and one ester group, $COOC_2H_5$.



Here the acidity of the H-atoms of methylene group is due to (*i*) its location between two strongly electron with-drawing groups, $C\equiv N$ and $COOC_2H_5$, and (*ii*) the resonance stabilisation of the anion left after the removal of a proton by sodium ethoxide, a strong base.



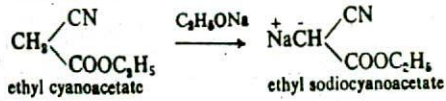
The canonical forms that contribute to resonance stabilisation of ethyl cyanoacetate anion are :



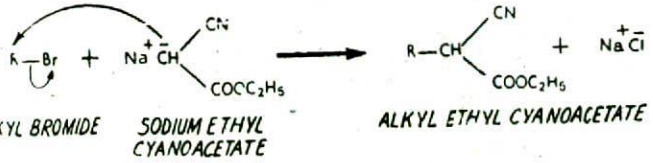
The ester anion being a potent nucleophile can participate in nucleophilic displacement reactions. The reactions of ethyl cyanoacetate are basically similar to those of diethyl malonate.

Synthetic Applications. The use of ethyl cyanoacetate depends on the following reactions.

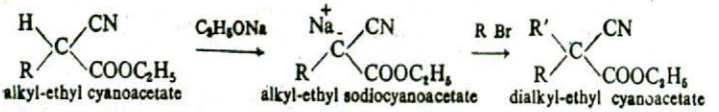
(1) *Formation of Ethyl Sodiocynoacetate.* Ethyl cyanoacetate forms its sodium derivatives by reaction with sodium ethoxide.



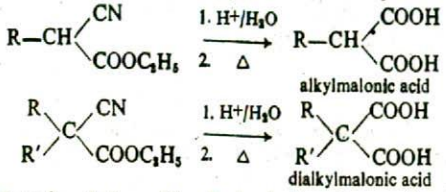
(2) *Alkylation.* The nucleophilic displacement reaction with alkyl halide produces alkyl-ethyl cyanoacetate.



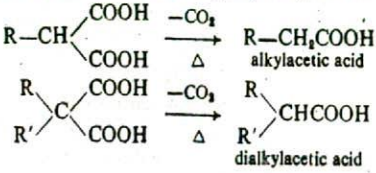
Alkyl-ethyl cyanoacetate still contains an acidic hydrogen. It can be made to react as above with another molecule (same or different) of alkyl halide to yield dialkyl-ethyl cyanoacetate.



(3) *Hydrolysis.* The alkyl derivatives of ethyl cyanoacetate can be readily hydrolysed by boiling with dilute mineral acid to give free dicarboxylic acids.

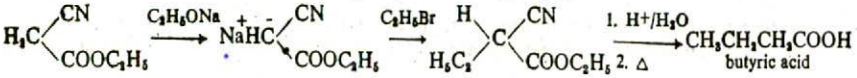


(4) *Decarboxylation.* The alkylmalonic acid upon heating above melting point eliminate a molecule of CO_2 from one of the COOH groups to yield the respective monocarboxylic acid.

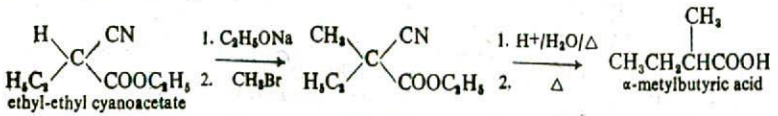


In ethyl cyanoacetate the methylene hydrogen atoms are somewhat more acidic than in diethyl malonate, although less acidic than in ethyl acetoacetate. Consequently ethyl cyanoacetate is more reactive than diethyl malonate. It has, therefore, often been used in place of the latter in synthetic applications.

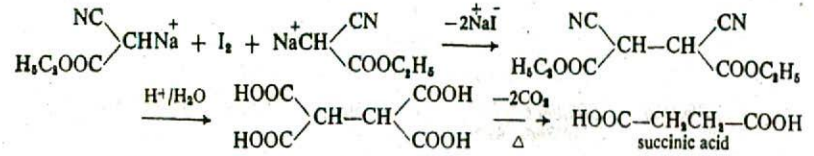
(1) **Synthesis of Monocarboxylic Acids.** Mono- and dialkyl derivatives of ethyl cyanoacetate upon hydrolysis yield alkyl-substituted malonic acids. These in turn undergo decarboxylation when heated to form monocarboxylic acids. For example,



All these steps when ethyl cyanoacetate replaced by ethyl-ethyl cyanoacetate using methyl bromide yield α-methylbutyric acid.

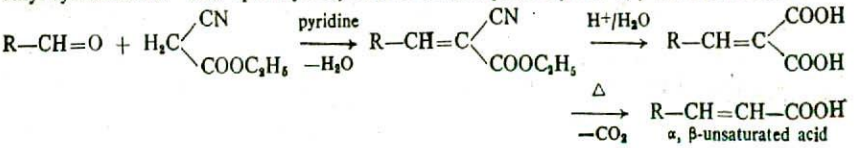


(2) **Synthesis of Dicarboxylic acids.** Two molecules of ethyl sodiocyanoacetate condense in presence of iodine to yield a product which after hydrolysis and decarboxylation gives succinic acid.

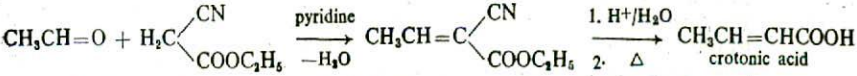


Similarly, glutaric acid can be prepared by taking methylene iodide (CH_2I_2) in place of I_2 in the above synthesis. But adipic acid can be obtained by repeating all the steps by using ethylene bromide. Higher acids may be synthesised by taking α, ω-dihalides, $X-(CH_2)_n-X$.

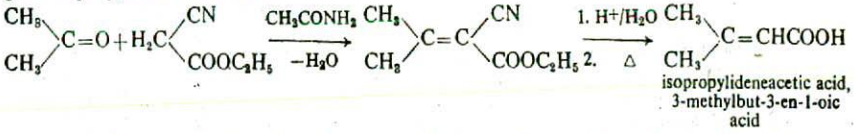
(3) **Synthesis of α, β-Unsaturated acids.** Aldehydes undergo Knoevenagel Condensation with ethyl cyanoacetate in the presence of secondary base such as pyridine to form alkylidene ethyl cyanoacetate. This upon hydrolysis and decarboxylation yields α, β-unsaturated acid.



For example, acetaldehyde will condense with ethyl cyanoacetate to give α, β-unsaturated acid.

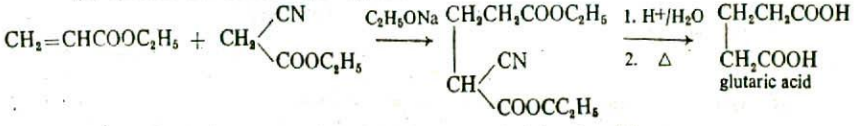


Unlike ethyl acetoacetate and diethyl malonate, ethyl cyanoactate also condenses with ketones in presence of acetamide in glacial acetic acid. The alkylidene ethyl cyanoacetate is the product which upon hydrolysis and decarboxylation gives α, β-unsaturated acids. Thus acetone gives isopropylideneacetic acid.

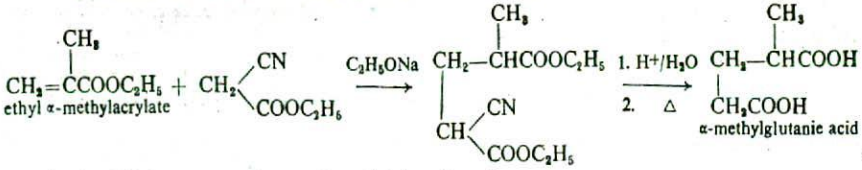


(4) **Synthesis of Glutaric acid and its Alkyl Derivatives.** Like ethyl acetoacetate and diethyl malonate, ethyl cyanoacetate gives Michael Condensation with α, β-unsaturated acids to yields glutaric acid and alkylglutaric acids.

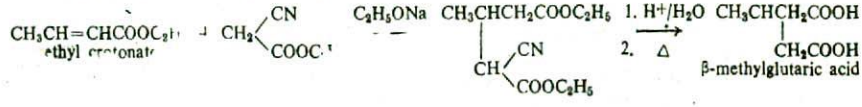
(*a*) Glutaric acid from Ethyl acrylate :



(*b*) Similarly, ethyl α-methyl acrylate gives α-methylglutaric acid



(*c*) Ethyl crotonate gives α, β-methylglutaric acid.



QUESTIONS

1. What do you understand by 'active methylene compounds'. Name three of them and give their structural formulae.
2. How do you interpret the activity of methylene hydrogen atoms in ethyl acetoacetate, diethyl malonate and ethyl cynoacetate. Why is CH_2 group in ethyl cyanoacetate more reactive than in diethyl malonate ?
3. How is ethyl acetoacetate synthesised ? Give its mechanism.
4. What is tautomerism ? Give one example and discuss this phenomeon in detail.

5. Define Keto-Enol tautomerism and apply it to ethyl acetoacetate. Describe in detail how the classical example of ethyl acetoacetate led to the general concept of tautomerism.

6. Give the mechanism of Catalysis by acid, and Catalysis by base as applied to ethyl acetoacetate equilibrium.

7. Bring out clearly the chief differences between resonance and tautomerism.

8. How can you estimate the composition of keto and enol forms in a tautomeric mixture. Why does it differ in different solvents ?

9. Discuss the general reactions of ethyl acetoacetate involved in its synthetic applications.

10. How do you define 'Acetoacetic ester Synthesis.' How are the following synthesised starting from sodio-ethyl acetoacetate ?

(*a*) Monocarboxylic acid ; (*b*) Dicarboxylic acid ;
(*c*) α, β-unsaturated acids ; (*d*) Ketones ;
(*e*) Diketones ; and (*f*) Alicyclic compounds.

11. How is diethyl malonate prepared ? Write its structural formula and point out the active methylene group present in it. Why are methylene hydrogens acidic ?

12. Write notes on the following reactions of diethyl malonate :

(*a*) Formation of diethyl sodio malonate ; (*b*) Alkylation ;
(*c*) Action with Nitrous acid ; and (*d*) Hydrolysis.

13. Write an account of the Synthetic applications of diethyl malonate.

14. Starting from diethyl sodiomalonate how will you prepare the following :

(*a*) Monocarboxylic acids ; (*b*) Dicarboxylic acids ;
(*c*) α, β-Unsaturated acids ; (*d*) Amino acids ;
(*e*) Glutaric acid ; and (*f*) Glutamic acid.

15. Give the preparation and properties of ethyl cyanoacetate. Why does it undergo condensation with ketones, while diethyl malonote does not ?

16. Give the preparation and important synthetic uses of ethyl acetoacetate. *(Bombay BSc, 1970)*

17. Starting from ethyl acetoacetate, how would you prepare the following compounds:

(*i*) Crotonic acid (*ii*) 4-methyluracil
(*iii*) Acetyl acetone. *(Delhi BSc II, 1981)*

18. (*a*) Write down the keto enol forms of ethyl acetoacetate. Indicate in which tautomeric form the ester can display intramoleuclar hydrogen bonding. *(Andhra BSc II, 1981)*

19. How will you prepare the following from ethyl acetoacetate:

(*a*) Methyl propyl ketone (*b*) Crotonic acid
(*c*) Succinic acid (*d*) n-Butane. *(North Bengal BSc III, 1981)*

20. What is meant by reactive methylene group ? Describe synthetic uses of one compound containing this group. *(Mysore BSc III, 1981)*

21. How is diethyl malonate prepared ? Indicate usefulness of this compound in organic synthesis. *(North Eastern BSc, 1981)*

22. (*a*) What do you understand by the reactive methylene group ? How can its hydrogen atoms be replaced by alkyl groups ?

(*b*) "Acetoacetic ester is an equilibrium mixture of the keto and enol forms". Give evidence in support of the statement. *(Nagpur BSc III, 1981)*

23. (*a*) Discuss the mechanism of the synthesis of Acetoacetic ester.

(*b*) Starting from acetoacetic ester how will you prepare any two of the following:

(*i*) Butane-1,4-dioic acid (*ii*) 3-Methyl-2-butanone
(*iii*) But-2-ene-1-oic acid. *(Himachal BSc III, 1981)*

24. Describe the method of preparing Diethyl malonate and its use in synthesising the following:

(*a*) Cyclopropane (*b*) Crotonic acid
(*c*) Glycine. *(Maharishi Dayanand BSc II, 1981)*

25. How is diethyl malonate prepared in the laboratory ? Starting from diethyl malonate, how can you obtain the following:

(*a*) Succinic acid (*b*) Crotonic acid
(*c*) n-Butyric acid (*d*) Barbituric acid. *(Meerut BSc II, 1981)*

26. (*a*) How is acetoacetic ester prepared from ethyl acetate ? Give the mechanism of the reaction.

(*b*) How is ethyl acetoacetate used in the synthesis of the following compounds:

(*i*) Acetonyl acetone (*ii*) n-Butyric acid
(*iii*) Methyl ethyl ketone. *(Rajasthan BSc II, 1981)*

27. How is ethyl acetoacetate prepared ? Starting from it how can you prepare :
(*i*) a mixed ketone; (*ii*) an aliphatic monocarboxylic acid;
(*iii*) a heterocyclic compound ? (*Utkal BSc, 1981*)

28. (*a*) How is acetoacetic ester prepared ?
(*b*) Discuss any three of its synthetic applications. (*Mysore BSc III, 1982*)

29. Starting with malonic ester how will you synthesise: (*i*) Barbituric acid and (*ii*) Alicyclic compound ? (*Delhi BSc Hons II, 1982*

30. Give any two synthetic applications of acetoacetic ester and discuss its keto-enol tautomerism. (*Gulbarga BSc II, 1982*)

31. (*a*) Explain the mechanism of Claisen-Condensation reaction.
(*b*) How will you distinguish between acetoacetic ester and ethyl acetate ?
(*c*) What happens when acetoacetic ester is treated with:
(*i*) Urea (*ii*) Acetyl chloride (*iii*) Acetaldehyde.
(*Nagpur BSc II, 1982*)

32. How will you synthesise the following compounds from diethyl malonate·
(*a*) Cyclobutane-carboxylic acid. (*e*) Crotonic acid
(*b*) Succinic acid. (*f*) Barbituric acid
(*c*) Adipic acid. (*g*) Acetoacetic acid ?
(*d*) Ethyl methyl acetic acid. (*Saugar BSc II, 1982*)

33. How is malonic ester synthesised ? How can barbituric acid, crotonic acid, and succinic acid be prepared from malonic ester ? (*Annamalai BSc, 1993*)

34. Describe the preparation and synthetic uses of malonic ester. (*Indore BSc, 1994*)

35. What is active methylene group ? How will you prepare the following compounds from malonic ester : (*a*) Succinic acid ; (*b*) Barbituric acid ; (*c*) Crotonic acid and (*d*) Dimethylacetic acid (*Nagpur BSc, 1994*)

36. Discuss the mechanism of Claisen condensation. (*Bundelkhand BSc Hons, 1993 ; Delhi BSc Hons, 1994*)

37. Write a note on : Keto-enol tautomerism (*Pandicherry BSc, 1993; Udaipur BSc, 1994*)

38. Give evidence for tautomerism in ethyl acetoacetate. How will you obtain the following from it : (*a*) Methyl ethyl ketone ; (*b*) *n*-Butyric acid and (*c*) Acetonyl acetone. (*Baroda BSc, 1993*)

39. Discuss synthetic uses of malonic ester and acetoacetic ester.
(*Dibrugarh BSc Hons, 1993; Kakatiya BSc, 1993; Anna BSc, 1994; Magadh BSc Hons, 1994*)

Chapter **27**

Fats, Oils and Waxes ; Soaps and Detergents

Fats, oils and waxes belong to the group of naturally occurring compounds called **Lipids** (Greek, *lipos* = fat). Lipids are those constituents of animals and plants which are soluble in organic solvents such as ether, chloroform, carbon tetrachloride, benzene, hexane etc., but insoluble in water. The lipids which yield fatty acids and alcohols on hydrolysis with aqueous base (saponified) are referred to as *Simple Lipids*. These can be further divided into two classes :

(*a*) *Fats and Oils*, which yield long-chain fatty acids and glycerol upon hydrolysis ;

and (*b*) *Waxes*, which yield long-chain fatty acids and long-chain alcohols upon hydroloysis.

We will first proceed to study the former class of compounds *i.e.*, Fats and Oils.

FATS AND OILS

Fats and oils are the most important lipids found in nature. They are one of the three major 'food factors' needed for human body, the other two being proteins and carbohydrates. Fats and oils are widely distributed in foods and are of great nutritional value. They provide concentrated reserve of energy in animal body for maintaining optimum body temperature. One gram of metabolised fat or oil yields 9 kcal, while the corresponding values for carbohydrate and protein are 4 kcal and 5·5 kcal respectively. Not only the edible fats and oils occupy a place of pride in human diet but they also find use as raw material for the manufacture of soaps and synthetic detergents, paints and varnishes, polishes, glycerol, lubricants, drying oils cosmetics, printing inks, linoleum oil cloth and pharmaceuticals. At the present time the human race uses an estimated 40 million tonnes a year of fats and oils which reflects both their nutritional and industrial importance.

NATURAL SOURCES

Fats and oils come from a variety of sources—animals, plants and marine organisms.

(1) **Animal Fats** are located particularly in adipose tissue cells. These are distended with oily droplets at body temperature but solidify after death. Thus we have *tallow* from cattle, sheep and goats, and *lard* from hogs. In the human body about 12% of its total weight is fat. At least half of it forms a protective heat insulating subcutaneous layer, while rest of it is to be found in the intermuscular connecting tissue, bones and around nervous tissue, kidneys, heart and other organs.

Butter and ghee are a special type of animal fat because they are made from milk.

(2) **Vegetable Oils**. They are chiefly present in seeds and nuts of plants. They are stored in seeds to serve as nourishment for the germination of embryo. There are quite a few seeds and nuts which are rich in 'fat content'. Thus, soya bean, groundnut, coconut and palm kernel, rape or mustard ; sesame seed and niger are all important sources of edible oils. Cotton seed, linseed, castor seed and mowrah give nonedible oils in various industries.

(3) **Marine Oils**. These are obtained from water animals — sardines, herrings, salmons, whales, dolphins, seals, porpoises etc.

In India animal fats are not used as food because a large section of the population is vegetarian. The traditional place of honour goes to ghee and butter-despite their having animal source – and vegetable oils particularly groundnut oil, coconut oil, rape or mustard oil, cotton seed oil, sesame oil etc.

EXTRACTION

(1) **Rendering.** Animal fats are recovered from the selected animal material by *Wet Rendering* or *Dry Rendering.*

(*a*) WET RENDERING. The selected chopped material is charged into a cylinder with a conical base. Steam is then blown through the cylinder for several hours, the pressure being kept constant at about 5 kg/cm² by releasing steam occasionally. After allowing settlement to take place, the floating fat is drawn off leaving the water and exhausted animal matter behind. This process is widely used for the extraction of edible fats such as lard.

The fish oils from 'blubber' or 'liver' are obtained by heating the chopped stuff in a giant pressure cooker or steam boiler, and running off the floating oil layer.

(*b*) DRY RENDERING. This process is carried out in large steam-heated tanks. During heating, the chopped animal tissue is churned by metal blades. The fat cells are ruptured and the molten fat so obtained is drained off from the bottom of the tanks. Although dry rendering is cheaper than wet rendering, the product is somewhat inferior. Hence this process is restricted to the extraction of non-edible fats.

(2) **Pressing and Solvent Extraction.** In India the most important source of edible oils are seeds such as mustard, groundnut, cottonseed, sesame, niger and sunflower which has been recently introduced under experimental conditions. The extraction from seeds is done by a variety of methods right from the village *ghani* to the more sophisticated *Expeller* and modern *Solvent Extraction Plant.*

(*a*) PRESSING BY EXPELLER. The oil bearing material is screened and crushed by passing between steel rollers. In order to get the maximum yield the '*meal*' or crushed material is then cooked at 70—100°C in steam-jacketed vessel to rupture the oil cells. The cooked meal is then pressed by a high pressure *expeller* (Continuous Screw Press) which has now completely replaced the Hydraulic Press. The expeller consists of a perforated cylindrical tube in which a screw shaft moves. As the meal is fed into the expeller tube, it is subjected to increasing pressure by the revolving screw. While the oil expelled from the seeds flows out of the holes in the expeller tube, the pressed oil cake is ejected from the other end of the tube. The exhausted oil cake still contains oil which the modern expeller can reduce to about 4 per cent. Most of the exhausted cake is used for cattle feed or subjected to 'solvent extraction' for the recovery of more oil.

(*b*) SOLVENT EXTRACTION. The screened seed is pressed into 'flakes' by passing through rollers. The rolled seed is carried along a moving belt of fine wire mesh beneath a succession of solvent sprays (Fig. 27·1).

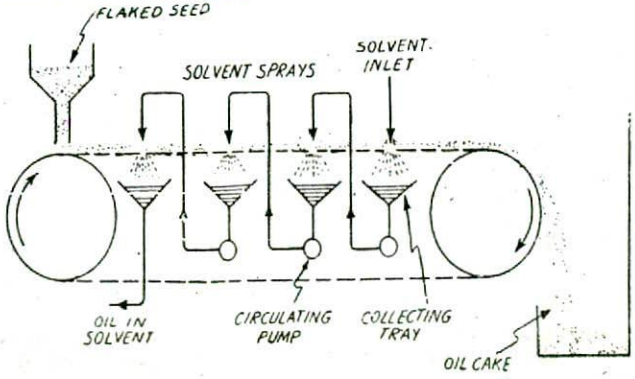


Fig. 27·1. Countercurrent Solvent Extraction of rolled oil seed.

The oil-bearing solvent, usually petroleum ether, is passed from spray to spray in the opposite direction to the moving belt (*Countercurrent Principle*). In this way fresh solvent washes the almost extracted cake at the end of the belt. The final solvent spray washing the flaked seed at the inlet is heavily loaded with oil. It is then sent to the distillation plant ('Stripper') when the solvent is recovered and the crudevege table oil is sent to the refining unit. The exhausted oil cake obtained at the end of the process contains only 0·5 to 1 per cent of the oil and is used as cattle feed or organic manure.

REFINING OF CRUDE FATS AND OILS

The crude fats and oils produced by the above techniques contain impurities which if not removed would give the product undesirable appearance, taste or odour. These include suspended or colloidal matter, free fatty acids, coloured and odiferous substances.

In the case of high quality fats such as lard, all that is required is filtration to remove suspended matter after coagulation by steam. The vegetable oils need to be given the following treatment for the removal of various impurities.

(*a*) *Filtration.* The suspended or colloidal matter is removed by filtration after coagulation with open steam after adding a coagulant such as citric acid.

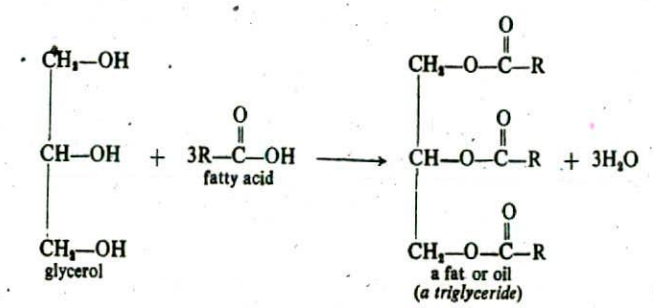
(*b*) *Neutralisation* (*Alkali refining*). The free fatty acids are removed as soaps by treatment with sodium hydroxide. The oil and alkali are agitated at about 90° until the fatty acids have been saponified. After standing, the soap settles down carrying down suspended and coloured matter. The soapy layer is run off, and the purified oil washed with water and dried by heating in vacuum.

(*c*) *Treatment with Fuller's earth.* Remaining traces of colour and odour are removed by treating the oil with about 1 per cent of Fuller's earth and filtration.

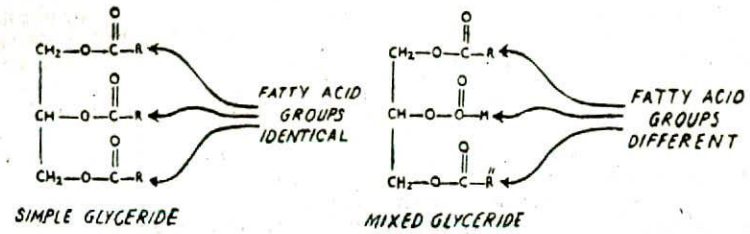
Alternatively the oil is heated under vacuum for several hours using super heated steam. Palm oil and certain other vegetable oils can be deodorised and bleached in this way.

STRUCTURE AND COMPOSITION OF FATS AND OILS

Animal and vegetable fats and oils have similar chemical structures. They are triesters formed from glycerol and long-chain carboxylic acids (often called fatty acids).



A triester of glycerol is called a *triglyceride* or *glyceride*. If all the R groups in the above general formula are identical, the triester is designated as a **Simple glyceride**, and if they are not a **Mixed glyceride**.



Most natural fats and oils are mixed triglycerides having two or three different fatty acid groups.

The carboxylic acids or fatty acids that go to form the fat or oil molecules (*glycerides*) have carbon chains with only even number of carbon atoms. The most common fatty acids have unbranched carbon chains of 14, 16 or 18 carbons. The chains may be saturated or may include one or more double bonds.

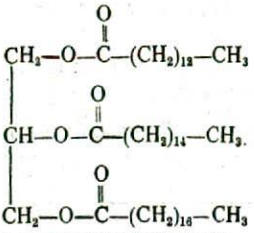
The glycerides are referred to as *saturated* or *unsaturated* depending on whether the fatty acid component chains are saturated or contain double bonds.

Table. 27·1. Structure and Melting Points of some Common Fatty acids

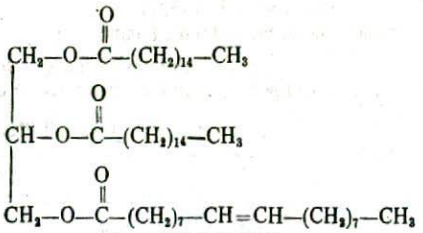
Name	*Structure*	*mp° C*
A. SATURATED :		
Caproic acid	$CH_3-(CH_2)_4-\overset{O}{\overset{\|}{C}}-OH$	−2°
Caprylic acid	$CH_3-(CH_2)_6-\overset{O}{\overset{\|}{C}}-OH$	17°
Capric acid	$CH_3-(CH_2)_8-\overset{O}{\overset{\|}{C}}-OH$	31°
Lauric acid	$CH_3-(CH_2)_{10}-\overset{O}{\overset{\|}{C}}-OH$	44°
Myristic acid	$CH_3-(CH_2)_{12}-\overset{O}{\overset{\|}{C}}-OH$	54°
Palmitic acid	$CH_3-(CH_2)_{14}-\overset{O}{\overset{\|}{C}}-OH$	63°
Stearic acid	$CH_3-(CH_2)_{16}-\overset{O}{\overset{\|}{C}}-OH$	70°
B. UNSATURATED :		
Oleic acid, *cis*-9-octadecanoic acid	$CH_3-(CH_2)_7\diagdown\diagup C=C\diagdown\diagup (CH_2)_7-\overset{O}{\overset{\|}{C}}-OH$ (H on each C=C)	16°
Linoleic acid, *cis-cis*-9, 12-octadecadienoic acid	$CH_3-(CH_2)_4\diagdown\diagup C=C\diagdown CH_2\diagup C=C\diagdown\diagup (CH_2)_7-\overset{O}{\overset{\|}{C}}-OH$ (H on each C=C)	−5°

The most common saturated fatty acids found in fats and oils are myristic acid, $C_{13}H_{27}COOH$, palmitic acid, $C_{15}H_{31}COOH$, and stearic acid, $C_{17}H_{35}COOH$. Amongst the unsaturated fatty acids, oleic acid, $C_{17}H_{33}COOH$, and linoleic acid, $C_{17}H_{31}COOH$, are widely distributed in almost all fats and oils. Oleic acid chain contains one double bond and linoleic acid chain two double bonds. We also know that the presence of a double bond in a fatty acid can cause *cis-trans* isomerism, depending on the configuration of the H atoms attached to the doubly-bonded carbon atoms. Thus oleic acid is the *cis*-isomer, while its *trans*-isomer is elaidic acid. Linoleic acid has two double bonds and both possess *cis* configuration. Generally speaking, the *cis*-isomers are found naturally occurring in the unsaturated fatty acid components of fats and oils. The structure and melting points of some common fatty acids are given in Table 27·1,

Composition of Fats and Oils. As already mentioned, fats and oils are invariably composed of a number of mixed glycerides, *e.g.*,



glyceryl myristopalmitostearate
(*mixed glyceride*)



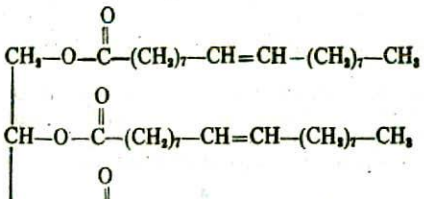
glyceryl dipalmitooleate
(*mixed glyceride*)

In the mixed glycerides present in fats and oils, a single molecule of glyceride may contain two or three different fatty acids linked by ester bonds to the glycerol. While it is difficult to know exactly as to which triglycerides are present in a particular fat or oil, the overall percentage composition of fatty acids which make up the fat or oil can be determined by analysis.

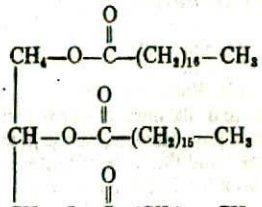
Table. 27·2. Composition (%) of some Common Fats and Oils

FAT OR OIL	*FATTY ACID*				
	Myristic acid	*Palmitic acid*	*Stearic acid*	*Oleic acid*	*Linoleic acid*
OILS:					
Olive oil	—	6—10	1—4	83—84	4—7
Peanut oil	—	6—9	2—5	50—60	20—30
Groundnut oil	—	6—14	2—7	46—72	13—38
Cottonseed oil	1—2	17—29	1—4	13—44	33—58
Mustard oil	—	1—3	1—3	8—40	10—29
Cocoanut oil	1—2	17—29	1—4	13—44	33—58
Sunflower oil	—	2—10	1—6	7—42	55—80
Soyabean oil	—	7—12	2—6	20—50	36—65
FATS:					
Beef tallow	2—6	24—32	15—25	37—43	2—3
Butter fat	7—12	23—30	8—13	30—40	4—5
Human fat	3—6	24—26	5—8	40—45	8—10
Lard	1—2	25—30	12—18	40—50	5—7
MARINE OILS					
Whale	5—10	10—20	2—5	33—40	—
Fish	6—8	10—25	1—3	—	—

Why are Animal fats solid and Vegetable oils liquid ? It is the degree of unsaturation of the constituent fatty acids which determines whether a triglyceride will be a solid or a liquid. The glycerides in which long-chain saturated acid components predominate tend to be solid or semi-solid, and are termed *fats*. On the other hand, oils are glyceryl esters which contain higher proportion of unsaturated fatty acid components. This difference of melting point or consistency is distinctively demonstrated by taking example of glyceryl trioleate and glyceryl tristearate. The former compound contains three unsaturated acid components and is an oil (liquid), while the latter compound is made of only saturated acid components and is a fat (solid).



glyceryl trioleate (*triolein*) ; *an oil*, mp −5°C



glyceryl tristearate (*tristearin*) ; *a fat*, mp 71°

The melting points of mixed glycerides would depend on the extent of unsaturated fatty acid components in the molecule. When two fatty acid components are unsaturated, the glyceride would tend to be an oil, while if two or all the acid components are saturated the triglyceride would tend to be a fat.

Fig. 27·3 is suggestive as to why the glyceride with mostly saturated acids present in their structure are solids, while unsaturated triglycerides are oils. A regular saw-tooth

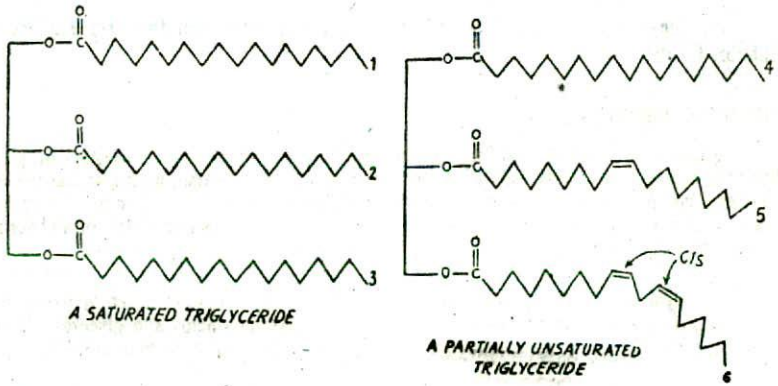


Fig. 27·3. Schematic representation of the conformations of the fatty acid chains in a *fat* and in an *oil*. Chains 1, 2, 3, 4 = stearic acid group ; 5 = oleic acid group ; 6 = linoleic acid group.

arrangement of the hydrocarbon chains of a saturated glycerides permit tight packing of the molecules and this results in a 'pseudocrystalline' solid substance (*fat*). However, the presence of a *cis* double bond in the chain of the unsaturated fatty acid component causes a big bend at that point, leading to less dense packing of the glyceride molecules. Thus unsaturated glycerides have low melting points and tend to be liquids. If there are two double bonds in the chain of the acid part of a glyceride, there result two bends, giving rise to a much more random conformation. Hence regular packing of molecules of such a glyceride is rendered unlikely. The 'polyunsaturated' glycerides, therefore, have very low melting points and are liquids (oils).

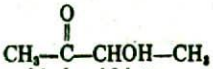
The terms 'Fat' and 'Oil' are more or less conventional and are now-a-days used in a very general fashion. Chemically common oils and fats are assortment of saturated and unsaturated triglycerides present in varying ratios. The apparent distinguishing difference between the two classes of compounds is their physical state. At ordinary temperature fats are solid or semisolid glycerides, while oils are liquids. But a given sample of glycerides (say *ghee*) may be a 'fat' in winter and an 'oil' in summer. In fact, it would be more advisable to use the term fat for both these classes of substances.

PHYSICAL PROPERTIES

(1) Oils and fats may be either liquids or noncrystalline solids at room temperature.

(2) When *pure* they are colourless, odourless and tasteless. The characteristic colours, odours, and flavours associated with natural oils and fats are imparted to them by foreign substances. For example, the yellow colour of butter is due to the presence of the pigment carotene ; and the taste of butter is due to the following two compounds which are produced by bacteria in the ripening of cream.


diacetyl


3-hydroxyl-2-butonone

(3) They are lighter than and insoluble in water and, therefore, form the upper layer when mixed with it. They are readily soluble in organic solvents like diethyl ether, acetone, alkanes, benzene, chloroform, carbon tetrachloride and carbon disulphide.

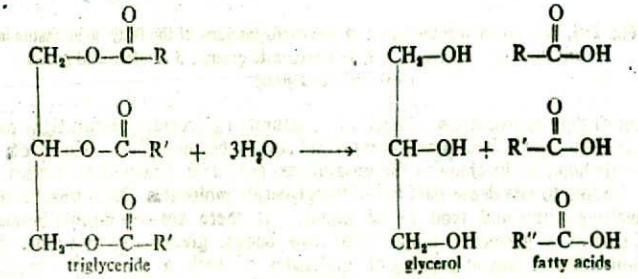
(4) They readily form emulsions when agitated with water in the presence of soap, gelatin or other emulsifiers.

(5) They are poor conductors of heat and electricity and, therefore, serve as excellent insulators for the animal body.

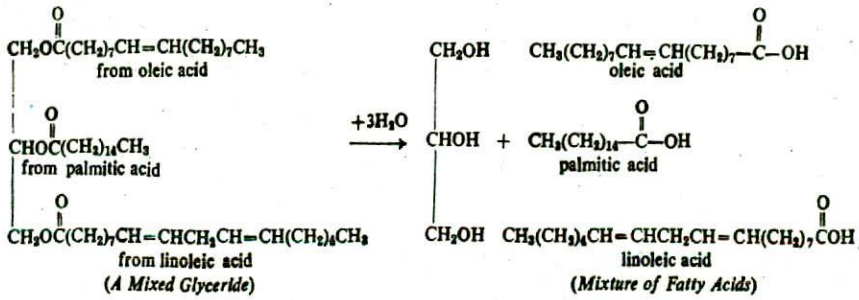
CHEMICAL PROPERTIES

The reactions of oils and fats are the reactions of triglycerides or triesters of glycerol. Thus they can undergo hydrolysis at all the three ester groups. Also, we know that the chains of the acid components of glycerides may contain one or more double bonds. Therefore the unsaturated glycerides give the addition and oxidation reactions characteristic of alkenes at the seats of these double bonds.

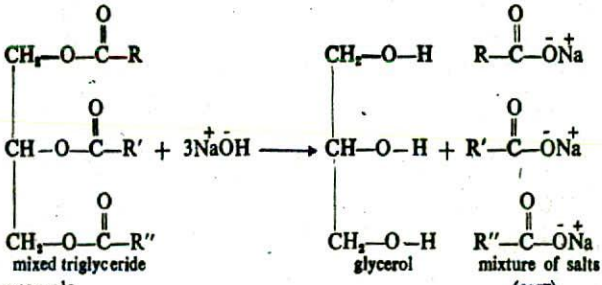
(1) **Hydrolysis.** Triglycerides are easily hydrolysed by enzymes called *lipases* (catalysts) in the digestive tracts of human beings and animals to give fatty acids and glycerol. The fatty acids so produced play an important role in the metabolic process in the animal body.


triglyceride glycerol fatty acids

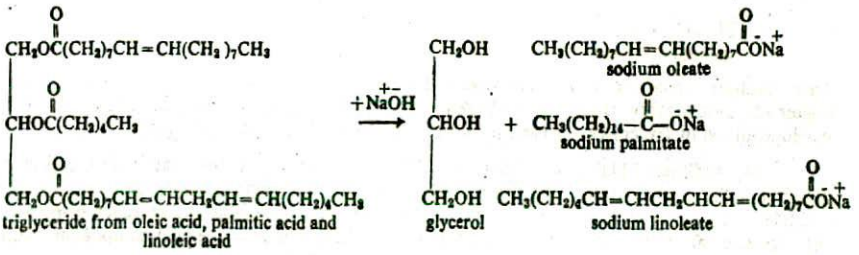
For example,



Saponification. When triglycerides are hydrolysed (saponified) by alkalis, glycerol plus the salts of fatty acids are produced. Generally the sodium or potassium salts are obtained which are termed *soaps.*

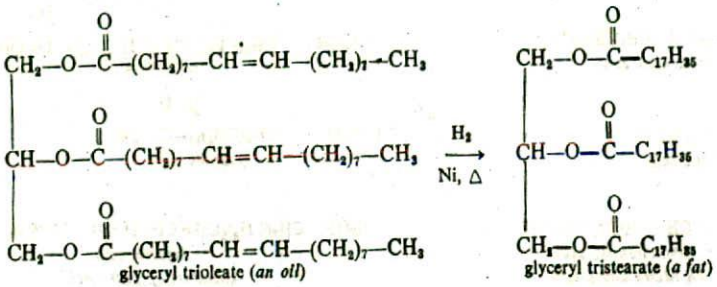


For example,



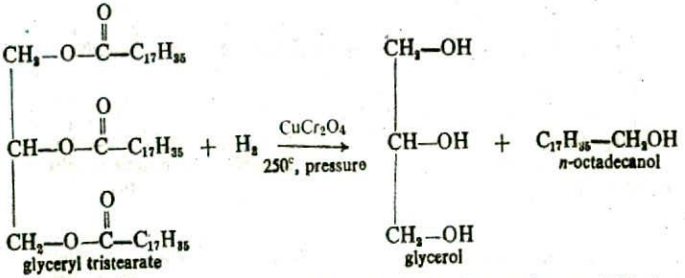
We will discuss the production of soaps and how they exert detergent action later in this chapter.

(2) **Hydrogenation or Hardening of Oils.** Unsaturated glycerides react with hydrogen in the presence of a metal catalyst (usually nickel) to give saturated glycerides. This reaction in similar to the catalytic hydrgenation of alkenes. Here, the hydrogenation process saturates the double bonds present in the fatty acid components of the glyceride; thereby converting them to saturated acid components. The result is the transformation of a liquid glyceride (an oil) into a semi-solid glyceride (a fat). For example, glyceryl trioleate (mp −5°) upon hydrogenation yields glyceryl tristearate (mp 71°).



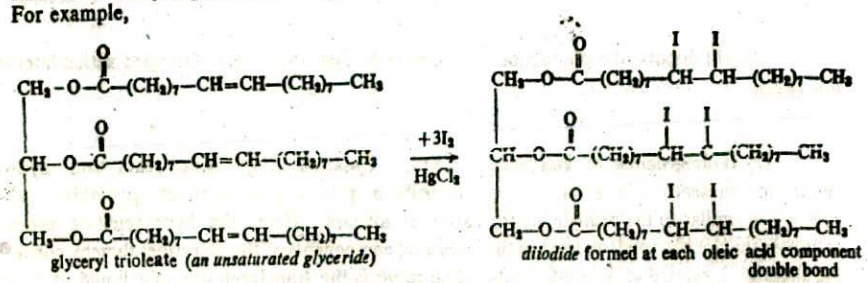
The process of hydrogenation which results in hardening of an oil owing to the formation of fat, is often referred to as **Hardening**. This reaction is used commercially to harden vegetable oils for the production of cooking fat (vegetable ghee or margarine). Hardened oils are also extensively used for making soaps and candles.

(3) **Hydrogenolysis (Reduction to Alcohols)**. Upon treatment with hydrogen at high pressure and temperature in the presence of copper chromite ($CuCr_2O_4$) as catalyst, glycerides are split up like other esters. The products are glycerol and the reduction products of the fatty acid, along chain alcohols. Thus glyceryl tristearate forms glycerol and octadecyl alcohol.



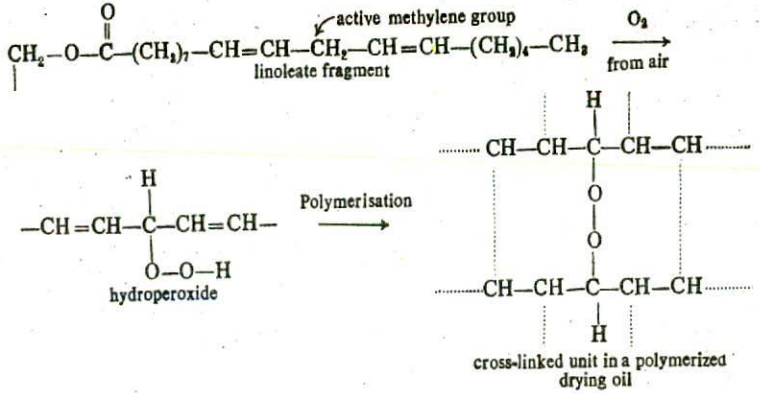
This reaction which causes the cleavage of the fat by hydrogenation to yield glycerol and a higher aliphatic alcohol. is termed *Hydrogenolysis*. The long-chain alcohols produced by the hydrogenolysis of glycerides are used in the manufacture of synthetic detergents.

(4) **Addition of Halogens** (*Halogenation*). Just as simple alkenes react with halogens by addition at the double bond, unsaturated glycerides add halogens to give the corresponding dihalides. Thus unsaturated glycerides on treatment with iodine in the presence of mercuric chloride as catalyst, give diiodides by addition at the double bonds in the acid component chains. For example,



Evidently the amount of iodine consumed by a glyceride will be proportional to the number of double bonds in the fatty acid components. This reaction is, therefore, used to determine the extent of unsaturation in a given fat or oil.

(5) **"Drying" of Oils** (Oxidation-Polymerization). The methylene groups flanked by doubly bonded carbon atoms present in highly unsaturated glycerides are very reactive. Linseed oil, the most widely used drying oil, contains about 63 per cent of its fatty acids as linoleates. The CH_2 group present in linoleic acid component of the unsaturated glyceride is readily attacked by oxygen of the air to form hydroperoxy group (—O—O—H) at these sites. These hydroperoxy groups then react with unchanged CH_2 groups in other glyceride molecules to form peroxide bridges. The hydroperoxide formation accompanied by polymerisation as illustrated below, converts polyunsaturated glycerides into a vast network of interlinked units. Such a network forms a dry, tough and durable film when exposed to air.

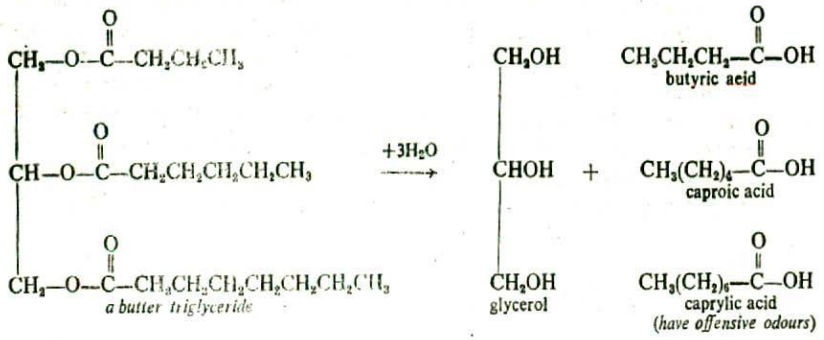


For this reason drying oils are used as the medium of paints and varnishes. In order to make oils 'faster drying' catalysts (lead and cobalt salts) are added. Other ingredients of paints are pigments and volatile thinners such as turpentine.

Oil Cloth is made by coating woven canvas with several layers of a linseed oil paint. To make *linolium*, rosin and ground cork are mixed with thickened linseed oil, and the mixture is allowed to harden.

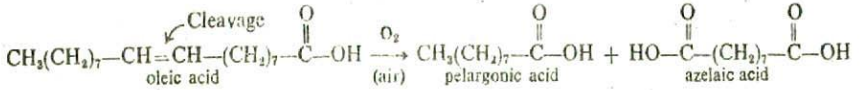
(6) **Rancidity** (Hydrolysis-Oxidation). The term rancid is applied to any fat or oil that develops a disagreeable odour when left exposed to warm, moist air for any length of time. Rancidity is chiefly caused by hydrolysis of the ester links and oxidation of double bonds of the triglycerides. The lower molecular weight acids that are produced are volatile and impart an offensive odour to fat or oil.

(*a*) HYDROLYTIC RANCIDITY. This type of rancidity is due to the liberation of lower fatty acids by hydrolysis of ester links of triglycerides. Hydrolytic rancidity is particularly applicable to butter. Under moist and warm conditions, hydrolysis of the glycerides in butter liberates the odorous butyric acid, caproic acid, caprylic acid, and capric acid.



Micro-organisms present in the air provide the enzymes (*lipases*) that catalyse the hydrolytic process. Rancidily so caused can be prevented by keeping butter covered in a refrigerator.

(*b*) OXIDATIVE RANCIDITY. It occurs in triglycerides containing unsaturated acid components. It is believed that first the ester linkages are hydrolysed to yield unsaturated acids. The acids so produced are subject to oxidative cleavage at the site of the double bonds forming short chain offensive aldehydes and acids. For example,



Oxidation leading to rancidity in fats and oils is catalysed by the presence of certain metallic salts. The addition of *antioxidants* will preserve edible fats for long periods of storage. Two antioxidants occurring in natural fats are vitamin E and ascorbic acid.

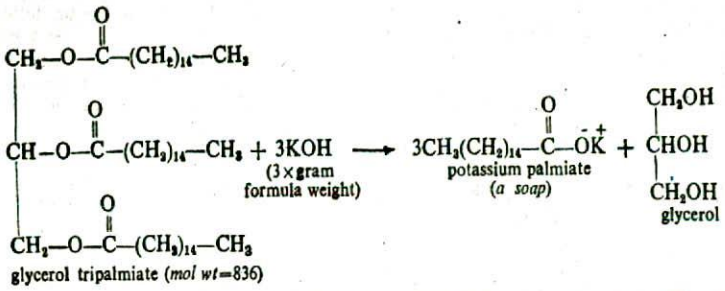
ANALYSIS OF FATS AND OILS

Since fats and oils are obtained from natural sources, their purity and composition is variable. They may contain free fatty acids produced by hydrolysis during storage, and non-fatty impurities, Also the suitability of a fat or oil as raw material for the manufacture of soaps, synthetic detergents, paints etc., depends on the carbon chain length and the degree of unsaturation of the acid components in the constituent glycerides.

A number of physical and chemical tests have been devised to evaluate a given fat or oil. The usual physical constants that are determined first are melting point, specific gravity and refractive index. The structure of glycerides has also been studied by using the modern physical methods such as X-ray analysis, absorption and mass spectrometery and NMR spectra. NMR spectra has been particularly used to detect isolated or multiple double bonds in unsaturated fatty acid chains.

The fat is subjected to many analytical tests. Some of the important of these are described here.

(1) **Saponification Number.** As already discussed, saponification is a term specifically applied to the hydrolysis of an ester when the reaction is carried out in alkaline solution. The saponification number of a fat or an oil is an arbitrary unit that is defined as the **Number of milligrams of potassium hydroxide required to saponify one gram of the fat or oil.**. Since there are three ester bonds in a molecule to hydrolyse, three equivalents of potassium hydroxide are needed to saponify one molecular weight of any fat or oil. The following equation depicting the saponification and sample calculation illustrate how saponification value could be determined.



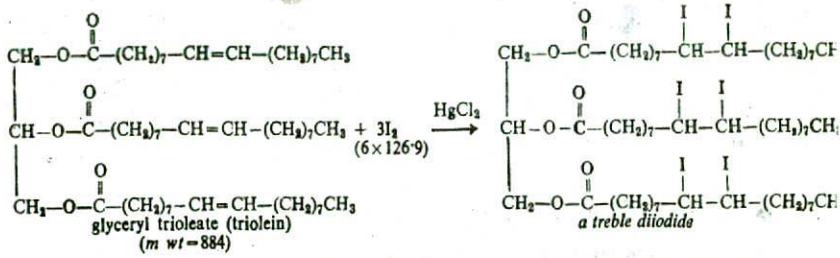
Here 836 grams of the fat require 168,000 milligrams KOH for saponification. Therefore, one gram of fat will require 168,000/836 mg of KOH. Hence,

$$\text{Saponification Number of glyceryl tripalmiate} = \frac{168{,}000 \text{ mg KOH}}{836 \text{ g fat}} = 208$$

If M be the molecular weight of the fat, the saponification number $=168{,}000/M$. Since the saponification value of a given fat can be determined experimentally, the average molecular weight of the fat can be found. The higher the saponification number of a fat, the greater the percentage of low-molecular-weight glycerides it contains. As the average molecular weight of the fat depends on the average length of the carbon chain of the fatty acid components, the saponification number also gives an indication of the average length of the carbon chain in the glycerides under examination.

The saponification number of a given sample of fat or oil is determined experimentally as follows. A weighed quantity of the fat is refluxed with excess of standard ethanolic KOH solution, and then titrating the unused alkali against a standard acid solution. Thus, the saponification number (or value) of a given sample of fat while it indicates the average molecular weight of the component glycerides and the chain lengths of the acid portions in them, also gives an estimate of non-fatty impurities if present. Further, it tells the amount of alkali which would be actually required by a fat sample for its conversion to soap.

(3) **Iodine Number.** The extent of unsaturation in a fat or oil is expressed in terms of its Iodine Number (or Iodine Value). The iodine number is defined as the **Number of grams of Iodine which will add to 100 grams of fat or oil.** The following equation and calculation illustrate the definition of Iodine Number.



The above equation tells that $6 \times 126{\cdot}9 = 761{\cdot}4$ g of iodine will add to 884 g of triolein. The number of grams of iodine that will add to 100 g of triolein will be $761{\cdot}4 \times 100/884$. Therefore

$$\text{Iodine Number of triolein} = \frac{761{\cdot}4 \times 100}{884} = 86$$

Obviously, the value of Iodine Number depends on the number of double bonds present in the acid component of the glycerides. A high iodine number indicates that the glycerides contain a large number of double bonds, while a low iodine number implies the presence of a few double bonds. The iodine number of tripalmitin with no double bonds would be zero.

Iodine number of a fat or oil can be experimentally determined by the following procedure (*Hubl's method*). A weighed amount of the fat or oil dissolved in carbon tetrachloride is allowed to react with a solution of iodine and mercuric chloride (catalyst) in ethanol. The unreacted iodine is titrated against standard thiosulphate solution and by difference the amount of iodine consumed by the weight of fat or oil taken calculated. In another method (*Wijs' method*) the molecular iodine has been replaced by the more reactive iodine monochloride (ICl), the rest of the procedure remaining the same.

The Iodine Numbers as also the Saponification Numbers of a few common oils and fats are given in the Table below.

Table. Iodine Number and Saponification Numbers of some Fats and Oils

Fat or Oil	*Iodine Number*	*Saponification Number*
FATS :		
Butter	30—40	210—230
Lard	46—70	195—203
Tallow	30—48	190—200
EDIBLE OILS :		
Soyabean oil	127—138	189—195
Cottonseed oil	105—114	190—198
Sunflower oil	140—156	188—194
NONEDIBLE OILS :		
Linseed oil	170—185	187—195
Tung oil	163—171	190—197

(3) **Acid Number.** The acid number (or value) of a fat or oil tells the amount of free fatty acids present in it. The acid number is expressed as the **Number of milligrams of potassium hydroxide required to neutralise one gram of fat.** It is determined by dissolving a weighed quantity of the fat in ethanol and titrating the solution against standard alkali. The acid number of a fat can give the extent of rancidity in a stored sample.

(4) **Reichert-Meissl Number.** The amount of free water soluble, volatile fatty acids (butyric — C_4 to capric — C_{10}) present in a fat or oil is expressed in terms of *Reichert-Meissl Number*. It is defined as the **Number of millilitres of 0·1 M potassium hydroxide solution required to neutralise 5 grams of fat.** Reichert-Meissl Number of a fat is determined by treating a known weight of it with ethanolic alkali and distilling the volatile acids. These are titrated against M/10 potassium hydroxide and Reichert-Meissl Number calculated.

MANUFACTURE OF 'VANASPATI' OR 'VEGETABLE GHEE'

Margarine, a substitute for butter, is manufactured in USA, UK and other European countries in large quantities by the hydrogenation of vegetable oils and soft fats (Norman, 1902). In India '*Vanaspati*' or '*Vegetable ghee*' was first introduced after the First World War (1919) and it has found immense popularity because it resembles natural ghee in appearance. It is made industrially by hydrogenation of vegetable oils such as groundnut oil, cottonseed oil, sesame oil, soyabean oil and sunflower oil. The hydrogenation is carried by passing hydrogen gas through the heated oil in the presence of metallic nickel as catalyst. The nickel catalyst required for the process is obtained by mixing a nickel salt (such as nickel formate or nickel carbonate) with unsaturated oil and then heating the mixture and passing hydrogen into it. Thus the salt is reduced to finely divided nickel dispersed in the oil and is ready for use.

The hydrogenation of an oil is actually carried in a 'hydrogenation tower' or 'converter'. It is a tall cylindrical steel vessel with cone-shaped base, fitted with a stirring device and also heating and cooling coils. The mixture of oil and nickel catalyst prepared as described above, is pumped into the converter. Here it is partially mixed by stirring and partially by the flow of hydrogen entering at the base through a perforated pipe. Steam is passed through the heating coils, while the oil mix is continuously pumped to the top of the converter where it is sprayed back down the tower. Since the reaction is exothermic, the steam-heating is stopped as the reaction gets going and the temperature is maintained at about 200° by passing cooling water through the coils if necessary. The hardening of the oil takes place most readily with a high catalyst concentration and low pressure (30—35 psi). When hardening has taken place to the required degree, the reaction is stopped by lowering the temperature to about 70°. The catalyst is filtered and the product is rebleached and deodorised under vacuum. The *Vanaspati* so prepared has melting point 31—37°C and has the texture of ghee which would melt like ghee when placed on the tongue.

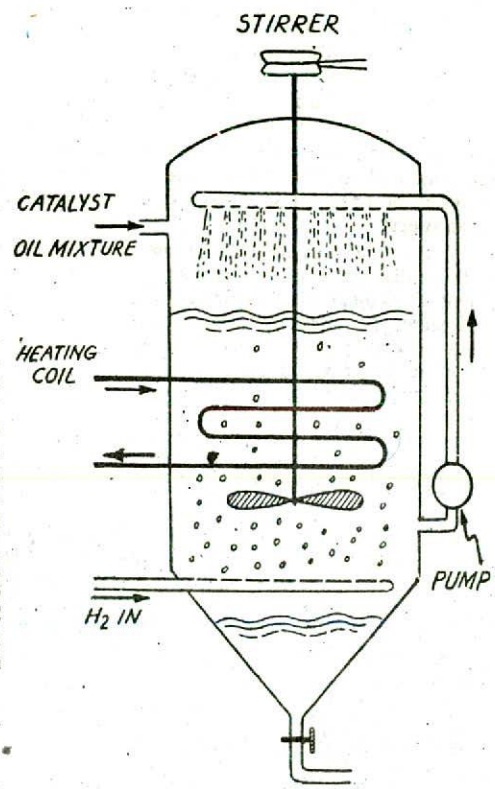
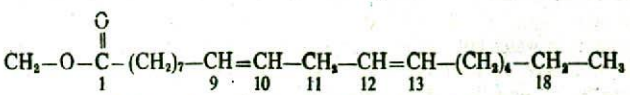
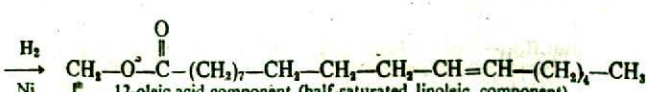


Fig. 27·4. Manufacture of 'Vegetable ghee' from Oil.

Composition of Vanaspati. Hydrogenation of an oil involves the saturation of the double bonds present in the acid components of glycerides. Thus the fatty acids with both single and two or more double bonds are saturated. However, due to the selective adsorption of the more unsaturated fatty acids on the catalyst surface, oleic acid with a single double bond is hydrogenated at a later stage than linoleic acid with two double bonds. For the same reason, hydrogenation of a chain containing two or more double bonds tends to stop on reaching the single double-bond stage. The reactions which take place on hydrogenation include saturation of oleic acid and linoleic acid to stearic acid, or half-saturation of linoleic acid to yield 9- or 12-oleic acid. Also *cis* double bonds are transformed to *trans* configuration.



linoleic acid component of a poly-unsaturated glyceride



12-oleic acid component (half-saturated linoleic component)

The composition of the fatty acids and iodine value of vanaspati and the original groundnut oil is illustrative.

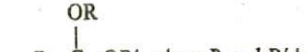
	Groundnut oil	*Vanaspati*
Iodine value	92	67—70
Total saturated	20 %	25 %
Oleic (*cis*-nonene)	55 %	35 %
Linoleic acid	25 %	5 %
trans-Nonene	Nil	35 %

It may be noted that linoleic acid content has fallen markedly as also the entire *cis*-nonene has been converted to *trans* form. Thus *Vanaspati* as made by hydrogenation contains a large proportion of linoleic acid converted to *trans*-nonene which is biologically antagonistic to human system.

There has been evidence in recent years that the presence of large amounts of saturated fats in the diet may lead to an increase in the level of *cholesterol* in the blood, while the high oil content of the diet tends to diminish cholesterol level in blood. The exeess of cholesterol in blood causes *arteriosclerosis* (hardening of the arteries) and consequent heart diseases, the most serious of which are coronary thrombosis and paralytic strokes. As a result of these findings, sunflower oil and other polyunsaturated oils are now increasingly used as cooking medium in preference to solid fats. For the same reason, the Government of India has made it mandatory since April 1972 to blend *vanaspati* with 2·5% sunflower and 7·5% sesame oil in order to raise the content of polyunsaturated acids, especially linoleic acid in the *cis* form. Vitamins A and D are also added to vanaspati as these are not present in the original oil and are necessary for good health of human body.

WAXES

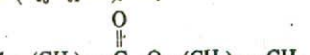
As we have already discussed, waxes are *lipids* which upon hydrolysis yield a long-chain fatty acid and a long-chain monohydric alcohol. The waxes differ from fats in that they are not esters of glycerol, but rather that they are esters of long-chain even-numbered fatty acids with long-chain even-numbered monohydric primary alcohols. Each wax molecule, therefore, contains only a single ester group as against three in fats. The general formula of a wax is essentially of a simple ester,



R—C(OR)—OR′, where R and R′ have long-chains of carbon atoms.

WAX

For example, *beeswax* is mostly myricyl palmitate, an ester of palmitic acid ($C_{15}H_{31}COOH$) with myricyl ($C_{30}H_{61}OH$), *i.e.*,



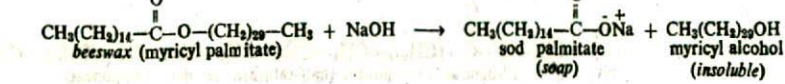
$CH_3-(CH_2)_{14}-C(=O)-O-(CH_2)_{29}-CH_3$ myricyl palmitate (*Beeswax*).

In general the acids and alcohols which make up waxes contain unbranched carbon chains having 12 to 36 carbon atoms.

In fact, naturally occurring waxes are invariably mixtures of several esters. In addition, they frequently contain small quantities of free fatty acids, alcohols and some long-chain solid alkanes. They are widely distributed in nature and are found both in plant and animal matter from which they are extracted by melting in boiling water and skimming the insoluble layer.

Waxes are solids having satiny "waxy feel". They melt over wide range of temperature (35—100°). They are insoluble in water but soluble in organic solvents and may be compounded into a number of useful everyday commodities. Such wax solutions are frequently used as protective coatings because waxes are not as easily hydrolysed as fats.

The chemistry of waxes resembles that of triglycerides (fats), and when saponified with alkali they yield soaps. For example,



$CH_3(CH_2)_{14}-C(=O)-O-(CH_2)_{29}-CH_3 + NaOH \longrightarrow CH_3(CH_2)_{14}-C(=O)-O^-Na^+ + CH_3(CH_2)_{29}OH$

beeswax (myricyl palmitate) — sod palmitate (*soap*) — myricyl alcohol (*insoluble*)

But since the alcohol produced is insoluble in water, waxes cannot be used for the preparation of soaps.

We may point out here that the common household paraffin wax is not chemically a wax at all. It is rather a mixture of straight-chain alkanes (C_{25} to C_{30}).

PLANT WAXES

They are found on the surfaces of leaves, stems and fruits of plants which grow in arid regions. They protect the plant from dehydration by providing a barrier to the evaporation of water. They also save the plant from the invasion by harmful organisms.

Carnauba Wax. It is isolated from the leaves of the Brazilian palm tree and contains several components, including largely myricyl cerotate, $C_{25}H_{51}—CO—O—C_{31}H_{63}$. This ester upon hydrolysis produces myricyl alcohol, $C_{31}H_{63}OH$, and cerotic acid, $C_{25}H_{51}COOH$.

Carnauba wax melts between 80—87°C. It is hard and impervious to water and is, therefore, used particularly in automobile and floor polishes. It is also used as a coating on carbon paper and mimeograph stencils.

ANIMAL WAXES

Animal waxes also serve as protective coating. They are found on the surface of hair, feathers and skin, and help to keep them soft and pliable. The majority of the animal waxes are obtained from marine sources, especially from the sperm and bottlenose whales. Beeswax and wool-fat are also commercially important.

Beeswax. It is obtained from the honeycomb of bees. It is composed of the esters *ceryl myristate*, $C_{13}H_{27}—CO—O—C_{28}H_{53}$, and myricyl palmitate, $C_{15}H_{31}—CO—O—C_{30}H_{61}$, among others. Beeswax also contains about 20 per cent of straight-chain alkanes such as n-$C_{31}H_{44}$ and n-$C_{29}H_{60}$. It melts between 62—65°C and is used for the preparation of shoe polishes, candles and paper coatings.

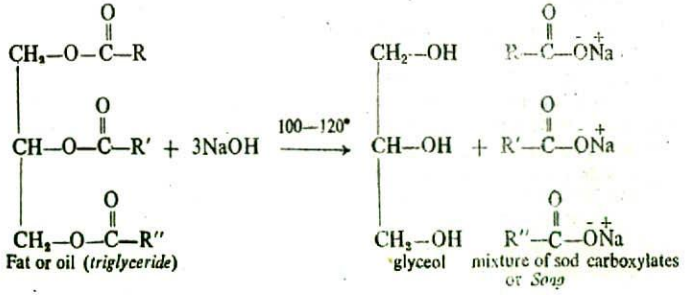
Supermaceti. This wax is obtained by chilling the oil which comes from the head cavity of the sperm whale. It consists mostly of *Cetyl palmitate*, $C_{15}H_{31}—CO—O—C_{16}H_{33}$. Spermaceti wax melts between 42—50°C. It is white, odourless and tasteless, and hence it is primarily used as a base for ointments and cosmetics. It is also used in the manufacture of candles.

SOAPS AND DETERGENTS

The term *detergent* (L., detergere = to wipe clean) is rather a general one and is used to denote any cleansing agent. This broad definition includes soaps as well. However, according to present-day popular terminology, the word **Detergent** generally refers to *synthetic detergents*, also called **Syndets.**

COMPOSITION OF SOAPS

As we have already discussed, soaps are the sodium or potassium salts of higher fatty acids containing from 12 to 18 carbon atoms. They are generally obtained by the hydrolysis of fats and oils with sodium hydroxide. The mixture of sodium salts of higher fatty acids so produced are called **Sodium Soaps.**



Fat or oil (*triglyceride*) glyceol mixture of sod carboxylates or *Soap*

Sodium carboxylates are the common toilet soaps. Potassium carboxylates or **Potassium Soaps** are obtained when the saponification of a fat or oil is carried with potassium hydroxide. Potassium soaps are softer than sodium soaps and they are used for special purposes when rapid solution is desired *e.g.*, in making shaving creams or liquid soaps (*shampoo*). The composition of sodium or potassium carboxylates constituting soap depends on the percentage of fatty acids bonded to glycerol in the original triglycerides. Solid fats give mixtures with higher proportion of sodium or potassium salts of higher fatty acids (palmitic acid, stearic acid) and give *hard soaps*. The vegetable oils give mixtures with a greater proportion of unsaturated fatty acids (oleic acid and linoleic acid) and give *soft soaps*.

SOAP MANUFACTRE

In India the main source of soap is coconut oil which is available in abundance in the southern states. Palm oil, groundnut oil and cottonseed oil are also used. Therefore, in actual practice, mixtures of solid fats (hardened oils) and oils are blended to produce a soap having properties best suited for a particular use.

Soaps can be made from fat blends in two ways :

(*a*) *Saponification of fats with alkali solutions*;

(*b*) *Direct neutralisation of fatty acids.*

The saponification methods are most commonly used for the manufacture of soaps. Increasing amounts, however, are now produced by direct neutralisation of fatty acids obtained from fat-splitting.

SAPONIFICATION METHODS

The saponification of a fat with alkali solution (*lye*) may be done by boiling (*Boiling Process*) or in cold (*Cold Process*). In the modern *Continuous Process*, saponification is carried in closed vessels at high temperature and pressure, and soap separated by centrifugation.

(1) **Boiling Process** (Hot Process). The manufacture of soap by the older (*Boiling Process*) is carried by the following steps.

(*a*) BOILING. The saponification of the fat is done by boiling the fat with sodium hydroxide solution (*soda lye*) in a large cylindrical steel vessel known as *soap pan* or *kettle*. The soap pan is usually open at the top. The lower part of the pan is funnel shaped and contains a system of steam heating coils which can be either 'open' or 'closed.' Molten fat and appropriate quantity of *soda lye* are simultaneously run into the pan. Steam is then admitted through the open 'steam coils' to boil the mixture which is thus kept in a good state of agitation all the time. Alkali is maintained in sufficient excess, more of it being added if necessary. Boiling is continued unless the greasy nature of the mix has almost disappeared and the fat is thus saponified to the extent of about 80 per cent.

$$\text{FAT} + \text{SODA LYE} \xrightarrow{\Delta} \text{GLYCEROL} + \text{SOAP}$$

(*b*) SALTING OUT. This step involves the separation of soap and glycerol, a process known as 'Salting Out'. Use is made of the fact that soap is insoluble in concentrated salt solution (*Common Ion Effect*), while glycerol is readily soluble.

Solid salt or brine is added to the mixture of soap, glycerol and excess lye resulting from step (*a*), which is then boiled and allowed to settle. The soap is thrown out of solution as a curdy mass which being of lower density than glycerol/brine mixture floats to the surface. The aqueous layer which also contains *spent lye*, salt and dirt is drawn off from the bottom of the pan and pumped to the glycerol recovery plant.

The soap left in the pan is dissolved in water and after boiling for a short time is salted out, the lye being removed after settling. This washing operation is repeated so as to reduce the glycerol content of the soap and to remove impurities. The soap which is relatively pure is once again boiled with fresh *soda lye* to complete the saponification. After settling out as before, the spent lye is run off and reused. Finally the soap is boiled with water and left to settle in the pan for two to ten days.

(*c*) FINISHING. The upper layer of soap obtained from step (2) is called 'neat soap'. While it is still liquid, the warm neat soap is pumped away using a *skimmer pipe*, which can be raised or lowered inside the pan on a swivel joint. The molten soap is received in a steam-

jacketed pan fitted with a mechanical stirrer (*crutcher*). Here soap is mixed with glycerol, colour perfumes, germicides etc till it becomes a hemogeneous mass. The crutched soap is then poured into open-topped 'moulds' or 'frames', and after solidification cut into small bars using steel wire cutters.

For making toilet soaps, traditionally the neat crutched soap is made into thin shreds, dried by hot air and milled with perfumes, colour etc to thin shavings. These are then stamped into cakes.

(2) **Cold Process.** The manufacture of soft coconut oil or potassium soaps cannot be carried out by the *Boiling Process*. This is because of their greater solubility in water which prevents them from being salted out. In this case, the *Cold Process* is used. The fat or oil is mixed with the required amount of *soda lye* in a steam heated vessel called crutcher (See Fig. 27·5). The saponification is allowed to take place in 'cold' with mechanical string. The process is continued till the soap begins to set. At this stage, the hot liquid soap is run into frames where saponification is completed. The by-product glycerol is not recovered and remains in the soap.

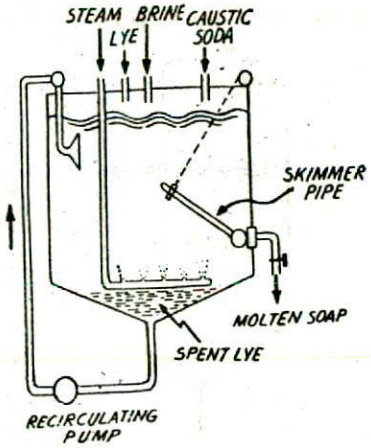


Fig. 27·5. Steam heated crutcher.

The Cold Process is also employed in India to prepare '*Washing Soap*' on a small scale for household use.

(3) **Modern Continuous Process.** In this process saponification can be carried out in about 15 minutes as compared to hours required for the open-pan method. This is achieved by reacting the fat/alkali mixture at elevated temperature and pressure in a closed vessel. This operation not only has the advantage of speed but is economical of space, heat and man power. After cooling, the soap is washed and salted out

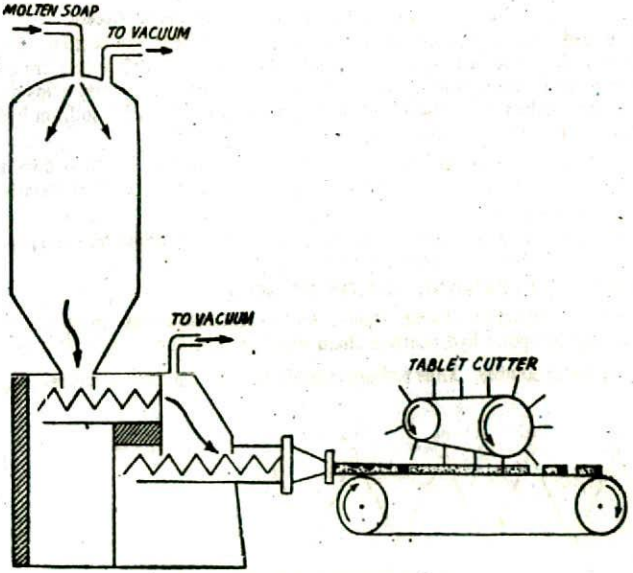


Fig. 27·6. Manufacture of Bar Soap.

separation of the soap and *spent lye* layers being effected by centrifugation. After filtering and centrifuging, the molten soap is partially dried and cooled by spraying from the top of a vacuum chamber (Fig. 26·7). The soap is scrapped from the walls of the spray drier and passed under vacuum through two 'plodders' which knead the soap and introduce colour and perfume. The soap comes out of the second 'plodder' in the form of a continuous bar which is chopped into tablets.

Direct Neutralisation of Fatty Acids. Soap manufacture by direct neutralisation of fatty acids is of recent introduction. The methods developed for the purpose are continuous and hence more economical. The fatty acids required in the process are obtained by hydrolysis of fats in the presence of specific catalysts.

(1) **Ittner Process.** In this process the hydrolysis of fat is carried out with water under pressure and at elevated temperature in the presence of lime or zinc oxide as catalyst (Fig. 27·7).

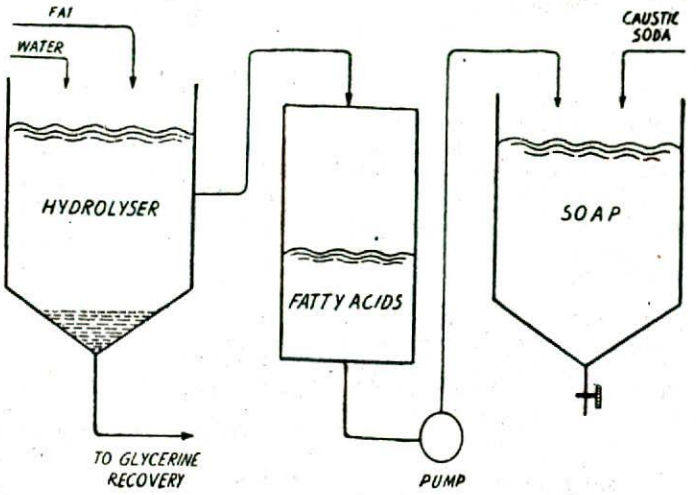


Fig. 27·7. Flowsheet for Continuous **Soap-making Process.**

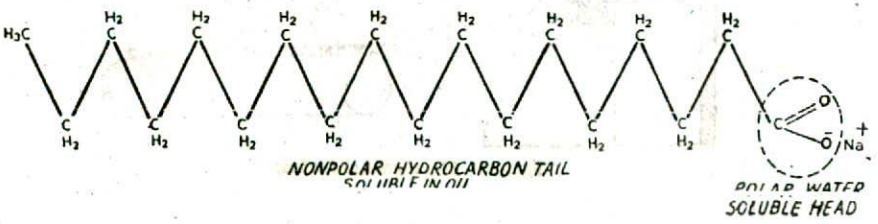
Hot water is fed into the *hydrolyser* near the top and fat near the bottom. The hydrolysis is rapid and complete. The fatty acids thus produced rise to the surface and are drawn out at the top, while glycerol is removed in water leaving at the bottom. The fatty acids are then pumped to another vessel, called *neutraliser*. Here they are neutralised with sodium hydroxide, or the cheaper sodium carbonate to form soap.

(2) **Twitchell Process.** In Twitchell process, the hydrolysis of fats is done using a catalyst consisting of dilute sulphuric acid and aromatic sulphonic acid. All other details are the same as for Ittner Process.

The drying and finishing of soaps obtained by the above methods is done exactly as described under the Modern Continuous Centrifugation Process.

MECHANISM OF CLEANSING ACTION OF SOAP

The cleansing action of soap depends on the fact that a soap molecule is made of two parts : (*i*) a long non-polar hydrocarbon chain which is oil-soluble ; and (*ii*) the salt-like polar head which is water-soluble. Thus sodium stearate ($C_{17}H_{35}\overset{+}{C}O\bar{O}Na$), a typical soap, can be represented as



When soap solution is poured onto a solid clothing or a greasy dish, the hydrocarbon tai of soap molecules dissolves in the oily or greasy layer. The grease layer with soap tails 'pegged'

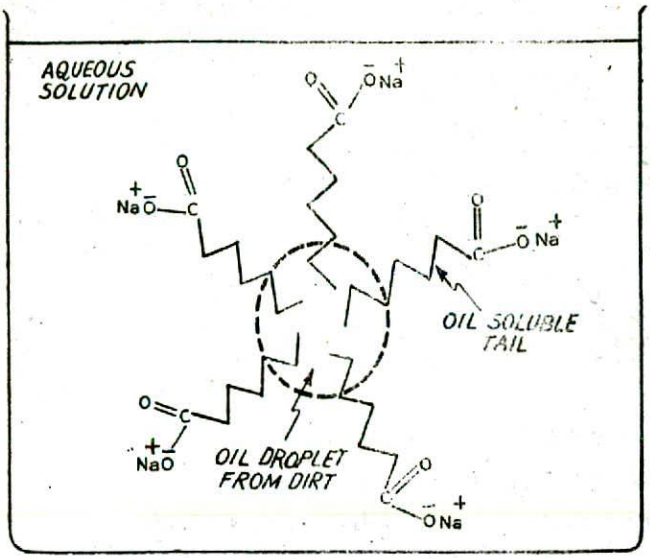


Fig. 27·8. Emulsified oil droplet from grease layer sticking to cloth or any other surface.

into it is then dislodged by the mechanical action of rubbing, tumbling or boiling. Once loosened, the grease layer breaks into tiny globules, each 'pin-cushioned' by soap molecules with 'heads' being attracted to the polar water molecules. Such tiny droplets of oil carry negative charges around them by virtue of the presence of carboxylate ions ($-COO^-$). They repel each other and do not coalesce. Thus the greasy or oily impurities are obtained as stable oil-in-water type emulsion which can be easily washed away by a stream of water. By this mechanism soaps are capable of functioning as cleansing agents for removing greasy dirt from skin, fabrics, flooring and crockery.

LIMITATION OF SOAPS AS DETERGENTS

Under certain circumstances the chemistry of soaps limits their usefulness as detergents. While sodium soaps are water-soluble, calcium and magnesium soaps are insoluble. Since hard water contains Ca^{2+} and Mg^{2+} ions, sodium soaps when added to it are converted to insoluble calcium magnesium or ferric soaps. For example,

$$\underset{\substack{\text{sodium soap}\\(\textit{soluble})}}{R-\overset{O}{\overset{\|}{C}}-O^-Na^+} + Ca^{2+} \longrightarrow \underset{\substack{\text{calcium soap}\\(\textit{insoluble})}}{\left(R-\overset{O}{\overset{\|}{C}}-O^-\right)_2 Ca^{2+}} + 2Na^+$$

$$\underset{\substack{\text{sodium soap}\\(\textit{soluble})}}{R-\overset{O}{\overset{\|}{C}}-O^-Na^+} + Mg^{2+} \longrightarrow \underset{\substack{\text{magnesium soap}\\(\textit{insoluble})}}{\left(R-\overset{O}{\overset{\|}{C}}-O^-\right)_2 Mg^{2+}} + 2Na^+$$

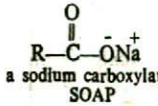
Thus ordinary soap in hard water produces insoluble precipitates of calcium and magnesium soaps which appear on the surface as insoluble sticky grey *scum*. This not only results in the waste of sodium soap but also discolours and hardens the fabrics being washed. This is the reason that the use of soaps for home laundrying has declined since World War II.

DETERGENTS OR SYNDETS

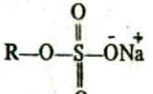
As we have already mentioned, the term *detergent* is now generally used for synthetic soaplike cleansing agents which are also referred to as **Syndets**. Detergents were first introduced in United States and Great Britain in 1920s. The detergent industry soon gained momentum and by 1950s soap was being replaced by syndets for all purposes except toilet use. At the present time the consumption of synthetic detergents far exceeds that of soaps. Syndets now account for over 80% of all detergents used in United States, France and West Germany. In India the consumption of syndets is small but likely to develop rapidly within the next few years as the raw materials from petroleum sources are made available.

WHAT ARE DETERGENTS AND HOW THEY FUNCTION ?

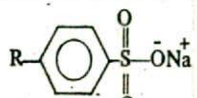
Whereas soaps are sodium salts of long-chain carboxylic acids, *detergents are either sodium salts of alkyl hydrogen sulphates or sodium salts of long-chain alkyl benzenesulphonic acids.*



a sodium carboxylate
SOAP



a sodium alkyl sulphate
DETERGENT

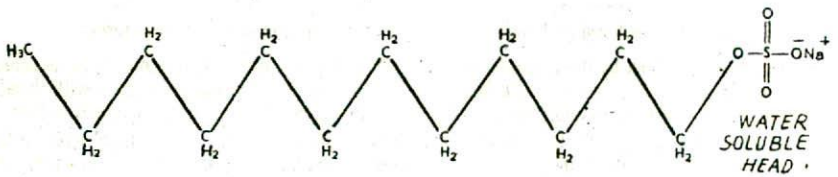


a sodium alkylbenzenesulphonate
DETERGENT

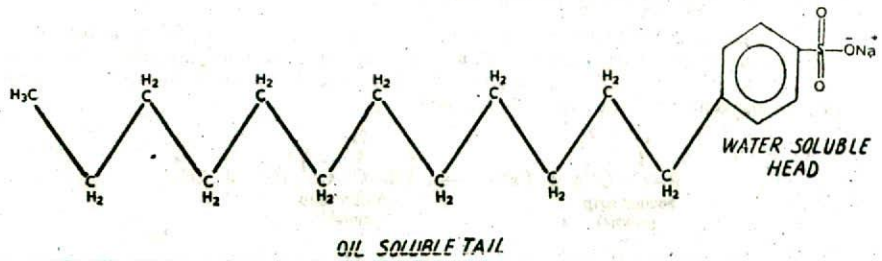
R— = a chain of 12 or 18 carbon atoms.

Examples of Detergents :

(*a*) Sodium Lauryl Sulphonate, $CH_3(CH_2)_{10}CH_2—O—SO_3^-Na^+$

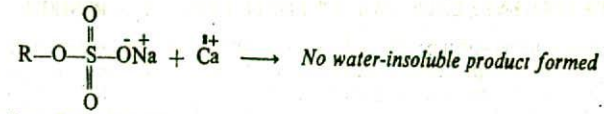


(*b*) Sodium *n*-dodecylbenzene sulphonate, $p\text{-}CH_3(CH_2)_{11}—C_6H_4—SO_3^-Na^+$



As evident from above, detergent molecules like those of soaps are made of a long oil-soluble chain and a polar salt-like head soluble in water. Thus the mechanism of the cleansing function of detergents is exactly the same as described for soaps.

Superiority of Detergents to Soaps. Synthetic detergents are superior to soaps because of their (detergents's) solubility in hard water. Calcium, Magnesium and other metal ions present in hard water form insoluble carboxylates (*scum*) with ordinary soaps, decreasing the efficiency of soaps. Detergents, on the other hand, form calcium and magnesium salts which are soluble in water.



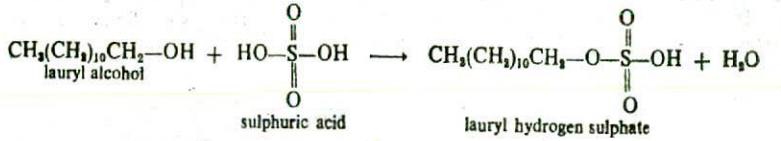
sodium alkyl sulphonate
(DETERGENT)



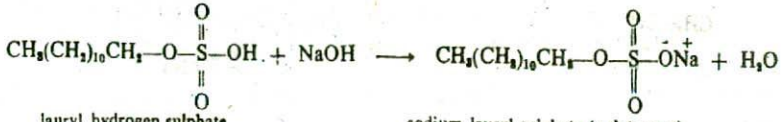
Thus detergents are effective cleansing agents even in hard water.

MANUFACTURE OF DETERGENTS

(1) **Sodium Alkyl Sulphates** are produced commercially from aliphatic long-chain alcohols (C_{10}—C_{14}) available from the hydrogenolysis of appropriate fats or oils. The alcohol is first sulphated with sulphuric acid. The resulting alkyl hydrogen sulphate when neutralised gives the sodium salt. For example, the most important detergent of this class *sodium lauryl sulphate* is synthesised from lauryl alcohol obtained by the hydrogenolysis of coconut or palm oil by the following steps.

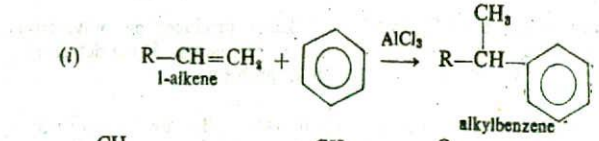


lauryl alcohol — sulphuric acid — lauryl hydrogen sulphate

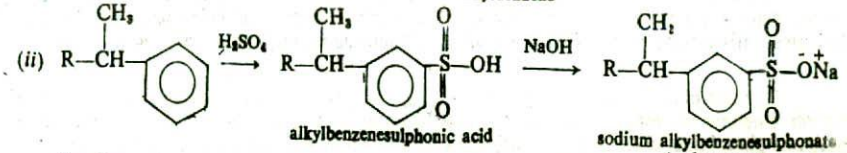


lauryl hydrogen sulphate — sodium lauryl sulphate (a detergent)

(2) **Sodium Alkylbenzenesulphonates.** (ABS detergents) are manufactured by a Friedel Crafts alkylation of benzene with long-chain alkenes (C_{10}—C_{12}). The resulting alkylbenzene then sulphonated to give alkylbenzenesulphonic acid which is converted to its sodium salt.

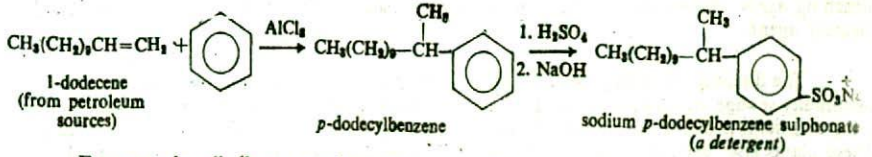


1-alkene — alkylbenzene



alkylbenzenesulphonic acid — sodium alkylbenzenesulphonate (*a detergent*)

For Example,

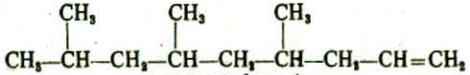


1-dodecene (from petroleum sources) — *p*-dodecylbenzene — sodium *p*-dodecylbenzene sulphonate (*a detergent*)

For example, alkylbenzene sulphonates are used in powder detergents (*e.g., Surf*)

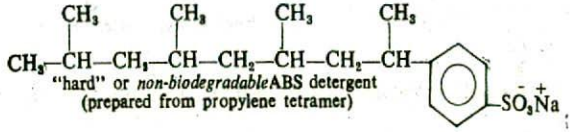
HOW DETERGENTS CAUSE WATER POLLUTION ? ITS REMEDY.

Soaps being sodium salts of long-chain fatty acids, are readily destroyed or degraded by microorganisms in septic tanks and sewage treatment tanks. They are *biodegradable* or "soft" and hence did not cause water pollution. Unfortunately till 1960s the commonest synthetic detergent was Alkyl Benzene Sulphonate($R—C_6H_4—SO_3^-Na^+$), or ABS type. It was made from a tetramer of propylene,

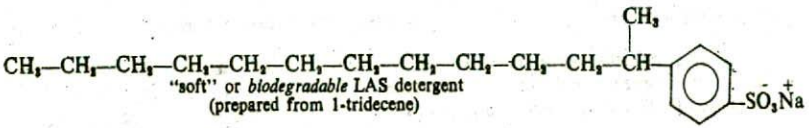


tetramer of propylene

by Friedel-Crafts reaction, followed by sulphonation and neutralisation. The carbon-chain R in the detergent was highly branched. It was "hard" and not *biodegradable*. Microorganisms degrade long carbon chains by first converting the terminal methyl group to a carboxyl group. Then they consume the rest of the chain, two carbons at a time, by further oxidation. Branching of the chain blocked this process of degradation and made the ABS detergent "hard" or nonbiodegradable. Such a detergent continued to foam and to make suds, clogging the waster-water disposal plant, and then killing fish and wild life in rivers and streams. The detergent even found way into ground water and thus contaminated the city drinking water. This posed a serious problem. The remedy was found in 1966 when Linear (or long-chain) Alkyl Sulphonate or LAS detergents were introduced in the market. These are "soft" and *biodegradable*. For illustration,



"hard" or *non-biodegradable* ABS detergent
(prepared from propylene tetramer)



"soft" or *biodegradable* LAS detergent
(prepared from 1-tridecene)

LAS detergents are now made from C_{10} to C_{13}. 1-alkenes produced by polymerisation of ethylene, $CH_2=CH_2$, or by cracking of kerosene fraction of petroleum. These detergents, although a bit costly to prepare, have solved the 'water pollution' problem.

The modern LAS detergents naturally will not foam in water. But the housewife does not reconcile with it since she associates the formation of foam with efficiency. For her psychological satisfaction, the manufacturers often add sudsing agents to their products.

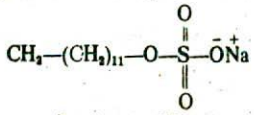
A packet of detergents contains about 20% of active detergent and an equal amount of sodium sulphate to make up the bulk of the powders. A further 30 to 50% is made up of inorganic phosphates which complex with the calcium and magnesium ions present in hard water and enhance the cleaning efficiency of the detergent. Other ingredients are sodium perborate, a bleaching agent ; *fluorescers*, organic compounds that make 'yellow' clothes appear 'white' ; and foaming agents.

The discharge of detergents with high phosphate content into the rivers and lakes from community sewage system has created a totally different pollution. The excess of phosphates being neutrients promote the growth of algae and weeds which appear as green surface sludge. These plants also deplete the water of available oxygen for fish and other sea animals. It is likely that legislation will have to be introduced to remove, or at least reduce, the phosphate content of detergents to eliminate this source of pollution.

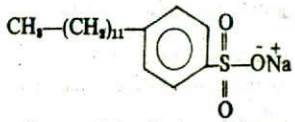
ANIONIC, CATIONIC AND NONIONIC DETERGENTS

The detergents could be classified into three types depending on the ionic charge present at the soluble end of their chain.

(1) **Anionic Detergents.** All the alkyl sulphate detergents as also the alkylbenzenesulphonate detergents since they bear an anion at the soluble end of the chain, are called *anionic* detergents. For example,



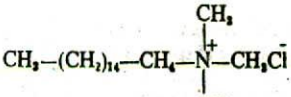
sodium lauryl sulphate



sodium *p-n*-dodecylbenzenesulphonate

(2) **Cationic Detergents.** These are also called *Invert Detergents* because they carry a cation at the soluble end of the chain. The cationic detergents are alkylammonium salts in which one of the four groups bonded to the nitrogen atom has a long carbon chain.

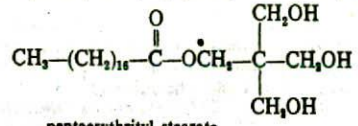
For example,



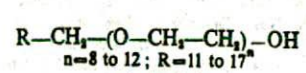
n-hexadecyl-trimethylmmonium chloride

Many invert detergents have a strong germicidel action.

(3) **Nonionic Detergents.** This type of detergents posses effective hydrogen bonding groups at one end of the alkyl chain which confer on them the required water-solubility. These include monoesters of polyhydric alcohols or polyethers derived from ethylene oxide.



pentaerythrityl stearate
(*monoester of polyhydric alcohol*)



(*polyether*)

They are particularly useful for dishwashing and on all occasions that call for the absence of inorganic ions.

QUESTIONS

1. What are lipids ? In what way Fats and Oils, are different from waxes.
2. Describe the various sources of fats and oils. How are they extracted and refined ?
3. What is the chemical composition of fats and oils ? Name five important fatty acids and write out their structural formulae.
4. Why fats are solids and oils liquid ?
5. Discuss the following reactions as applied to fats and oils.
   (*a*) Hydrolysis ; (*b*) Hardening ; (*c*) Hydrogenolysis ; (*d*) Halogenation ; (*e*) Drying ; and (*f*) Rancidity.
6. Define Saponification Number and Iodine Number. In what way these have proved useful in the analysis of oils and fats.
7. Describe in detail the manufacture of vanaspati in India. In what way is it harmful to the human system ? Can this disadvantage be eliminated ?

8. What are waxes ? List the name of five importynt waxes, their composition and uses. Are these different from paraffin waxes ?

9. What are soaps ? How soaps made from oils differ from those obtained from solid fats ? Why do we use blends of oils and fats in soap manufacture ?

10. Describe the 'Boiling Process' for the manufacture of soaps. Why it is being superseded by modern methods of making soaps by Neutralisation of fatty acids ?

11. Give in detail the modern Centrifugation Process for the industrial production of toilet soaps. How the finishing process technique been modernised ?

12. Discuss the mechanism of the cleansing action of soaps and detergents ? Discuss the limitations of soaps as detergents ?

13. What are detergents ? How are they obtained ? In what way they are superior to soaps ? Illustrate with one example.

14. How detergents cause water pollution ? How has it been remedied ?

15. What do you understand by ABS and LAS detergents ? Give one example of each and discuss the significance of each type.

16. Describe the various types of detergents. Give one example of each of the anionic, cationic and nonionic detergents.

17. Write notes on: (*i*) Saponification value; (*ii*) Hardening of oils; (*iii*) Reichert-Meissl value. *(Himachal BSc III, 1982)*

18. (*i*) What are fats and oils ?
(*ii*) How does oil structurally differ from fat ?
(*iii*) What structural changes take place when hardening of oil is carried out ? *(Punjabi BSc II, 1981)*

19. What is meant by iodine value and saponification value ? *(Manipur BSc Hons, 1981)*

20. What do you mean by saponification and spent lye ?
ow is glycerol recovered from spent lye ? *(Rajasthan BSc II, 1981)*

21. Explain the difference between a fat and an oil.
What does the saponification value of a fat indicate ? *(Kerala BSc III, 1982)*

22. Write a note on Hardening of oils. *(Mysore BSc III, 1982)*

23. Explain the following terms :
(*a*) Iodine Value
(*b*) Saponification Value. *(Delhi BSc Hons, 1982)*

24. (*a*) Write a note on the hydrogenation of oils.
(*b*) Define the Iodine value of oils and indicate its significance.
(*c*) Describe the manufacture of Soap. *(Gulbarga BSc II, 1982)*

25. How do soaps differ from detergents ? *(Baroda BSc II, 1982)*

26. (*a*) Describe the different types of detergents based on the charge on the soluble chains. How are detergents an improvement on soaps ? How does soap bring about the cleaning action ?
(*b*) What is rancidity of fat ? How is it caused ? How could it be prevented ? *(Delhi BSc Hons III, 1982)*

27. Discuss the cleansing action of soap. *(Delhi BSc Hons, 1993; Kerala BSc, 1993; Madras BSc, 1994; Osmania BSc Hons, 1994)*

28. Define : (*a*) Iodine value; and (*b*) Saponification value. *(Madurai BSc, 1994)*

29. Write a note on : Hydrogenation oils. *(Karnataka BSc, 1993)*

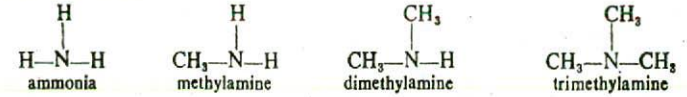
30. Write a note on : Detergents. *(Madurai BSc, 1993; Delhi BSc, 1994)*

31. What is meant by saponification? Describe the manufacture of soap. What important by-product can be obtained in this industry ? *(Mangalore BSc, 1994)*

Chapter **28**

Aliphatic Amines

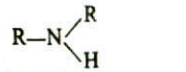
Amines are typical organic bases structurally related to the inorganic base ammonia. They contain alkyl groups attached directly to nitrogen atom. They could be thought of as derivatives of ammonia (NH_3) in which one, two or all the three hydrogens have been replaced by alkyl groups. Thus,



Primary, Secondary and Tertiary Amines. Amines are designated as *primary* (1°), *secondary* (2°), or *tertiary* according as one, two or three hydrogen atoms in ammonia molecule have been substituted by alkyl groups (R). The general formula and the characteristic functional groups of the three classes of amines are stated below.

Class	*General Formula*	*Functional Group*
Primary (1°)	$R-N\begin{matrix}H\\H\end{matrix}$ or RNH_2	$-N\begin{matrix}H\\H\end{matrix}$ or $-NH_2$ amino
Secondary (2°)	$R-N\begin{matrix}R\\H\end{matrix}$ or R_2NH	$-N\begin{matrix}\\H\end{matrix}$ or $>NH$ imino
Tertiary (3°)	$R-N\begin{matrix}R\\R\end{matrix}$ or R_3N	$-N\begin{matrix}\\\end{matrix}$ or $\begin{matrix}\\>N\\\end{matrix}$ tertiary nitrogen atom

In secondary and tertiary amines, the alkyl groups bonded to the nitrogen atom may be same or different. When all the alkyl groups are same the amine is referred to as a **Simple Amine** or **Symmetrical Amine** ; and when two or all the three alkyl groups are different, the amine is often called a **Mixed Amine** or **Unsymmetrical**

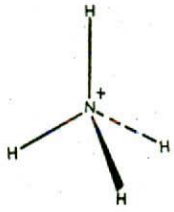


Tetraalkylammonium Salts or Quaternary Sa

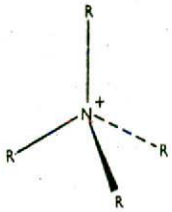
symmetrical ion having a structure, quite similar to that of methane. It is possible to replace one or more of the H atoms of the ammonium ion by alkyl groups. When all the four hydrogens of ammonium ion have been replaced by alkyl groups, we have *tetraalkylammonium ion* or *quaternary ammonium ion.*



methane

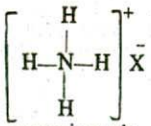


ammonium ion

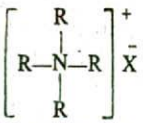


tetraalkylammonium ion

The tetraalkylammonium ion has "built in" ionic charge and interacts with anions (X^-) to form salts analogous to ammonium salts.

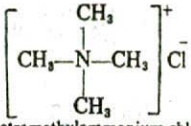


ammonium salt

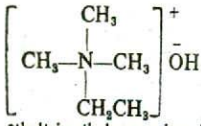


tetraalkylammonium salt

Here $\bar{X}$ may be $\bar{Cl}$, $\bar{I}$, $\bar{HSO_4}$ or $\bar{OH}$. For example,

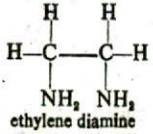


tetramethylammonium chloride

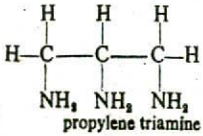


ethyltrimethylammonium hydroxide

Diamines and Triamines. It is possible that a single organic molecule may contain two or more amino groups in its structure. If two are present, the compound is named as a *diamine* ; if there are three $-NH_2$ groups present it is referred to as a *triamine*, and so on.

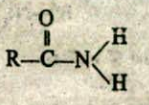


ethylene diamine



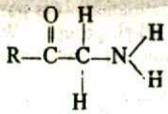
propylene triamine

The term 'amine' is widely used in organic chemistry for those compounds in which the carbon attached directly to N has single bonds to other groups. Thus,



or $R-CO-NH_2$ *IS NOT AN AMINE*

but



or $R-CO-CH_2-NH_2$ *IS AN AMINE*

Any compound, regardless of structure, which has a 1°, 2°, or 3° function in its molecule is termed an amine. This large class of organic compounds includes many substances that are biologically important. Both as free materials and in chemical combination with other molecules, amines are widely distributed in nature. They as particularly present in the nervous systems of vertebrates. Adrenaline which is rapidly released in the body during times of stress is a secondary amine. Benzedrine is a primary amine which produces frenetic "highs" in the nervous system. Benadryl, a tertiary amine, is useful in inducing sleep as also in treating the symptoms of allergies. Some of the most valuable drugs (connine, nicotine, amphetamine) obtained from plant extracts contain one or more basic nitrogens in their structures and have, therefore, been assigned the general name *alkaloids*.

NOMENCLATURE

Amines are named both by *Common* and *IUPAC* systems.

(1) **Common System.** In this system the name of an individual amine is derived by listing the alkyl group(s) attached to N atom in order of increasing size and adding the word *amine*. The name of the amine emerges as a single continuous *one word*. If an alkyl group occurs twice or thrice on the N-atom, the prefix *di-* or *tri-* is placed before the name of the alkyl group.

Table. Common Names of Amines.

Structure	*Name*	*Structure*	*Name*
$CH_3—NH_2$	metylamine	$CH_3—NH—CH_3$	dimethylamine
$CH_3—CH_2—NH_2$	ethylamine	$CH_3—N(CH_3)—CH_3$	trimethylamine
$CH_3—CH_2—CH_2—NH_2$	*n*-propylamine	$CH_3—CH_2—NH—CH_3$	methylethylamine
$CH_3—CH(CH_3)—NH_2$	isopropylamine	$CH_3—CH_2—N(CH_3)—CH_3$	dimethylethylamine
$CH_3—C(CH_3)_2—NH_2$	*tert*-butylamine	$CH_3—CH_2—N(CH_3)—CH(CH_3)_2$	methylethyl-isopropylamine

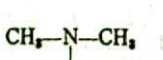
The prefix *sec-* or *tert-* is used just to indicate the type of amine and has no structural bearing as in the case of alcohols.

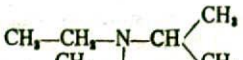
(2) **IUPAC SYSTEM.** This system adopts the common names for lower members. However, in modern practice the alkyl groups on nitrogen are written in alphabetical order and not in order of size or complexity. For example,

$CH_3—CH_2—NH—CH_3$
ethylmethylamine

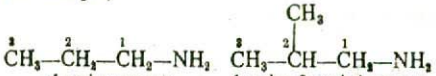
$CH_3—N(CH_3)—CH_2—CH_3$ with $CH(CH_3)_2$
ethyl isopropyl methylamine

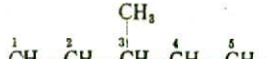
When two of the alkyl groups attached to N atom are identical, they are written as dialkyl and alphabetised. Thus,


dimethylethylamine

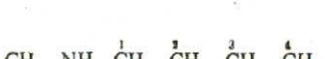

diisopropylethylamine

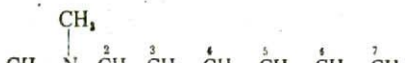
The IUPAC System is only used to name long chain substituted amines. These names are derived by regarding the amino group ($-NH_2$) as a substituent and naming the given amine as *aminoalkane*. As usual the longest continuous hydrocarbon chain containing the amino group is the parent structure and the position on this chain is indicated by arabic numerals. The counting of the carbons is done from the end that gives lowest number to the amino group. For example,


1-aminopropane 1-amino-2-methylpropane

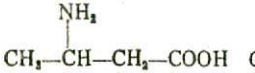

2-amino-3-methylpentane

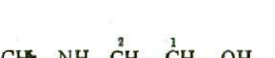
Further, if the amino group contains alkyl groups (R) as substituent, the word *N*-alkyl or *N*, *N*-dialkyl is prefixed to the word 'amino'. Thus,

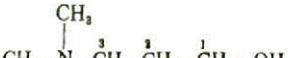

1-(*N*-methylamino)-butane


2-(*N*, *N*-dimethylamino)-heptane

If the amino group ($-NH_2$) or substituted amino group ($-NHR$ or $-NR_2$) is part of a molecule that contains another functional group, the second functional group (say $-COOH$ or $-OH$) determines the parent name of the compound.


3-amino-1-butanoic acid


N-methylamino-1-ethanol


3-(*N*, *N*-dimethylamino)-1-butanol

ISOMERISM

Amines exhibit the following types of isomerism.

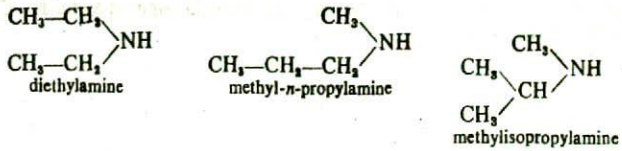
(1) **Chain Isomerism.** Like other classes of organic compounds, amines show chain isomerism arising from the different structure of the alkyl groups bonded to the amine function. Thus,


n-butylamine isobutylamine

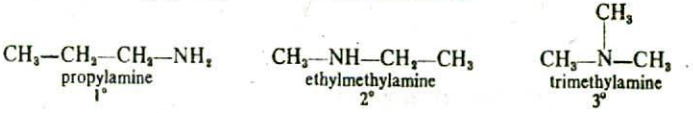
(2) **Position Isomerism.** Amines show position isomerism due to different location of the amine function $-NH_2$, $-NHR$ or $-NR_2$ on the carbon chain. For example,


1-aminopentane 2-aminopentane 3-aminopentane

(3) **Metamerism** in amines is exhibited because of the different alkyl groups bonded to the amine function, molecular formula of the amine remaining the same.

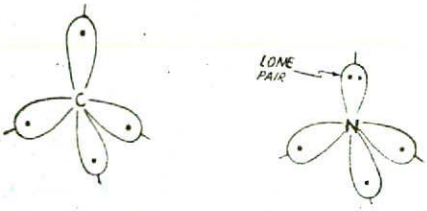


(4) Same Molecular Formula represents 1°, 2°, 3° amine. Amines show another type of isomerism in which the same molecular formula may stand for a primary, a secondary and a tertiary amine. Thus C_3H_9N represents the following amines



STRUCTURE

The electronic configuration of N atom can be written as $1s^2, 2s^2, 2p^1_x, 2p^1_y, 2p^1_z$. The $2s$ orbital and three $2p$ orbitals hybridise to give four sp^3 orbitals. Thus as in case of carbon atom, the four sp^3 orbitals of nitrogen are directed towards the four corners of a regular tetrahedron.



Orbital structure of C Orbital structure of N

In contrast to carbon, three of the sp^3 hybrid orbitals in nitrogen are occupied by single electrons while the fourth has a pair of electrons. The three half-filled orbitals are capable of forming σ bonds by overlap with s orbital of hydrogen atoms or sp^3 orbitals of carbons of alkyl groups (R). Thus the orbital structure of 1°, 2° and 3° amines can be drawn as

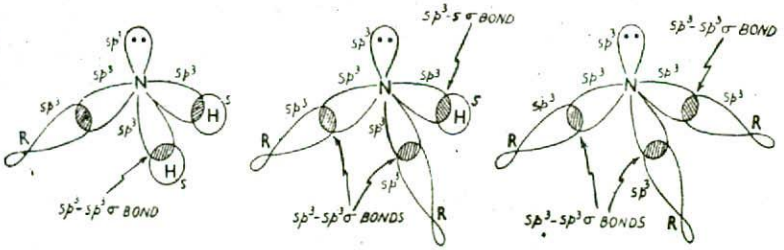


Fig. 28·1. Orbital structure of 1°, 2° and 3° amines.

Simplifying, the structure of the three types of amines RNH_2 (1°), R_2NH (2°) and R_3N(3°) may be shown as in Fig. 28·2.

It may be noted that in contrast to tetrahedral carbon in methane, the fourth vertex of tetrahedral nitrogen in amines is occupied by the unshared electron pair. Thus amines have the pyramidal molecules. The N-atom occupies the apex of the pyramid, while the rest of the H atoms or R groups be the at the corners of a triangular bases.

The geometry of amines is supported by the electron diffraction studies of trimethylamines which have shown that its molecule is pyramidal having C—N—C bond angle of 108°

This is very nearly the same as the H—N—H bond angle in ammonia and H—C—H angle in tetrahedral carbon in methane.

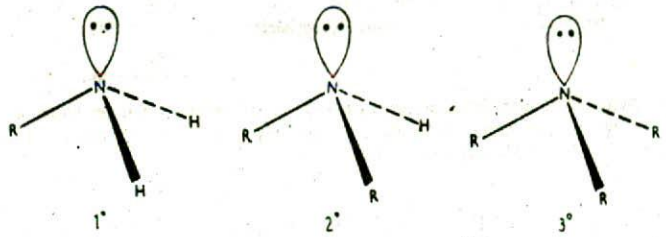
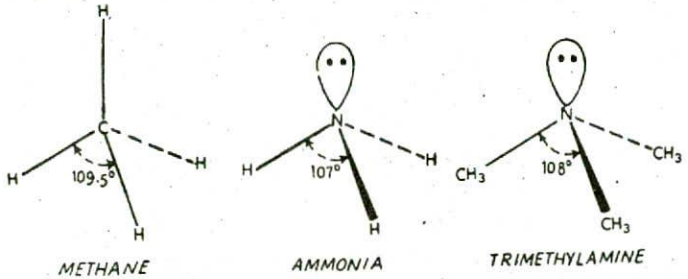


Fig. 28·2. Structural reresentation of the three types of ammines.

The value of bond angle of 107° in ammonia is accounted by the fact that lone pair-bond pair interactions are greater than bond pair—bond pair interactions, thereby contracting the angle from normal tetrahedral value of 109·5° to 107°. The bond angle in trimethylamine is 108° which is slightly more than the bond angle of ammonia. This can be attributed to greater



steric hindrance between the two adjacent methyl groups than that between two hydrogen atoms, thereby widening the bond angle from 107° (in ammonia) to 108° (in trimethylamine).

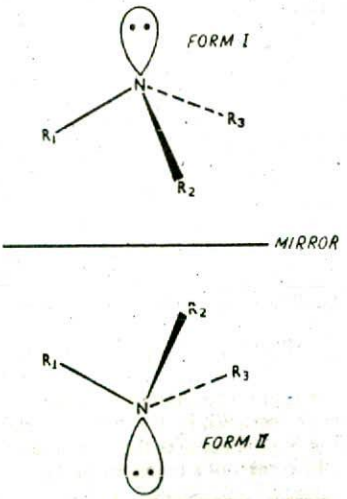
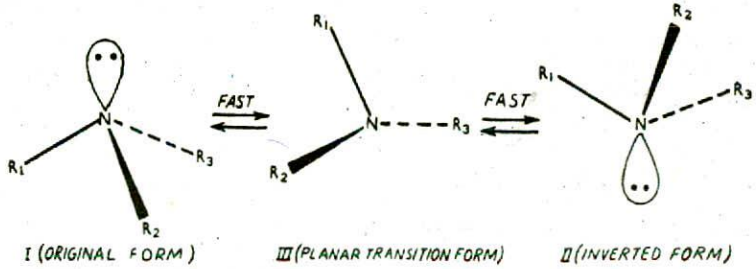


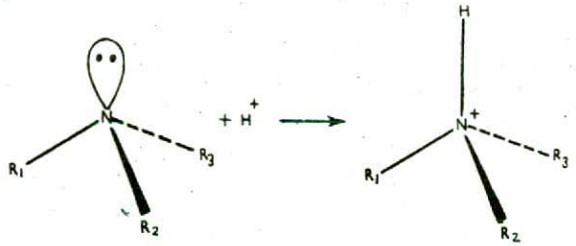
Fig. 28·3. Mirror image forms of a tertiary amine.

Why Asymmetric Amines cannot be Resolved into Enantioners ? Let us examine the molecule of an amine containing three different alkyl groups attached to nitrogen in light of the orbital structure discussed above. It will be revealed (Fig. 28·3) that this is not superimposable on its mirror image. Therefore, such an amine is asymmetric or disymmetric and should exist in two enantiomeric forms (I and II) similar to compounds with an asymmetric carbon atom. But all attempts to resolve this type of amine *e.g.*, ethylmethyl-*n*-propylamine, have failed. Spectroscopic evidence, however, suggests that an asymmetric amine undergoes a rapid inversion of FORM I to its mirror image FORM II. This inversion of I to II could be visualised to take place through a planar transition state like the umbrella in a windstorm.



The inversion from form I to II requires only a small amount of energy ($\Delta E_{inv} = 5$ kcal/mole). This energy barrier of 5 kcal/mole is easily met at room temperature by the thermal collisions of amine molecules. Therefore, a fast transformation between the forms I and II takes place. For that reason, no resolution of the enantiomers of asymmetric amines is possible.

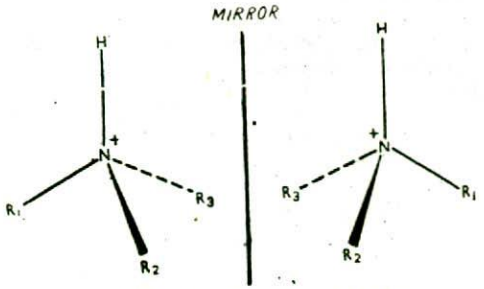
However, the inversion of enantiomers in asymmetric amines can be suppressed by ammonium cation formation. The coordination of the nonbonding electron pair with a proton fixes them in a σ bond and thus prevents the inversion.



asymmetric 3° amine
can undergo inversion

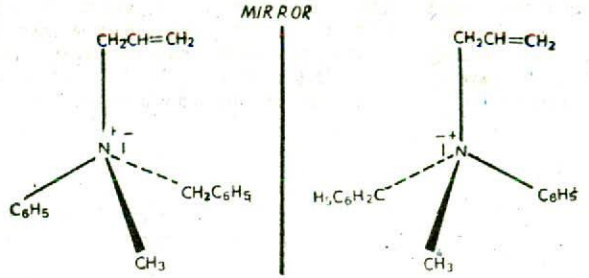
substituted ammonium cation
does not undergo inversion

Substituted ammonium cations, therefore, are capable of exhibiting enantiomerism.



Enantiomers of substituted ammonium cation

This has been confirmed experimentally. Alkylbenzylmethylphenylammonium iodide in which four different groups are attached to nitrogen atom of the substituted ammonium ion, has been resolved into two enantiomeric forms each of which is optically active.

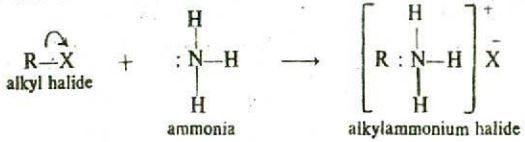


Enantiomeric forms of alkylbenzylmethylphenylammonium iodide

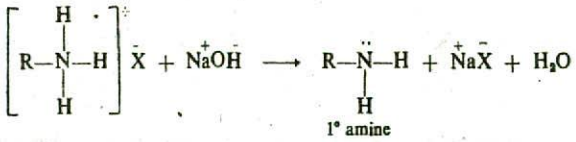
METHODS OF PREPARATION OF PRIMARY AMINES

The synthetic methods for the preparation of primary amines ($R—NH_2$) are listed below.

(1) **Reaction of Alkyl halides with Ammonia.** Primary amines can be obtained by reaction of alkyl halides with excess of ammonia.

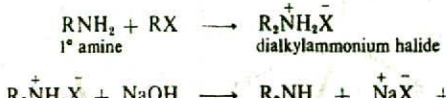


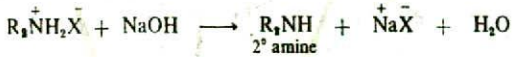
The resulting alkylammonium salt ($R\overset{+}{N}H_2\bar{X}$) on subsequent treatment with a strong base (NaOH) liberates the free primary amine.



Although this method appears so simple it is not suitable for laboratory synthesis. The replacement of hydrogens on N atom in ammonia does not stop at the first stage when a primary amine is produced as shown above. The process of alkylation of hydrogens on N atom continues to form a secondary and a tertiary amine. The tertiary amine reacts with a fourth molecule of alkyl halide to produce a tetraalkylammonium salt. The following series of reaction illustrate the progressive alkylation of ammonia to form secondary amines, tertiary amines along with tetraalkylammonium salts.

(*i*)





(*ii*)



$$R_3\overset{+}{N}H\overset{-}{X} + NaOH \longrightarrow \underset{3^\circ \text{ amine}}{R_3N} + NaX + H_2O$$

(*iii*)
$$\underset{3^\circ \text{ amine}}{R_3N} + RX \longrightarrow \underset{\text{tetraalkylammonium salt}}{R_4\overset{+}{N}\overset{-}{X}}$$

$$R_4\overset{+}{N}\overset{-}{X} + NaOH \longrightarrow \textit{No Reaction}$$

The resultant mixture of a primary amine, a secondary amine, a tertiary amine and a quaternary salt is not easily separated. Hence this method of preparing a primary amine by reaction of alkyl halide on ammonia is of limited application. It is generally used on industrial scale where special processes are employed for the isolation of the primary amine from the rest of the components.

(2) **Reaction of Alcohols with Ammonia.** When a mixture of excess of ammonia and alcohol vapours is passed over a dehydrating catalyst such as alumina or thoria at 300—400°, a primary amine results.

$$\underset{\text{methanol}}{CH_3—OH} + \underset{\text{ammonia}}{H—NH_2} \xrightarrow[300-400^\circ]{ThO_2} \underset{\substack{\text{methylamine}\\(1^\circ \text{ amine})}}{CH_3—NH_2} + H_2O$$

Unfortunately the reaction does not stop here. The methylamine produced in the first step reacts with a second molecule of methanol to give a secondary amine. The secondary amine further reacts with a third molecule of methanol to yield a tertiary amine.

$$\underset{}{CH_3—NH_2} + \underset{\text{methanol}}{CH_3—OH} \xrightarrow[300^\circ-400^\circ]{ThO_2} \underset{\substack{\text{dimethylamine}\\(2^\circ \text{ amine})}}{(CH_3)_2NH} + H_2O$$

$$(CH_3)_2NH + \underset{\text{methanol}}{CH_3—OH} \xrightarrow[\textit{conditions}]{\textit{similar}} \underset{\substack{\text{trimethylamine}\\(3^\circ \text{ amine})}}{(CH_3)_3N} + H_2O$$

Thus the resulting mixture contains primary, secondary and tertiary amines. However when a large excess of ammonia vapours are used in the initial mixture, primary amine is the chief product.

(3) **Reduction of Nitroalkanes.** Primary amines can be obtained by reduction of nitroalkanes which can best be effected with lithium aluminium hydride.

$$\underset{\text{nitroalkane}}{R—CH_2—NO_2} + 6H \xrightarrow[\text{ether}]{LiAlH_4} \underset{\text{alkylamine}}{R—CH_2—NH_2} + 2H_2O$$

This reduction can also be carried by using hydrogen in the presence of a metal catalyst (Raney nickel or platinum), or with metal and acid (Sn/HCl or Fe/HCl). For example,

$$\underset{\text{1-nitropropane}}{CH_3—CH_2—CH_2—NO_2} \xrightarrow{Fe/HCl} \underset{n\text{-propylamine}}{CH_3—CH_2—CH_2—NH_2}$$

$$\underset{\text{2-nitrobutane}}{CH_3—CH_2—\overset{\displaystyle NO_2}{\overset{|}{C}}H—CH_3} \xrightarrow[\text{ether}]{LiAlH_4} \underset{\text{2-aminobutane}}{CH_3—CH_2—\overset{\displaystyle NH_2}{\overset{|}{C}}H—CH_3}$$

However, nitroalkanes are not easily prepared. Only the lower members nitromethane, nitroethane, and the nitropropanes are commonly available from vapour-phase nitration of alkanes. Therefore, this method although most useful for the synthesis of aromatic amines has limited utility for the preparation of alkylamines.

(4) **Reduction of Amides.** Primary amines are formed by the reduction of unsubstituted amides with lithium aluminium hydride,

$$\underset{\text{amide}}{R-\overset{\overset{O}{\|}}{C}-NH_2} \xrightarrow[\text{ether}]{LiAlH_4} \underset{\text{a primary amine}}{R-CH_2-NH_2}$$

$$\underset{\text{propionamide}}{CH_3-CH_2-\overset{\overset{O}{\|}}{C}-NH_2} \xrightarrow{LiAlH_4} \underset{n\text{-propylamine}}{CH_3-CH_2-CH_2-NH_2}$$

The amide required in this method can be readily prepared by the reaction of the corresponding acyl halide with ammonia. For example, the following sequence shows how this reaction may be used to good advantage for obtaining ethylamine from ethyl alcohol.

$$\underset{\text{ethyl alcohol}}{CH_3CH_2OH} \xrightarrow{H_2Cr_2O_7} \underset{\text{acetic acid}}{CH_3COOH} \xrightarrow{SOCl_2} \underset{\text{acetyl chloride}}{CH_3-\overset{\overset{O}{\|}}{C}-Cl} \xrightarrow{NH_3} \underset{\text{acetamide}}{CH_3-\overset{\overset{O}{\|}}{C}-NH_2} \xrightarrow{LiAlH_4} \underset{\text{ethylamine}}{CH_3CH_2-NH_2}$$

(5) **Reduction of Oximes of Aldehydes and Ketones.** Good yields of primary amines are obtained by reducing oximes of aldehydes and ketones. The common reducing agents are sodium and absolute ethanol or hydrogen and nickel catalyst.

$$\underset{\text{an oxime}}{\begin{matrix}R\\R\end{matrix}\!\!>C=N-OH} \xrightarrow{2[H]} \begin{matrix}R\\R\end{matrix}\!\!>CH-NHOH \xrightarrow{2[H]} \underset{\text{a primary amine}}{\begin{matrix}R\\R\end{matrix}\!\!>CH-NH_2} + H_2O$$

e.g.,

$$\underset{\text{an oxime}}{CH_3(CH_2)_5-\overset{\overset{CH_3}{|}}{C}=N-OH} \xrightarrow{2[H]} CH_3(CH_2)_5-\overset{\overset{CH_3}{|}}{CH}-NHOH \xrightarrow{2[H]} \underset{\text{2-aminooctane}}{CH_3(CH_2)_5-\overset{\overset{CH_3}{|}}{CH}-NH_2} + H_2O$$

This reaction provides a method for converting aldehydes and ketones to primary amines

(6) **Reduction of Alkyl Cyanides or Nitriles.** Alkyl nitriles are reduced to primary amines by catalytic hydrogenation (nickel catalyst), sodium metal in ethanol (*Mendius Reaction*) or lithium aluminium hydride in ether.

$$\underset{\text{alkyl nitrile}}{R-C\equiv N} + 4H \longrightarrow \underset{1^\circ \text{ amine}}{R-CH_2-NH_2}$$

This method is particularly useful for the preparation of alkylamines because alkyl nitriles are easily made by the reaction of alkyl halides with cyanide ion. For example, *n*-butylamine can be synthesised from *n*-propyl bromide as follows.

$$\underset{n\text{-propylbromide}}{CH_3CH_2CH_2-Br} \xrightarrow{NaCN} \underset{n\text{-butyronitrile}}{CH_3CH_2CH_2-C\equiv N} \xrightarrow[\text{ether}]{LiAlH_4} \underset{n\text{-butylamine}}{CH_3CH_2CH_2CH_2-NH_2}$$

OR

$$CH_3CH_2CH_2-C\equiv N \xrightarrow[140^\circ,\ 130\ atm]{H_2/Ni} CH_3CH_2CH_2CH_2-NH_2$$

The above sequence converts an alkyl halide to a 1° amine with extension of the carbon chain.

(7) **Reductive Amination of Aldehydes and Ketones.** Primary amines may also be prepared by passing a mixture of an aldehyde or a ketone. and a large excess of ammonia and hydrogen over nickel at 150°.

$$\underset{\text{an aldehyde}}{R-\overset{\overset{O}{\|}}{C}-H} + NH_3 + H_2 \xrightarrow[300\ atm]{Ni,\ 150^\circ} \underset{\text{primary amine}}{R-CH_2-NH_2} + H_2O$$

$$\underset{\text{a ketone}}{R-\overset{O}{\overset{\|}{C}}-CH_3} + NH_3 + H_2 \xrightarrow[\text{conditions}]{\text{similar}} \underset{\text{an alkylmethylamine}}{R-\overset{CH_3}{\overset{|}{C}}H-NH_2} + H_2O$$

The reaction probably takes place by formation of Schiff's base first, which on catalytic hydrogenation yields a primary amine.

$$\rangle C=O + H_2N \xrightarrow{-H_2O} \underset{\text{Schiff's base}}{\rangle C=NH} \xrightarrow{+H_2\ (cat)} \underset{\text{primary amine}}{\rangle CH-NH_2}$$

This process of introducing an amino group into the molecule of an aldehyde or ketone is termed *Reductive amination*. It may be illustrated by the following example.

$$\underset{\text{2-pentanone}}{CH_3-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-CH_3} + NH_3 + H_2 \xrightarrow[\text{300 atm}]{\text{Ni, 150°}} \underset{\text{2-aminopentane}}{CH_3-\overset{NH_2}{\overset{|}{C}}H-CH_2-CH_2-CH_3} + H_2O$$

(8) **Hydrolysis of Isocyanides and Isocyanates.** Primary amines are produced by the hydrolysis of alkyl isocyanides with an aqueous mineral acid.

$$\underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}} + 2H_2O \xrightarrow{HCl} \underset{1^\circ\text{ amine}}{R-NH_2} + \underset{\text{formic acid}}{HCOOH}$$

e.g., $\underset{\text{propyl isocyanide}}{CH_3CH_2CH_2-\overset{+}{N}\equiv\overset{-}{C}} + 2H_2O \longrightarrow \underset{\text{propylamine}}{CH_3CH_2CH_2-NH_2} + HCOOH$

Alkyl isocyanates when hydrolysed with alkali also yield primary amines.

$$\underset{\text{alkyl isocyanate}}{R-N=C=O} + 2KOH \longrightarrow \underset{1^\circ\text{ amine}}{R-NH_2} + K_2CO_3$$

e.g., $\underset{\text{ethyl isocyanate}}{CH_3CH_2-N=C=O} + 2KOH \longrightarrow \underset{\text{ethylamine}}{CH_3CH_2-NH_2} + K_2CO_3$

The isocyanate required for the reaction is obtained from alkyl halides by interaction with silver isocyanate.

$$CH_3CH_2-I + \underset{\text{silver isocyanate}}{Ag-N=C=O} \longrightarrow \underset{\text{ethyl isocyanate}}{CH_3CH_2-N=C=O} + AgI$$

(9) **Hofmann Degradation.** It is a simple laboratory method for conversion of an amide to primary amine having one less carbon atom. The amide is treated with bromine in the presence of alkali (NaOH), and the overall reaction may be written as

$$\underset{\text{an amide}}{R-\overset{O}{\overset{\|}{C}}-NH_2} + Br_2 + 3NaOH \longrightarrow \underset{1^\circ\text{ amine}}{R-NH_2} + 2NaBr + NaHCO_3 + H_2O$$

For example,

(*i*) $\underset{\text{propionamide}}{CH_3-CH_2-\overset{O}{\overset{\|}{C}}-NH_2} \xrightarrow{Br_2/NaOH} \underset{\text{ethylamine}}{CH_3-CH_2-NH_2}$

(*ii*) $\underset{\text{\textit{tert}-butylacetamide}}{CH_3-\overset{CH_3}{\overset{|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-NH_2} \xrightarrow{Br_2/NaOH} \underset{\text{neopentylamine}}{CH_3-\overset{CH_3}{\overset{|}{C}}-CH_2-NH_2}$

This reaction, also known as *Hofmann Rearrangement*, gives an amine with one less carbon, in contrast to straight reduction of amide with $LiAlH_4$ which yields an amine with the same number of carbon atoms.

(10) **Curtius Degradation.** Primary amines can be prepared in good yield by treating acyl azides ($RCON_3$) in acidic or alkaline medium. The overall reaction which proceeds by the elimination of nitrogen from acyl azide yields a 1° amine containing one carbon less, is called *Curtius Degradation.*

$$\underset{\text{acyl azide}}{R-\overset{O}{\overset{\|}{C}}-N_3} \xrightarrow{-N_2} \underset{\text{alkyl isocyanate}}{R-N=C=O} \xrightarrow{H_2O/H^+} \underset{1^\circ \text{ amine}}{R-NH_2}$$

Alkyl isocyanate is obtained as an intermediate which is hydrolysed to give the respective primary amine.

The acid azide required in this method is prepared from the corresponding acyl chloride by reaction with sodium azide ($Na^+N_3^-$). Thus the sequence leading to the production of a primary amine from a carboxylic acid would be :

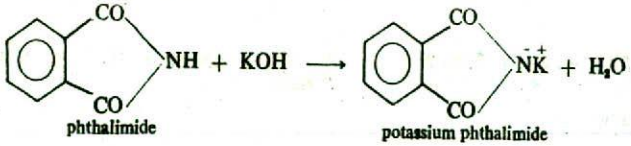
$$\underset{\text{carboxylic acid}}{R-\overset{O}{\overset{\|}{C}}-OH} \longrightarrow \underset{\text{acyl chloride}}{R-\overset{O}{\overset{\|}{C}}-Cl} \xrightarrow{NaN_3} \underset{\text{acyl azide}}{R-\overset{O}{\overset{\|}{C}}-N_3} \longrightarrow \underset{\text{isocyanate}}{R-N=C=O} \longrightarrow \underset{1^\circ \text{ amine}}{R-NH_2}$$

The conversion $RCOOH \longrightarrow RNH_2$ can also be carried with the help of **Schmidt Reaction** which is a modification of *Curtius Degradation.* In this reaction, a carboxylic acid is warmed with sodium azide ($Na^+N_3^-$) and concentrated sulphuric acid. The carboxylic acid is directly converted to the corresponding primary amine without the necessity of isolating alkyl azide.

$$R-\overset{O}{\overset{\|}{C}}-OH \xrightarrow[\text{conc } H_2SO_4,\ \text{warm}]{NaN_3} R-NH_2 + N_2 + CO_2$$

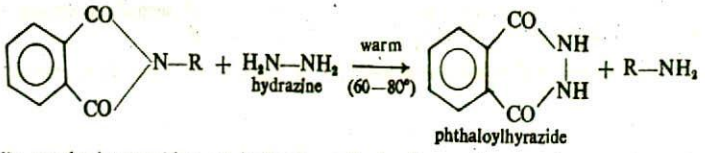
Schmidt reaction has the advantage of experimental simplicity as compared to the Hofmann and Curtius degradations.

(11) **Gabriel Synthesis.** In this method advantage is taken of the fact that phthalimide readily forms potassium phthalimide when treated with potassium hydroxide. The potassium phthalimide when reacted with an alkyl halide, is converted to *N*-alkylphthalimide. This upon hydrolysis with hydrochloric acids yields a primary amine.





N-alkylphthalimide is often resistant to hydrolysis but it readily reacts with hydrazine (H_2N-NH_2) to give phthalolhydrazide and a primary amine.



Gabriel's synthesis provides an indirect method of carrying on the transformation $RX \rightarrow RNH_2$ without the formation of secondary or tertiary amine as by-products.

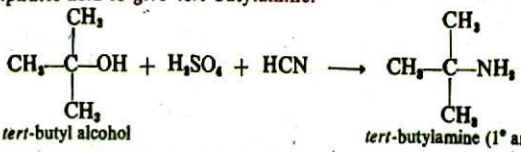
(12) **From Chloramine and Grignard Reagents.** Primary amines can be obtained by coupling chloramine with Grignard reagents.

$$\underset{\text{Grignard reagent}}{R—MgCl} + \underset{\text{chloramine}}{Cl—NH_2} \xrightarrow{\text{ether}} \underset{1^\circ \text{ amine}}{R—NH_2} + MgCl_2$$

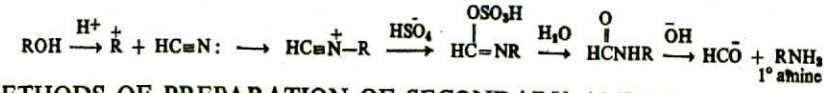
Chloramine required for the process is derived from ammonia and sodium hypochlorite.

$$NH_3 + \underset{\substack{\text{sodium}\\\text{hypochlorite}}}{Cl\bar{O}\overset{+}{N}a} \longrightarrow \underset{\text{chloramine}}{NH_2—Cl} + \overset{+}{N}a\bar{O}H$$

(13) **Ritter Reaction.** It is an important method for preparing primary amines having a tertiary group. Thus *tert*-butyl alcohol is reacted with hydrogen cyanide in the presence of conc sulphuric acid to give *tert*-butylamine.



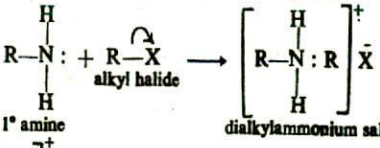
If the carbonium ion derived from alcohol be represented as R^+, the course of the above reaction would be as follows.

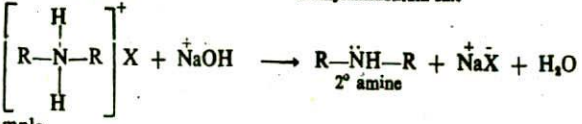


METHODS OF PREPARATION OF SECONDARY AMINES

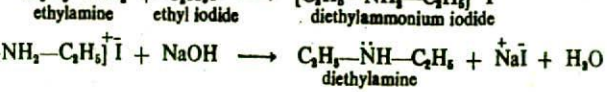
The general methods of synthesis of secondary amines (R—NH—R) are discussed below.

(1) **Alkylation of Primary Amines.** When one mole of a primary amine in ethanolic solution is heated with one mole of alkyl halide, a dialkylammonium salt is produced. This when treated with NaOH solution gives the free secondary amine.





For example,



This is not a method of choice for the preparation of secondary amines. The product ıvariably contains tertiary amine and tetraalkylammonium salt.

(2) **Reduction of *N*-substituted amides.** *N*-substituted amides when reduced with $LiAlH_4$, ield secondary amines.

$$\underset{\text{N-alkylamide}}{R-\overset{\overset{O}{\|}}{C}-NH-R'} + 4H \xrightarrow{LiAlH_4} \underset{2^\circ \text{ amine}}{R-CH_2-NH-R'} + H_2O$$

e.g. $\underset{\text{N-methylpoprionamide}}{CH_3-CH_2-\overset{\overset{O}{\|}}{C}-NH-CH_3} + 4H \xrightarrow{LiAlH_4} \underset{\text{methylpropylamine}}{CH_3-CH_2-CH_2-NH-CH_3} + H_2O$

(3) **Reduction of Alkyl Isocyanides or Isonitriles.** When alkyl isocyanides or isonitriles ıre reduced with nascent hydrogen, alkylmethylamines are obtained.

$$\underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}} + 4H \longrightarrow \underset{\substack{\text{alkylmethylamine}\\(2^\circ \text{ amine})}}{R-NH-CH_3}$$

This method is of academic interest only.

(4) **Reduction of Schiff's Bases.** Primary amines react with aldehydes and ketones to give Schiff's bases. The Schiff's bases so obtained upon reduction with hydrogen and platinum yield econdary amines.

$$\underset{\text{aldehyde}}{R-\overset{\overset{H}{|}}{C}=O} + H_2N-R' \longrightarrow \underset{\text{Schiff's base}}{R-CH=N-R'} + H_2O$$

$$R-CH=N-R' + 3/2\ H_2 \xrightarrow{Pt} \underset{2^\circ \text{ amine}}{R-CH_2-NH-R'}$$

(5) **Reductive Alkylation of Aldehydes and Ketones.** When a primary amine is reacted vith an aldehyde or a ketone , imines are formed. The imines are readily reduced with hydrogen nd Raney nickel, or sodium borofluoride to give a secondary amine.

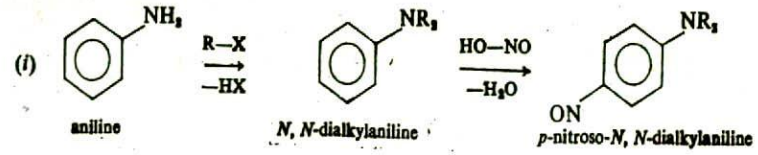
$$\underset{1^\circ \text{ amine}}{R-NH_2} + \underset{\text{ketone}}{O=C\begin{matrix}R\\R\end{matrix}} \longrightarrow \underset{\text{imine}}{R-N=C\begin{matrix}R\\R\end{matrix}} + H_2O$$

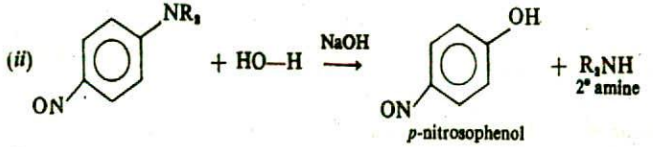
$$R-N=C\begin{matrix}R\\R\end{matrix} + H_2 \xrightarrow{\text{Raney Ni}} \underset{2^\circ \text{ amine}}{R-NH-CH\begin{matrix}R\\R\end{matrix}}$$

e.g., $\underset{\text{methylamine}}{CH_3NH_2} + \underset{\text{acetone}}{O=C\begin{matrix}CH_3\\CH_3\end{matrix}} \xrightarrow{-H_2} \underset{\text{imine}}{CH_3N=C\begin{matrix}CH_3\\CH_3\end{matrix}} \xrightarrow[Ni]{+H_2} \underset{\text{isopropyl methylamine}}{CH_3NH-CH\begin{matrix}CH_3\\CH_3\end{matrix}}$

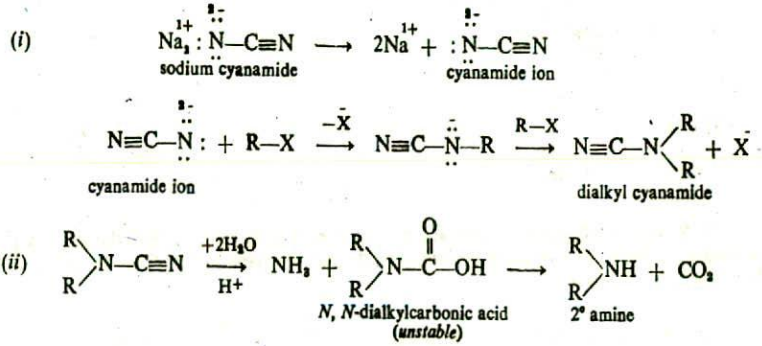
The advantage of this method over alkylation with alkyl halide is that over alkylation with the formation of tertiary amine and tetraalkylammonium salt cannot take place.

(6) **Hydrolysis of *p*-Nitroso-*N*, *N*-dialkylanilines.** In this method aniline is first heated with an alkyl halide to form *N*, *N* dialkylaniline. This is then nitrosated by reaction with nitrous acid when *p*-nitroso-*N*, *N*-dialkylaniline is obtained which upon boiling with sodium hydroxide yields a pure secondary amine.





(7) **Hydrolysis of Dialkylcyanamides.** Pure secondary amines may be obtained by synthesising dialkylcyanamides by the action of alkyl halide on sodium cyanamide. The dialkylcyanamide is then hydrolysed by aqueous acids or bases to produce a secondary amine.



(8) **From Chloroamines and Grignard Reagents.** Secondary amines can also be prepared by reaction between the corresponding chloroamines (RNHCl) and Grignard reagents. The chloroamine needed for the reaction is obtained by the reaction of a primary amine with sodium hypochlorite (Na^+ClO^-).

$$\underset{1^\circ \text{ amine}}{R{-}NH_2} + ClO^-Na^+ \longrightarrow \underset{\text{chloroamine}}{R{-}NH{-}Cl} + Na^+OH^-$$

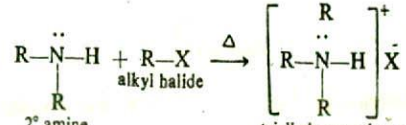
$$R{-}NH{-}Cl + R'{-}MgCl \xrightarrow{\text{ether}} \underset{2^\circ \text{ amine}}{R{-}NH{-}R'} + MgCl_2$$

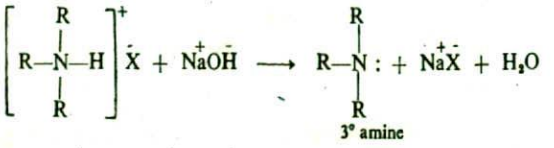
This method is particularly suited for the preparation of secondary amines having two tertiary alkyl groups, such as di-*tert*-butyl amine, $(CH_3)_3C{-}NH{-}C(CH_3)_3$.

METHODS OF PREPARATION OF TERTIARY AMINES

The methods listed below are available for the preparation of tertiary amines (R_3N).

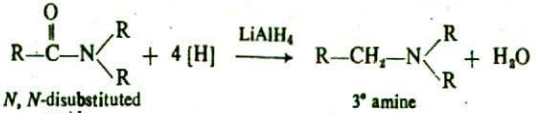
(1) **Alkylation of a Secondary Amine.** When a secondary amine in ethanolic solution is heated with a calculated amount of the appropriate alkylhalide, the corresponding trialkylammonium salt is obtained. This on treatment with NaOH liberates the tertiary amine.

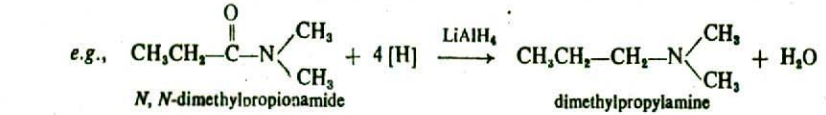




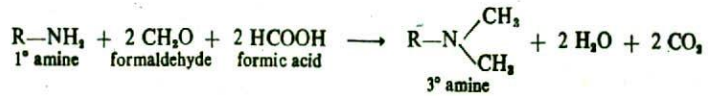
This is a fairly practical method for the preparation of tertiary amines. The tetraalkylammonium salt is also produced which is stable to alkali. Thus upon distillation of the reaction mixture after treatment with alkali yields the tertiary amine.

(2) **Reduction of *N*, *N*-Disubstituted Amides.** Tertiary amines may be prepared by reduction of *N*, *N*-disubstituted amides with $LiAlH_4$.



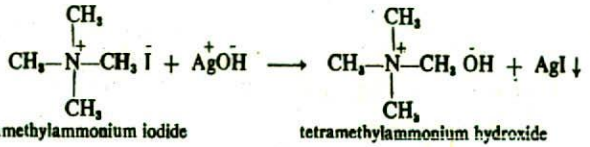


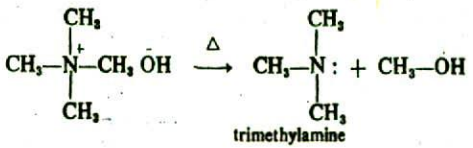
(3) **Reductive Alkylation.** Tertiary amines can be obtained by methylation of a primary or secondary amine by a mixture of formic acid and formaldehyde. This is referred to as *Eschweiler-Clarks* reaction.



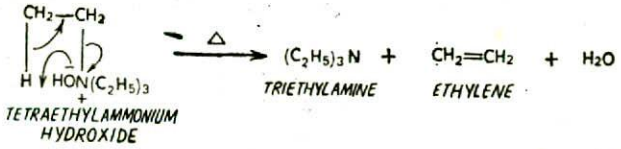


(4) **Decomposition of Tetraalkylammonium Hydroxides.** Tertiary amines are best prepared by decomposing the tetraalkylammonium hydroxide upon heating strongly. The required tetraalkylammonium hydroxide is obtained by treating the corresponding tetraalkylammonium salt with moist silver oxide (AgOH). For example,

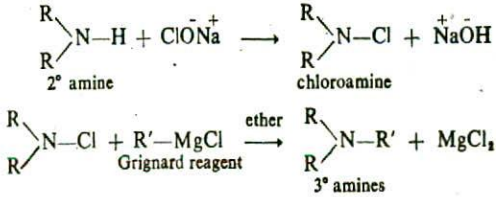




With a higher tetraalkylammonium hydroxide, however, the decomposition follows a different route.



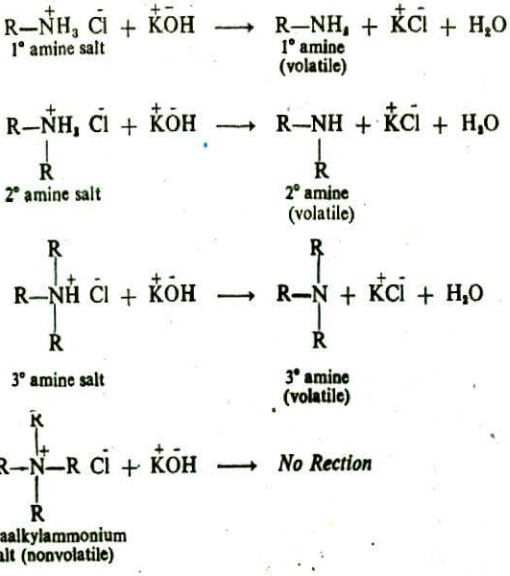
(5) **From Chloroamines and Grignard Reagents.** Tertiary amines can also be prepared by coupling the corresponding chloramine (R_2NCl) with Grignard Reagents in ether. The required chloroamine is derived from a secondary amine by reaction with sodium hypochlorite (Na^+ClO^-).



This is the only satisfactory method for the preparation of tertiary amines having two or more tertiary alkyl groups *e.g.*, tri-*tert*-butylamine, $[(CH_3)_3—C]_3N$.

HOW TO SEPARATE MIXTURES OF AMINES

When the mixture contains salts of primary, secondary and tertiary amines along with the tetraalkylammonium salt, it is first distilled with potassium hydroxide solution. The three amines are salt free and distil over. The tetraalkylammonium hydroxide, however, remains unaffected by alkali and being nonvoltatile is left behind. Thus,



The distillate contains the three free amines *i.e.*, primary, secondary and tertiary, which may then be separated by the following methods.

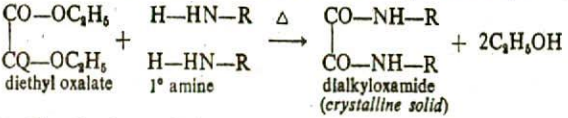
(1) **Fractional Distillation.** A mixture of primary, secondary and tertiary amines can be separated into the individual components by fractional distillation since their boiling points are fairly apart. For example,

$$\underset{\text{1° amine (bp 17°)}}{CH_3CH_2NH_2} + \underset{\text{2° amine (bp 56°)}}{(CH_3CH_2)_2NH} + \underset{\text{3° amine (bp 98°)}}{(CH_3CH_2)_3N} \xrightarrow{\text{F.D.}} \begin{matrix}(1)\ CH_3CH_2NH_2\\(2)\ (CH_3CH_2)_2NH\\(3)\ (CH_3CH_2)_3N\end{matrix}$$

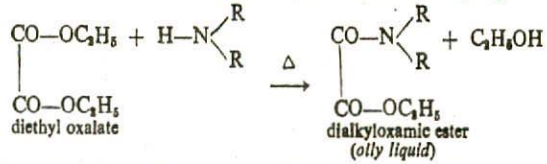
This is the most satisfactory method and is used industrially. The success of this method is primarily due to the high efficiency of the modern industrial fractionation apparatus which ensures almost complete separation of the amines.

(2) **By reaction with Diethyl oxalate ; Hofmann Method.** The given mixture of 1°, 2° and 3° amines is heated with diethyl oxalate, when

(*i*) the 1° amine forms a dialkyl oxamide which is crystalline solid.



(*ii*) the 2° amine forms dialkyloxamic ester which is an oily liquid.

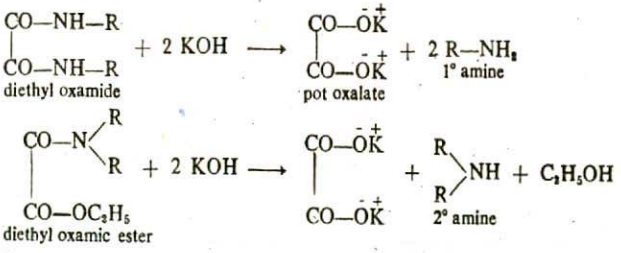


The second ester group does not react presumably because of steric hindrance.

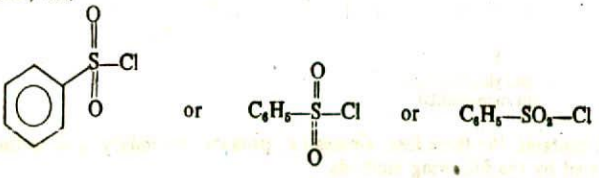
(*iii*) the 3° amine does not react as it does not contain a replaceable hydrogen atom on nitrogen.

The reaction mixture is now fractionally distilled. The 3° amine distils over and forms the first fraction. This is followed by dialkyloxamic ester which forms the second fraction. The dialkyloxamide remains behind in the distillation flask.

The dialkyloxamide and the dialkyloxamic ester separated as above are hydrolysed with KOH to generate the free amines which are distilled off.



(2) **Reaction with Benzenesulphonyl chloride ; Hinsberg Method.** This method makes use of the different reaction of 1°, 2° and tertiary amines with benzenesulphonyl chloride, (*Hinsberg reagent*) *i.e.*,



The given mixture of three amines is treated with benzenesulphonyl chloride and then alkalified with aqueous sodium hydroxide.

(*i*) 1° amine forms *N*-alkyl-benzenesulphonamide which is soluble in base.

$$\underset{\text{benzenesulphonyl chloride}}{C_6H_5{-}SO_2{-}Cl} + \underset{\text{1° amine}}{H_2N{-}R} \longrightarrow \underset{\text{\textit{N}-alkyl-benzenesulphonamide}}{C_6H_5{-}SO_2{-}NH{-}R} + HCl$$

$$C_6H_5{-}SO_2{-}NH{-}R + NaOH \longrightarrow \underset{\substack{\text{\textit{N}-alkyl-sodium benzenesulphonamide}\\(\textit{soluble})}}{[C_6H_5{-}SO_2{-}\overset{-}{N}{-}R]\overset{+}{Na}} + H_2O$$

(*ii*) 2° amine forms *N*, *N*-dialkylbenzenesulphonamide which is insoluble in NaOH solution. This is so because the resulting sulphonamide has no replaceable hydrogen atom to yield the sodium salt.

$$\underset{\text{benzenesulphonyl chloride}}{C_6H_5{-}SO_2{-}Cl} + \underset{\text{2° amine}}{H{-}N(R)(R)} \longrightarrow \underset{\substack{\text{\textit{N}, \textit{N}-dialkyl-benzenesulphonamide}\\(\textit{insoluble})}}{C_6H_5{-}SO_2{-}N(R)(R)} + HCl$$

(*iii*) 3° amine does not react with benzenesulphonyl chloride at all.

The reaction mixture obtained after treatment with benzenesulphonyl chloride in the presence of NaOH is now distilled. The tertiary amine passes over first. The remaining mixture is filtered and the filtrate on acidification gives the sulphonamide of the 1° amine, while the solid residue is the sulphonamide of the 2° amine. The two sulphonamides thus isolated are hydrolysed with hydrochloric acid to regenerate the individual 1° and 2° amines which are fractionally distilled.

$$\underset{\text{\textit{N}-alkyl-benzenesulphonamide}}{C_6H_5{-}SO_2{-}NH{-}R} + HO{-}H \xrightarrow{(H^+)} \underset{\text{benzenesulphonic acid}}{C_6H_5{-}SO_2{-}OH} + \underset{\text{1° amine}}{R{-}NH_2}$$

$$\underset{\substack{\text{\textit{N}, \textit{N}-dialkyl-benzenesulphonamide}}}{C_6H_5{-}SO_2{-}N(R)(R)} + HO{-}H \xrightarrow{(H^+)} C_6H_5{-}SO_2{-}OH + \underset{\text{2° amine}}{HN(R)(R)}$$

Now a days benzenesulphonic chloride has been replaced by *p*-toluenesulphonyl chloride, $CH_3{-}C_6H_4{-}SO_2Cl$, since the substituted sulphonamides thus formed are stable solids which can be easily crystallised.

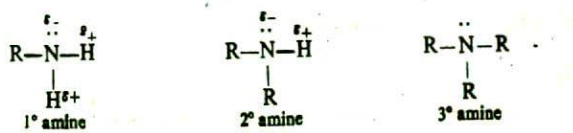
PHYSICAL PROPERTIES

(1) The lower amines are colourless gases at room temperature. Those with four or more carbons are volatile liquids. The higher-molecular-weight amines are colourless solids.

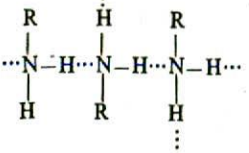
(2) **Odour**. Low-molecular-weight amines, such as methylamine and dimethylamine, have strong odours like the smell of ammonia. The odour resembles that of a decaying fish as the size of the alkyl group attached to nitrogen increases. In general, aliphatic amines are said to possess 'fishy' or fishlike odours.

(3) They are all lighter than water.

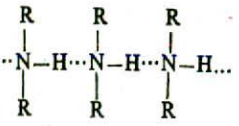
(4) **Boiling points**. Simple amines are polar compounds. Primary amines have two polar N—H bonds, secondary amines have one polar N—H bond, while tertiary amines have none.



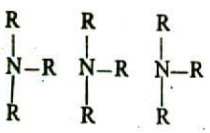
Therefore, primary and secondary amines are polar and capable of forming intermolecular hydrogen bonds by virtue of the presence of unshared electron pair on nitrogen atom. Tertiary amines are also polar but they are not capable of intermolecular hydrogen bonding.



1° amine associated by hydrogen bonds (...)



2° amine associated by hydrogen bonds (...)



hydrogen bonding absent in 3° amines

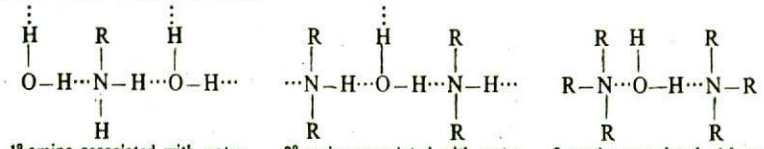
The hydrogen bonds formed by amines (N–H···N) are not as strong as the hydrogen bonds for alcohols (O–H···O) of comparable molecular weight. This is so because nitrogen is less electronegative than oxygen.

On account of their less degree of intermolecular association, the boiling points of primary and secondary amines are lower than those of alcohols of comparable molecular weight. The boiling points of tertiary amines which form no hydrogen bonds are near those of alkanes of comparable molecular weight.

Table. Boiling Points of Amines, Alcohols and Alkanes of comparable molecular weight.

Structure	*Name*	*Molecular Weight*	*Boiling Point °C*
CH_3-OH	methyl alcohol	32	65
CH_3-NH_2	methylamine	31	−6
CH_3-CH_3	ethane	30	−89
CH_3-CH_2-OH	ethyl alcohol	46	78
$CH_3-CH_2-NH_2$	ethylamine	45	17
$CH_3-NH-CH_3$	dimethylamine	45	7
$CH_3-CH_2-CH_3$	propane	44	−42
$CH_3-CH_2-CH_2-OH$	*n*-propyl alcohol	60	97
$CH_3-CH_2-CH_2-NH_2$	*n*-propylamine	59	48
$CH_3-CH_2-NH-CH_3$	ethylmethylamine	59	35
$CH_3-CH_2-CH_2-CH_3$	*n*-butane	58	−0·5
$CH_3-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-OH$	isopropyl alcohol	60	82
$CH_3-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-NH_2$	isopropylamine	59	33
$CH_3-\underset{\displaystyle CH_3}{\underset{\vert}{N}}-CH_3$	trimethylamine	59	4
$CH_3-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_3$	isobutane	58	−12

(5) **Solubility.** All amines including tertiary amines are capable of hydrogen-bond association with water molecules.



1° amine associated with water 2° amine associated with water 3 amine associated with water

Therefore, low-molecular-weight amines (less than six carbon atoms) are very soluble in water. The water solubility of amines decreases with increasing size of the alkyl group.

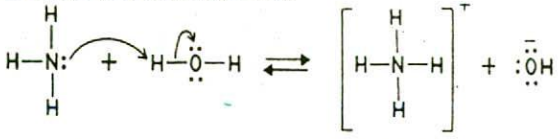
Amine	CH_3NH_2	$(CH_3)_2NH$	$(CH_3)_3NH$	$CH_2C_2NH_2$	$(CH_3CH_2)_2NH$	$(CH_3CH)_{33}N$
Solubility in 100 g H_2O	very soluble	very soluble	91 g	very soluble	very soluble	14 g

Large aliphatic amines are soluble in organic solvents such as benzene, ethanol, ether and chloroform.

(6) Many amines are capable of producing serious physiological effects. The low-molecular weight volatile amines are irritants and cardiac stimulants, like ammonia.

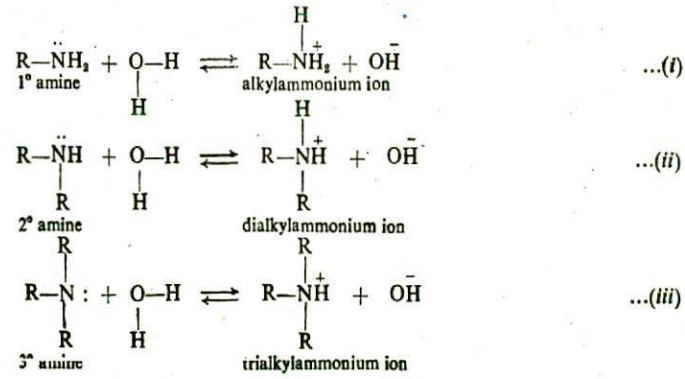
BASICITIES OF AMINES

The unshared electron pair on the nitrogen atom of ammonia and amines is responsible for their basic character. Ammonia when dissolved in water abstracts a proton from water molecule to form ammonium ion and hydroxide ion.



AMMONIA AMMONIUM ION

Similarly, all the three types of amines (1°, 2° and 3°) react reversibly with water to form the alkyl-substituted ammonium ions and hydroxide ions.



1° amine alkylammonium ion ...(*i*)

2° amine dialkylammonium ion ...(*ii*)

3° amine trialkylammonium ion ...(*iii*)

Evidently, aqueous solutions of ammonia and amines are alkaline in nature because of the formation of hydroxide ions as a result of the above equilibria. The value of K_b (also called dissociation constant of the base) gives a measure of the base strength. Therefore equation (*i*) for a 1° amine the value of K_b may be expressed as

$$K_b = \frac{[R\overset{+}{N}H_3]\,[\overset{-}{O}H]}{[RNH_2]\,[H_2O]}$$

Since water is present in large excess its concentration remains practically constant, and the above expression is therefore written as

$$K_b = \frac{[\overset{+}{R}\overset{}{N}H_3]\,[\overset{-}{O}H]}{[RNH_2]}$$

It is clear from this expression that larger the value of K_b, the stronger would be the base. The value of K_b for ammonia and a few amines are given below.

Structure	*Name*	K_b	*Structure*	*Name*	K_b
NH_3	ammonia	$0{\cdot}2\times10^{-4}$			
CH_3-NH_2	methylamine	$4{\cdot}2\times10^{-4}$	$CH_3CH_2-NH_2$	ethylamine	$4{\cdot}7\times10^{-4}$
$CH_3-NH-CH_3$	dimethylamine	$6{\cdot}0\times10^{-4}$	$CH_3CH_2-NH-CH_2CH_3$	diethylamine	$3{\cdot}5\times10^{-4}$
$CH_3-N(CH_3)-CH_3$	trimethylamine	$0{\cdot}6\times10^{-4}$	$CH_3CH_2-N(CH_2CH_3)-CH_2CH_3$	triethylamine	$5{\cdot}5\times10^{-5}$

A look at the values of K_b listed in the table shows that all amines are stronger bases than ammonia. It is also revealed that 2° amines are more basic than 1° amines but 3° amines are less basic than 2° amines. Thus the value of K_b for methylamine is $4{\cdot}2\times10^{-4}$, that of dimethylamine is slightly higher ($6{\cdot}0\times10^{-4}$) and for trimethylamine the value of K_b again declines to as low as $0{\cdot}6\times10^{-4}$. The sequence of basic strengths in general is

$$\underset{\text{1° amine}}{R-\overset{+}{N}H_3} < \underset{\text{2° amine}}{R-NH-R} > \underset{\text{3° amine}}{R-N(R)-R}$$

Interpretation of Relative Strengths of Amines. The differences in the base strengths of amines are accounted for by the degree of availability of the unshared electron pair on the nitrogen of an amine. Alkyl groups are electron-releasing compared to hydrogen atom. Thus when in a primary amine hydrogen of ammonia is replaced by an alkyl group, electrons will shift toward the nitrogen relative to the situation in ammonia.



ammonia 1° amine

Fig. 28·4 Shift of electrons to nitrogen (indicated by ⟶) enhances the availability of unshared electron pair of nitrogen.

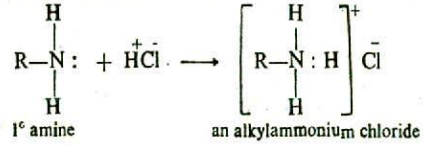
Hence there will be more electrons close to nitrogen in RNH_2 than in ammonia, and the unshared electron pair on nitrogen is more available to react with proton from water molecule. That is why methylamine is a stronger base than ammonia. Following the same line of argument dimethylamine having two electron-releasing methyl groups attached to the nitrogen atom, is a stronger base than methylamine. If so, trimethylamine having three methyl groups attached to nitrogen should be expected to be more basic than dimethylamine. But actually trimethylamine is considerably less basic than dimethylamine. Why so? In methylamine and dimethylamine the 'electronic effect' described above increases the base strength of the amine. However, in trimethylamine the overcrowding of the three methyl groups attached to nitrogen causes the 'steric effect' to dominate over the 'electronic effect'. This steric effect retards the protonation of nitrogen which results in an appreciably lower base strength of trimethylamine.

CHEMICAL PROPERTIES

The chemical reactions of amines are due to (*i*) their basic character; and (*ii*) the reactive hydrogen atoms attached to nitrogen. Some of these reactions are listed below.

(1) **Formation of Salts with Mineral Acids.** Owing to the presence of an unshared electron pair on nitrogen, amines act as Lewis bases. Thus they react with aqueous mineral acids to form substituted ammonium salts. For illustration with aqueous hydrochloric acid,

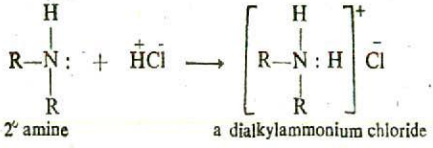
(i) 1° amines form alkylammonium salts :



or $R{-}NH_2 + H\overset{+}{C}l\overset{-}{} \longrightarrow R{-}\overset{+}{N}H_3\overset{-}{C}l$

e.g., $CH_3{-}NH_2 + H\overset{+}{C}l\overset{-}{} \longrightarrow CH_3{-}\overset{+}{N}H_3\overset{-}{C}l$
methylammonium chloride

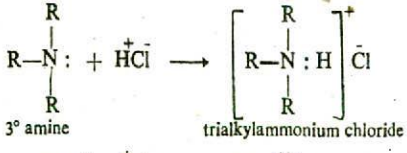
(ii) 2° amines form dialkylammonium salts :



or $R{-}\underset{R}{\underset{|}{N}}H + H\overset{+}{C}l\overset{-}{} \longrightarrow R{-}\underset{R}{\underset{|}{\overset{+}{N}}}H_2\overset{-}{C}l$

e.g., $CH_3{-}\underset{CH_3}{\underset{|}{N}}H + H\overset{+}{C}l\overset{-}{} \longrightarrow CH_3{-}\underset{CH_3}{\underset{|}{\overset{+}{N}}}H_2\overset{-}{C}l$
dimethylamine — dimethylammonium chloride

(iii). 3° amines form trialkylammonium salts :



or $R_3N + H\overset{+}{C}l\overset{-}{} \longrightarrow R_3\overset{+}{N}H\overset{-}{C}l$

e.g., $(CH_3)_3N + H\overset{+}{C}l\overset{-}{} \longrightarrow (CH_3)_3\overset{+}{N}H\overset{-}{C}l$
trimethylamine — trimethylamine chloride

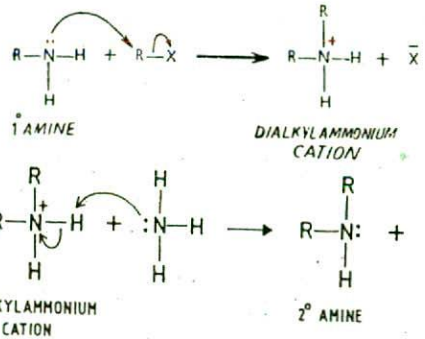
The amine salts are generally well-defined crystalline substances with sharp melting points and are often useful for the identification of amines. Further, these amine salts, unlike the amines, are water soluble and regenerate the amines on treatment with a strong alkali such as NaOH *e.g.*,

$$\underset{\text{alkylammonium salt}}{R{-}\overset{+}{N}H_3\overset{-}{C}l} + NaOH \longrightarrow \underset{1° \text{ amine}}{R{-}NH_2} + H_2O + \overset{+}{N}a\overset{-}{C}l$$

This property is made use of in purifying amines from nonbasic contaminants.

(2) **Alkylation Reactions.** The unshared electron pair on the nitrogen atom makes amines behave as strong nucleophiles. Thus when a primary amine is treated with an alkyl halide in a basic medium such as ammonia, the halogen atom of the alkyl halide is displaced

yielding dialkylammonium salt. The dialkylammonium salt in the presence of ammonia at once gives a secondary amine.



The net alkylation reaction of a primary amine with alkyl halide may be written as

$$\underset{1^\circ \text{ amine}}{R{-}NH_2} + \underset{\text{ethyl halide}}{R{-}X} \longrightarrow \underset{2^\circ \text{ amine}}{R{-}NH{-}R} + \underset{\text{halogen acid}}{HX}$$

The secondary amine undergoes similar reaction with a second molecule of alkyl halide to form a tertiary amine. The tertiary amine finally reacts with a third molecule of alkyl halide to produce the tetraalkylammonium salt. These multiple alkylation reactions of amines may be illustrated by the action of methyl bromide on methylamine.

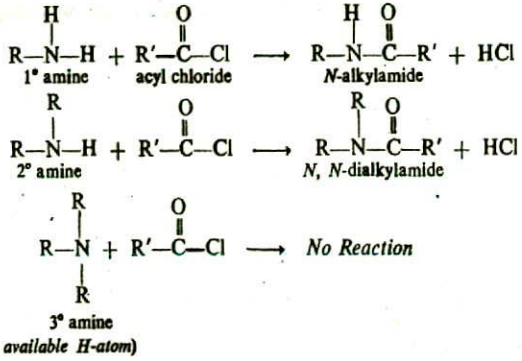
$$\underset{\substack{\text{methylamine}\\(1^\circ \text{ amine})}}{CH_3{-}\ddot{N}H_2} + CH_3{-}Br \longrightarrow \underset{\substack{\text{dimethylamine}\\(2^\circ \text{ amine})}}{CH_3{-}NH{-}CH_3} + HBr$$

$$CH_3{-}NH{-}CH_3 + \underset{\text{(2nd molecule)}}{CH_3{-}Br} \longrightarrow \underset{\substack{\text{trimethylamine } (3^\circ \text{ amine})\\ \text{(tertiary amine)}}}{CH_3{-}N(CH_3)_2} + HBr$$

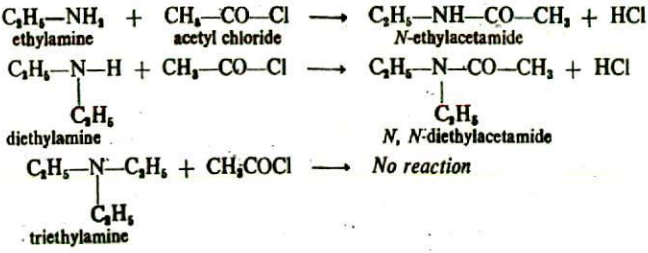
$$CH_3{-}N(CH_3)_2 + \underset{\text{(3rd molecule)}}{CH_3{-}Br} \longrightarrow \underset{\text{tetramethylammonium bromide}}{[(CH_3)_4N]^+Br^-}$$

From the above equations it is clear that a primary amine will need three molecules of alkyl halide per molecule of amine, secondary amine two molecules, and a tertiary amine only one molecule to form the final tetraalkylammonium salt. Thus by experimentally determining the amount of alkyl halide actually used for the conversion of a given amine to the tetralkylammonium salt, it is possible to distinguish between primary, secondary and tertiary amines. Also, the alkylation of a primary and secondary amine under regulated conditions provides an industrial method for the preparation of secondary and tertiary amine respectively.

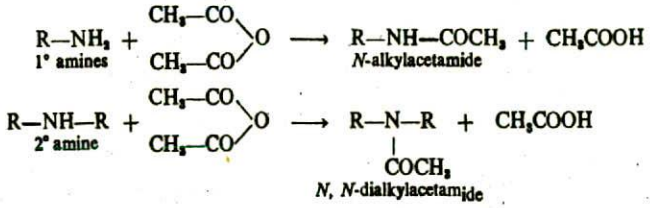
(3) **Acylation.** Primary and secondary amines react with acyl halides (RCOCl) and carboxylic anhydrides whereby the hydrogen atom attached to nitrogen atom is replaced by acyl group (RCO—). By this process of *acylation* a primary amine produces *N*-substituted amide while a secondary amine yields *N, N*-disubstituted amide. A tertiary amine having no available hydrogen on nitrogen, does not react at all either with acyl halides or carboxylic anhydrides.



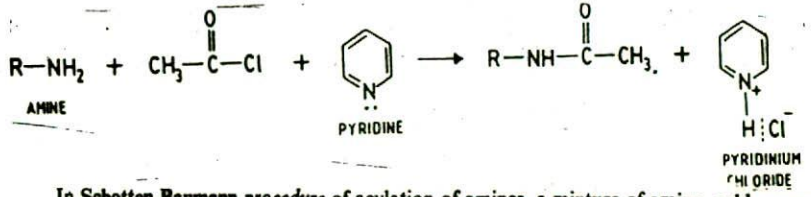
For example,



As stated above, primary and secondary amines also react with carboxylic anhydrides to give substituted amides.



In all the above reactions, acylation of amines is carried out effectively in the presence of tertiary amines which help the removal of the acid (HCl or CH_3COOH). The tertiary amine which is most often used as 'acid scavenger' is the aromatic base pyridine. Thus

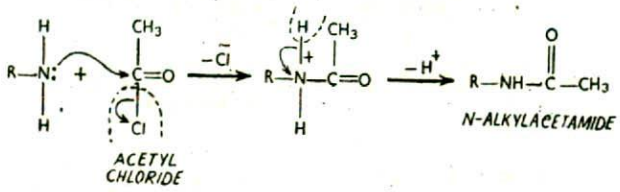


In **Schotten-Baumann** *procedure* of acylation of amines, a mixture of amine, cold aqueous base (NaOH or Na_2CO_3) is shaken together. The aqueous alkali acts as scavenger for the HX produced.

$$R{-}NH_2 + CH_3COCl + NaOH \xrightarrow{\text{cold}} R{-}NH{-}COCH_3 + NaCl + H_2O$$

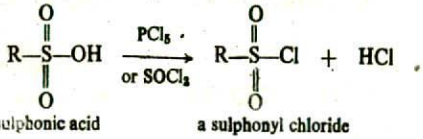
Mechanism of Acylation of Amines. The unshared electron pair on nitrogen plays a key role in amide formation by acylation of amines. The reaction takes place by the nucleophilic

attack of the primary or secondary amine on to the carbonyl group of acyl chloride. This is accompanied by the loss of Cl^- and a proton.

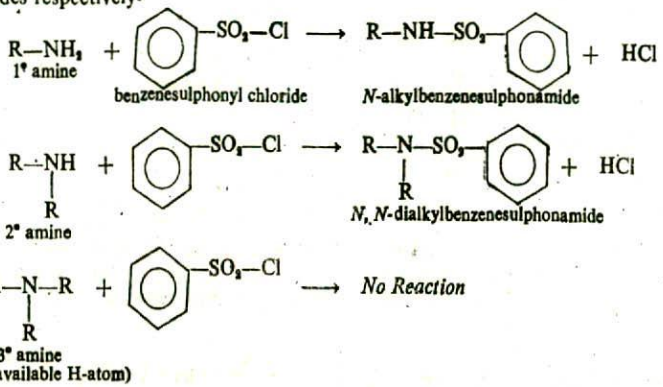


The above mechanism of acylation of amines also shows why only one of the two hydrogens of a primary amine is replaced by acyl group in actual practice. The *N*-acylamine first produced is far less basic than the original amine, because of electron-withdrawal from the nitrogen atom by induction and resonance. Therefore, further acylation of *N*-acylamine does not take place and as a result only one acyl group can be introduced into a primary amines.

(4) **Sulphonylation.** Sulphonyl chlorides are the acid chlorides produced by the reaction of phosphorus pentachloride or thionyl chloride ($SOCl_2$).



They react with amines in a manner similar to acyl chlorides. Thus benzenesulphonyl chloride ($C_6H_5SO_2Cl$) reacts with primary and secondary amines to from *N*-alkyl and *N*, *N*-dialkyl-sulphonamides respectively.



Most sulphonamides are crystalline solids. Their preparation and determination of melting point is used for the identification of primary and secondary amines.

Hinsberg Test for distinguishing 1°, 2° and 3° amines. The reactions of amines with benzenesulphonyl chloride form the basis of the classical *Hinsberg Test* to determine the class of an amine. In this test the given amine is treated with benzenesulphonyl chloride (Hinsberg Reagent) in the presence of cold aqueous NaOH.

(*a*) A PRIMARY AMINE produces *N*-alkylsulphonamide which contains an acidic hydrogen and hence dissolves in NaOH solution to form the soluble sodium salt. The acidification of the solution gives a precipitate of the nonbasic free sulphonamide.

$$\underset{1^\circ\text{ amine}}{RNH_2} + C_6H_5{-}SO_2{-}Cl \xrightarrow[H_2O]{NaOH} \underset{\text{acidic hydrogen}}{R{-}NH{-}SO_2{-}C_6H_5} \xrightarrow{NaOH} \underset{\substack{\text{sodium salt}\\(\textit{water soluble})}}{R{-}\overset{-}{N}{-}SO_2{-}C_6H_5}\ (\overset{+}{Na})$$

$$R{-}\overset{-}{N}{-}SO_2{-}C_6H_5\ (\overset{+}{Na}) \xrightarrow[H_2O]{H^+} \underset{\substack{\text{free sulphonamide}\\(\textit{insoluble in acid})}}{R{-}NH{-}SO_2{-}C_6H_5}$$

The unusual acidity of *N*-alkylsulphonamides is due to the powerful electron-withdrawing inductive effect of the sulphonyl group ($-SO_2-$).

(*b*) A SECONDARY AMINE yields *N*, *N*-dialkylsulphonamide which has no acidic hydrogen precipitates immediately as it is incapble of forming soluble sodium salt with NaOH.

$$\underset{2^\circ\text{ amine}}{R_2NH} + C_6H_5{-}SO_2{-}Cl \xrightarrow[H_2O]{NaOH} \underset{\substack{\text{no acidic hydrogen}\\N,\,N\text{-dialkylsulphonamide}\\(\textit{insoluble ppt})}}{R_2N{-}SO_2{-}C_6H_5} \xrightarrow{NaOH} \textit{No Reaction}$$

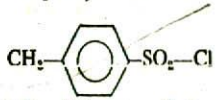
(*c*) A TERTIARY AMINE having no available hydrogen does not react and remain as insoluble material.

To apply the Hinsberg test, the amine to be tested is shaken with benzenesulphonyl chloride and cold aqueous NaOH. If a homogeneous solution results which on acidification forms a precipitate, the amine is primary. If an insoluble material is produced in the reaction mixture straightaway (without acidification), the amine is either secondary (the insoluble material being dialkylsulphonamide) or tertiary (insoluble material being unreacted amine). To distinguish between the secondary and tertiary amines, the insoluble material is acidified. A tertiary amine if present will form a soluble quaternary salt and dissolve, while a sulphonamide from a secondary amine being neutral remains insoluble material.

Table. Summary of Hinsberg Test

$\underset{1^\circ\text{ amine}}{R{-}NH_2} + C_6H_5{-}SO_2{-}Cl$	$\xrightarrow[H_2O]{NaOH}$ *clear solution*	$\xrightarrow{\text{acidify}}$ *insoluble material*
$R{-}\underset{\underset{R}{\vert}}{NH} + C_6H_5{-}SO_2{-}Cl$ (2° amine)	$\xrightarrow[H_2O]{NaOH}$ *insoluble material*	$\xrightarrow{\text{acidify}}$ *insoluble material*
$R{-}\underset{\underset{R}{\vert}}{N}{-}R + C_6H_5{-}SO_2{-}Cl$ (3° amine)	$\xrightarrow[H_2O]{NaOH}$ *insoluble material*	$\xrightarrow{\text{acidify}}$ *clear solution*

In modern practice benzenesulphonyl chloride is also replaced by *p*-toluenesulphonyl chloride,



(5) **Reaction with Nitrous Acid.** Nitrous acid is an unstable substance prepared when required, by reaction between a mineral acid and sodium nitrite ($NaNO_2$).

$$\overset{+}{Na}\overset{-}{NO_2} + HCl \longrightarrow \underset{\text{nitrous acid}}{HO{-}N{=}O} + H_2O$$

Primary, Secondary and Tertiary amines give characteristic reactions with nitrous acid.

(*i*) *Primary amines* (RNH_2) which have two available hydrogen atoms on nitrogen react with nitrous acid in aqueous solution to form the corresponding alcohols.

$$\underset{1^\circ \text{ amine}}{R{-}NH_2} + \underset{\text{nitrous acid}}{O{=}N{-}OH} \longrightarrow \underset{\textit{unstable}}{R{-}N{=}N{-}OH} \longrightarrow \underset{\text{alcohol}}{R{-}OH} + N_2\uparrow$$

The reaction is not that simple as stated above. In fact, primary amines react with nitrous acid to give mixtures of a variety of products which contain alcohols, alkenes, and even halides, if halide ion is present. For example, if the primary amine taken is *n*-propylamine, the products will include *n*-propyl alcohol, isopropyl alcohol, propene, propyl chloride and isopropyl chloride.

$$\underset{n\text{-propylamine}}{CH_3CH_2CH_2NH_2} \xrightarrow[(HCl)]{HONO} \left|\begin{array}{l} CH_3CH_2CH_2{-}OH \\ \\ CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3 \\ \\ CH_3{-}CH{=}CH_2 \\ \\ CH_3CH_2CH_2{-}Cl \\ \\ CH_3{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}CH_3 \end{array}\right| + N_2 + H_2O$$

The exact nature and proportions of products obtained depends very much on the structure of the amine and the specific reaction conditions employed.

The formation of various products obtained from *n*-propylamine by the above mechahism may be indicated as below.

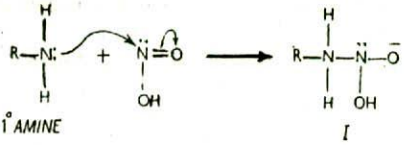
$$\underset{\text{I}}{CH_3{-}\overset{+}{C}H_2{-}CH_3} \left|\begin{array}{lcl} + \ddot{H}_2O & \longrightarrow & CH_3{-}CH_2{-}CH_2{-}\overset{+}{O}H_2 \xrightarrow{-H^+} CH_3CH_2CH_2OH \\ - H^+ & \longrightarrow & CH_3{-}CH{=}CH_2 \\ + Cl^- & \longrightarrow & CH_3{-}CH_2{-}CH_2Cl \end{array}\right.$$

$$\underset{\text{II}}{CH_3{-}\overset{+}{C}H{-}CH_3} \left|\begin{array}{lcl} & & \overset{+}{O}H_2 \\ & & | \\ + \ddot{H}_2O & \longrightarrow & CH_3{-}CH{-}CH_3 \xrightarrow{-H^+} \underset{\displaystyle OH}{\underset{|}{CH_3{-}CH{-}CH_3}} \\ - H^+ & \longrightarrow & CH_3{-}CH{=}CH_2 \\ & & \underset{\displaystyle Cl}{\underset{|}{} } \\ + Cl^- & \longrightarrow & CH_3{-}CH{-}CH_3 \end{array}\right.$$

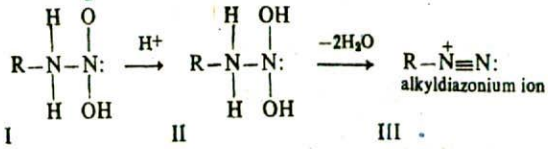
It may be noted particularly that whatever may be the products of the reaction, nitrogen is always evolved.

MECHANISM. The various products obtained from primary amines by reaction with nitrous acid are formed by the following steps.

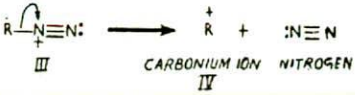
(*a*) Nucleophilic addition of the amine RNH_2 to nitrogen-oxygen double bond of nitrous acid to give the adduct I.



(*b*) Protonation of I followed by elimination of the molecules of water to form alkyldiazonium ion.



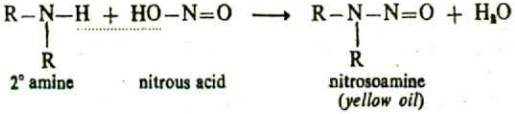
(*c*) Alkyldiazonium ion III is unstable and loses nitrogen (N≡N) to generate carbonium ion IV.



The carbonum ion IV may rearrange to give more stable carbonium ion V (not shown).

(*d*) The carbonium ion IV and V may react with water (H_2O) to form alcohols, lose a proton to form alkanes, or add halide ion (Cl^-) to yield alkyl halides.

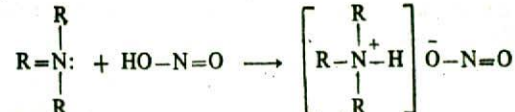
(*ii*) *Secondary amines* (R_2NH) react with nitrous acid (HO−N=O) to give neutral, yellow oily substances called *Nitrosoamines*. The process which involves the replacement of the available hydrogen on nitrogen by nitroso group (−N=O) is termed **Nitrosation**.



When warmed with a little phenol and a few drops of conc H_2SO_4, nitrosoamines produce green solution which turns deep blue or violet on alkalification with NaOH. This reaction known as **Liebermann Nitrosoamine Reaction** is used as a test for secondary amines.

Nitrosoamines are generally poisonous and are considered to be cancer-causing agent. In some foods sodium nitrite is used as preservative and in the stomach it combines with hydrochloric acid to produce nitrous acid. This can react with any secondary amines present in foods to form a dangerous nitrosoamine. Therefore, the intake of sodium nitrite in any form should be avoided.

(*iii*) *Tertiary amines* (R_3N) having no available hydrogen on nitrogen fail to give a replacement reaction with nitrous acid. They simply form soluble trialkylammonium salts of nitrous acid.



The tertiary amine can be regenerated from the salt solution by addition of alkali.

The reaction of aliphatic amines with nitrous acid is used as a test for distinguishing primary, secondary and tertiary amines.

(*a*) *Primary amines* react with rapid evolution of nitrogen gas.

$$R-NH_2 \xrightarrow{HONO} \underset{\text{carbonium ion}}{R^+} + N_2\uparrow$$

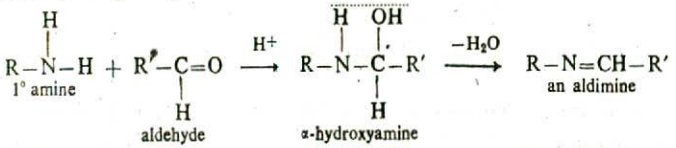
(*b*) *Secondary amines* form an insoluble yellow oily layer.

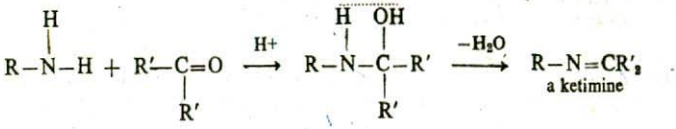
$$R_2NH \xrightarrow{HONO} \underset{\text{nitrosoamine}}{R_2N-NO}$$

(*c*) *Tertiary amines* form a homogeneous solution.

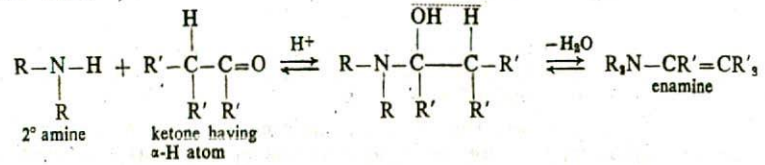
$$R_3N \xrightarrow{HONO} \underset{\text{soluble salt}}{[R_3NH]^+\ O-N=\bar{O}}$$

(6) **Reaction with Aldehydes and Ketones.** (*a*) *Primary amines* add readily to the C=O group of aldehydes and ketones to form α-hydroxyamines, also called *Carbinolamines*. These undergo spontaneous elimination of a water molecule yielding substituted *imines* or *Schiff bases*. The reaction is catalysed by acids.





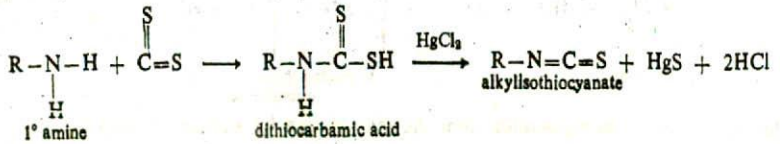
(*b*) *Secondary amines* react with aldehydes and ketones that have α−H atoms when transitory α-hydroxyamine at once splits out a water molecule to form compounds known as *enamines*. Thus,



In enamine the basic nitrogen is attached directly to an olefinic carbon. These compounds are useful synthetic intermediates.

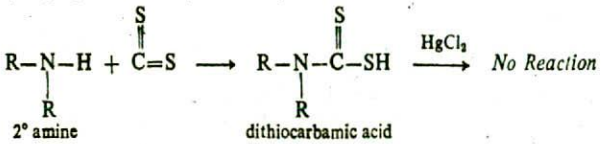
(*c*) *Tertiary amines* having no hydrogen on nitrogen naturally cannot react with aldehydes and ketones.

(7) **Reaction with Carbon disulphide.** (*a*) *Primary amines* when reacted with carbon disulphide (CS_2) form dithiocarbamic acids which on subsequent treatment with $HgCl_2$ give an alkyl isocyanate or 'mustard oil'.



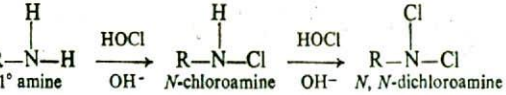
The isothiocyanate thus produced has a pungent 'mustard like' odour which can be easily recognised. Hence this reaction (*Hofmann Mustard Oil Reaction*) is used as a test for primary amines.

(*b*) *Secondary amines* react with carbon disulphide to give dithiocarbamic acid which is not decomposed by $HgCl_2$ to form alkyl isothiocyanate.

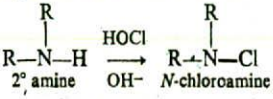


(*c*) *Tertiary amines* having no available hydrogen atom on nitrogen do not react with CS_2.

(8) **Halogenation.** Primary and secondary amines react rapidly with a solution of hypochlorous acid in the presence of a base to produce *N*-chloroamines or *N*, *N*-dichloroamines.

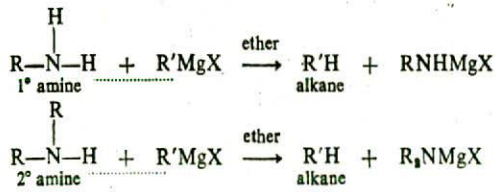


Secondary amines give mono-*N*-chloroamines

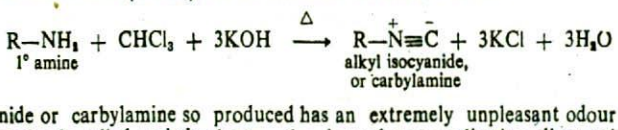


The chlorination of amines is carried more conveniently with *t*-butyl hypochlorite, $(CH_3)_3C{-}OCl$.

(9) **Reaction with Grignard Reagents.** Primary and secondary amines react with Grignard reagents to form alkanes. Tertiary amines do not react since they do not contain a replaceable hydrogen atom.



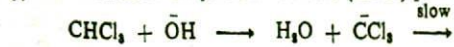
(10) **Carbylamine Reaction.** Primary amines form isocyanides or *carbylamines* when warmed with chloroform ($CHCl_3$) and an ethanolic solution of KOH.



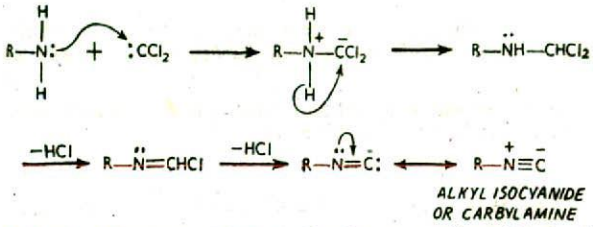
The isocyanide or carbylamine so produced has an extremely unpleasant odour and hence this reaction, frequently called *carbylamine reaction*, is used as a qualitative diagnostic test (**Carbylamine Test**) for primary amines. Secondary and tertiary amines do not respond to this test.

MECHANISM. The formatian of carbylamine takes the following pathway.

(*i*) Chloroform in the presence of base (KOH) produces dichlorocarbene ($:CCl_2$).



(*ii*) Nucleophilic addition of primary amine to dichlorocarbene and subsequent elimination of two HCl molecules yields the isocyanide.



(11) **Oxidation of Amines.** All types of amines are easily oxidised. The course of the reaction is very variable and depends very much on the structure of the amine and the specific oxidant used.

(*a*) *Primary amines* on oxidation with acidified $KMnO_4$ give aldehydes and ammonia.

$$R{-}CH_2{-}NH_2 \xrightarrow{O} R{-}CH{=}NH \xrightarrow[H^+]{+H_2O} R{-}CH{=}O + NH_3$$

aldimine — aldehyde

$$R{-}\underset{R}{\underset{|}{CH}}{-}NH_2 \xrightarrow{O} R{-}\underset{R}{\underset{|}{C}}{=}NH \xrightarrow[H+]{+H_2O} R{-}\underset{R}{\underset{|}{C}}{=}O + NH_3$$

ketimine — ketone

$$R{-}\underset{R}{\overset{R}{\overset{|}{\underset{|}{C}}}}{-}NH_2 \xrightarrow{O} R{-}\underset{R}{\overset{R}{\overset{|}{\underset{|}{C}}}}{-}NO_2$$

a nitroalkane

(*b*) Secondary amines on oxidation with $KMnO_4$ give tetraalkylhydrazine, while with H_2O_2 or peracid they yield dialkylhydroxylamine.

$$2\,R{-}\underset{R}{\underset{|}{N}}{-}H + [O] \xrightarrow{KMnO_4} R{-}\underset{R}{\underset{|}{N}}{-}\underset{R}{\underset{|}{N}}{-}R + H_2O$$

tetraalkylhydrazine

$$R{-}\underset{R}{\underset{|}{N}}{-}H + [O] \xrightarrow[\text{or peracid}]{H_2O_2} R{-}\underset{R}{\underset{|}{N}}{-}OH$$

dialkylhydroxylamine

(*c*) *Tertiary amines* from amine oxides when oxidised with H_2O_2 or peracids.

$$R{-}\underset{R}{\overset{R}{\overset{|}{\underset{|}{N}}}}{:} + \ddot{O}: \xrightarrow[\text{or peracid}]{H_2O_2} R{-}\overset{R}{\overset{|}{\underset{R}{\overset{|}{\overset{+}{N}}}}}{-}\overset{-}{O}$$

amine oxide

e.g., $(CH_3)_3N + [O] \xrightarrow{H_2O_2} (CH_3)_3\overset{+}{N}{-}\overset{-}{O}$

trimethylamine — trimethylamine *N* oxide

IR AND NMR SPECTRA OF AMINES

A characteristic feature of infrared spectra of 1° and 2° amines in dilute solutions is the absorption at 3500–3300 cm^{-1}, corresponding to N–H stretching. 1° amines have two such bonds, 2° amines only one, while 3° amines (which contain no N–H bond) do not absorb in this region. Furthermore, the area generated by one or two amino protons is generally quite small as compared with the rest of the spectrum. Hence, the amino protons are sometimes observed by absorptions arising from other parts of the molecular structure. This complicates the interpretation of the spectrum.

The NMR spectra of amines show characteristic absorptions for $N-\overset{|}{\underset{|}{C}}-N$ protons around 2·7 ppm. The resonances of N—H bonds are not easily identified. Thus in case of diethylamine (Fig. 28·1), the N—H resonance has nearly the same chemical shift as the resonance of C—CH_3 protons.

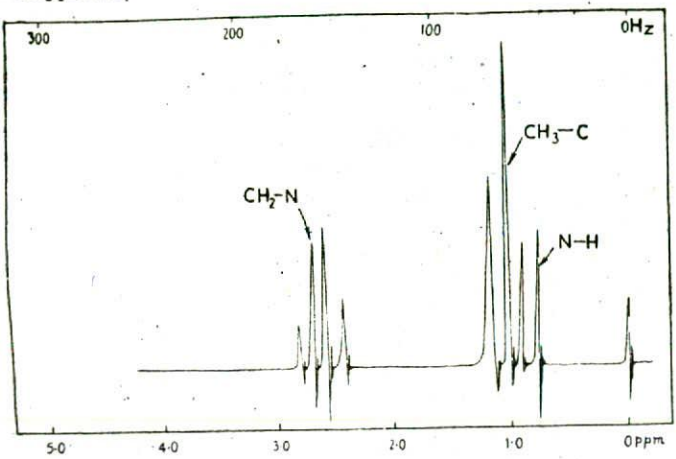


Fig. 28·4. NMR spectrum of Diethylamine.

METHYLAMINE, $CH_3—NH_2$

It is the simplest amine known. It is produced during the dry distillation of wood and bones

Preparation. (1) Methylamine is best prepared in the laboratory by the action of alkali on acetamide (*Hofmann Degradation Reaction*).

$$\underset{\text{acetamide}}{CH_3—CO—NH_2} + Br_2 + 3NaOH \longrightarrow \underset{\text{methylamine}}{CH_3—NH_2} + 2NaBr + NaHCO_3 + H_2O$$

(2) Industrially, it is obtained by heating ammonium chloride with two equivalents of formaldehyde (formalin).

$$\underset{}{\overset{+}{N}H_4\bar{C}l} + \underset{\text{formaldehyde}}{2HCHO} \longrightarrow \underset{\text{methylammonium chloride}}{CH_3\overset{+}{N}H_3\bar{C}l} + HCOOH$$

Free methylamine is, however, liberated by treating the salt with a base.

(3) By passing a mixture of the vapours of methyl alcohol and ammonia over heated alumina.

$$\underset{\text{methyl alcohol}}{CH_3-OH} + \underset{\text{ammonia}}{H-NH_2} \xrightarrow[450°]{Al_2O_3} \underset{\text{methylamine}}{CH_3—NH_2} + H_2O$$

Here methylamine further reacts with excess of methyl alcohol to form dimethylamine and trimethylamine. Methylamine being a gas can be easily separated from di- and trimethylamines.

Properties. (*Physical*). Methylamine is a colourless gas having ammonia-like fishy odour. Upon cooling it condenses to a liquid which boils at $-6°C$. It is exceedingly soluble in water, giving alkaline solution. Its K_b (at 25°C) is $4·2 \times 10^{-4}$. Thus it is a far weaker base than sodium hydroxide.

(*Chemical*). Chemically, methylamine behaves as a typical primary amine and gives all the general reactions described before. It combines with hydrochloric acid to form methylammonium chloride which is hygroscopic in nature

$$\underset{}{CH_3—NH_2} + \overset{+}{H}\bar{C}l \longrightarrow \underset{\text{methylammonium chloride}}{CH_3—\overset{+}{N}H_3\bar{C}l}$$

Methylamine is used as a refrigerant.

ETHYLAMINE, $CH_3CH_2—NH_2$

It is the second member of the homologous series of primary amines.

Preparation. (1) In the laboratory, ethylamine is prepared by Hofmann's degradation using propionamide.

$$\underset{\text{propionamide}}{CH_3CH_2—CO—NH_2} + Br_2 + 3NaOH \longrightarrow \underset{\text{ethylamine}}{CH_3CH_2—NH_2} + 2NaBr + NaHCO_3 + H_2O$$

(2) Industrially, it is obtained by passing a mixture of ethylene and ammonia under a high pressure (20 atmos.) over a cobalt catalyst at 400–500°.

$$CH_2=CH_2 + NH_3 \xrightarrow[400—540°]{\text{Co catalyst}} \underset{\text{ethylamine}}{CH_3—CH_2—NH_2}$$

Properties. Ethylamine is a colourless liquid, bp. 17°C. It has strong ammonia-like odour and a bitter taste. It is highly soluble in water. It is slightly more basic than methylamine, its K_b being $4{\cdot}7 \times 10^{-4}$.

Ethylamine gives all the chemical reactions typical of a 1° amine

$C_2H_5—NH_2$
ethylamine

$+ \overset{+}{H}\overset{-}{Cl} \longrightarrow \underset{\text{ethylammonium chloride}}{C_2H_5\overset{+}{N}H_3\overset{-}{Cl}}$

$+ CH_3Br \xrightarrow[OH^-]{-HBr} \underset{\text{ethylmethylamine}}{C_2H_5NHCH_3} \xrightarrow{CH_3Br} \underset{\text{ethyldimethylamine}}{C_2H_5N(CH_3)_2} \xrightarrow{CH_3Br} \underset{4° \text{ salt}}{C_2H_5\overset{+}{N}(CH_3)_3\bar{B}r}$

$+ CH_3COCl \longrightarrow \underset{N\text{-ethylacetamide}}{C_2H_5—NH—COCH_3} + HCl$

$+ C_6H_5SO_2Cl \longrightarrow \underset{N\text{-ethylbenzenesulphonamide}}{C_2H_5—NH—SO_2—C_6H_5} \xrightarrow{NaOH} \underset{\text{soluble sod. salt}}{C_2H_5—\overset{+}{N}\overset{Na}{}—SO_2—C_6H_5}$

$+ HONO \longrightarrow \underset{\text{ethyl alcohol}}{C_2H_5OH} + N_2\uparrow + H_2O$

$+ RCHO \longrightarrow \underset{\text{aldimine}}{C_2H_5—N=CH—R}$

$+ CS_2 \longrightarrow \underset{\text{dithiocarbamic acid}}{C_2H_5—NH—CS—SH} \xrightarrow{HgCl_2} \underset{\text{ethyl isothiocyanate}}{C_2H_5—N=C=S} + HgS + 2HCl$

$+ HOCl \xrightarrow{O\bar{H}} \underset{N\text{-chloroethylamine}}{C_2H_5—NHCl} \xrightarrow[OH^-]{HOCl} \underset{N,N\text{-dichloroethylamine}}{C_2H_5—NCl_2}$

$+ RMgX \xrightarrow[\text{alkane}]{\text{ether}} RH + C_2H_5NHMgX$

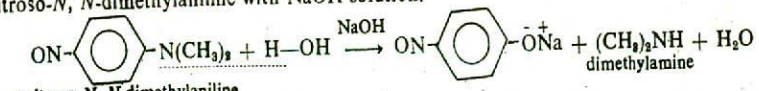
$+ CHCl_3 + 3KOH \xrightarrow{\Delta} \underset{\text{ethyl isocyanide}}{C_2H_5—\overset{+}{N}\equiv\bar{C}} + 3KCl + 3H_2O$

$+ O \xrightarrow{KMnO_4} \underset{\text{aldimine}}{CH_3—CH—NH} \xrightarrow[H^+]{+H_2O} \underset{\text{acetaldehyde}}{CH_3—CHO} + NH_3$

DIMETHYLAMINE, $CH_3—NH—CH_3$

It occurs in small quantities in *Peruvian guano* and pyroligneous acid.

Preparation. (1) Dimethylamine can be prepared in a pure state by the hydrolysis of *p*-nitroso-*N*, *N*-dimethylaniline with NaOH solution.



p-nitroso-*N*, *N*-dimethylaniline

(2) By heating ammonium chloride with four equivalents of formaldehyde (formalin).

$$NH_4Cl + 4HCHO \longrightarrow \underset{\text{Dimethylammonium chloride}}{(CH_3)_2NH_2Cl} + 2HCOOH$$

$$(CH_3)_2NH_2Cl + NaOH \longrightarrow \underset{\text{dimethylamine}}{(CH_3)_2NH} + NaCl + H_2O$$

Properties. Dimethylamine is a colourless gas having strong ammoniacal odour. On cooling it condenses to a liquid, bp 7°. It is very soluble in water and a stronger base ($K_b = 6 \times 10^{-4}$) than methylamine.

Chemically it behaves as a typical secondary amine.

$$+ HCl \longrightarrow \underset{\text{dimethylammonium chloride}}{(CH_3)_2NH_2Cl}$$

$$+ CH_3Br \xrightarrow[OH^-]{-HBr} \underset{\text{trimethylamine}}{(CH_3)_3N} \xrightarrow{CH_3Br} \underset{\text{tetramethylammonium bromide}}{(CH_3)_4NBr}$$

$$+ CH_3COCl \longrightarrow \underset{N,\,N\text{-dimethylacetamide}}{(CH_3)_2N—COCH_3} + HCl$$

$$+ C_6H_5SO_2Cl \longrightarrow \underset{\substack{N\text{-dimethylbenzene}\\ \text{sulphonamide}\\ (\textit{insoluble in NaOH soln.})}}{(CH_3)_2N—SO_2—C_6H_5} \xrightarrow{NaOH} \textit{No Reaction}$$

$$+ HONO \xrightarrow{-H_2O} \underset{\substack{N\text{-nitroso-di-}\\ \text{methylamine}\\ (\textit{yellow oil})}}{(CH_3)_2N—NO} \xrightarrow{H_2SO_4} \textit{green} \xrightarrow{NaOH} \textit{deep blue or violet}$$

H_3C, H_3C >NH dimethylamine

$$+ R_2CH—CO—R \longrightarrow \underset{\text{enamine}}{(CH_3)_2N—CR=CR_2}$$

$$+ CS_2 \longrightarrow \underset{\text{dithiocarbamic acid}}{(CH_3)_2N—CS—SH} \xrightarrow{HgCl_2} \textit{No Reaction}$$

$$+ HOCl \xrightarrow{OH^-} \underset{N\text{-chlorodimethylamine}}{(CH_3)_2N—Cl}$$

$$+ R'MgX \xrightarrow{\text{ether}} R'H + (CH_3)_2NMgX$$

$$+ [O] \xrightarrow{KMnO_4} \underset{\text{tetramethylhydrazine}}{(CH_3)_2N—N(CH_3)_2} + H_2O$$

Dimethylamine is used for dehairing of hides.

TRIMETHYLAMINE, $H_3C-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{N}}}}-CH_3$

It is the simplest tertiary amine. It occurs in beet sugar, molasses and excreta of fish.

Preparation. (1) Trimethylamine is prepared by heating a solid mixture of ammonium chloride and paraformaldehyde.

$$2\overset{+}{N}H_4\overset{-}{Cl} + 9HCHO \longrightarrow \underset{\text{trimethylammonium chloride}}{2(CH_3)_3\overset{+}{N}H\overset{-}{Cl}} + 3CO_2 + 3H_2O$$

$$(CH_3)_3\overset{+}{N}H\overset{-}{Cl} + NaOH \longrightarrow \underset{\text{trimethylamine}}{(CH_3)_3N} + \overset{+}{N}a\overset{-}{Cl} + H_2O$$

(2) It is obtained on a large scale by the distillation of beet sugar residues (*molasses*) which contain betaine.

$$\underset{\text{betaine}}{2(CH_3)_3\overset{+}{N}CH_2\overset{-}{C}OO} \xrightarrow{\Delta} \underset{\text{trimethylamine}}{2(CH_3)_3N} + CH_2{=}CH_2 + 2CO_2$$

(3) It may also be prepared by thermal decomposition of tetramethylammonium hydroixde.

$$(CH_3)_4\overset{+}{N}O\overset{-}{H} \xrightarrow{\Delta} (CH_3)_3N + CH_3OH$$

Properties. Trimethylamine is a colourless gas, bp 4°C. It has ammoniacal-fishlike odour. It is fairly soluble in water, solubility 91g/100 g H_2O. It is a weaker base ($K_b = 0{\cdot}6 \times 10^{-4}$) than even dimethylamine.

Chemically, it gives all the reactions of a typical tertiary amine. When oxidised with H_2O_2 or peracid, it forms *N*-oxide.

$$(CH_3)_3N + [O] \xrightarrow{H_2O_2} \underset{\text{trimethylamine-}N\text{-oxide}}{(CH_3)_3\overset{+}{N}-\overset{-}{O}}$$

On heating under pressure with hydrochloric acid, it decomposes to form methyl chloride.

$$\underset{\text{trimethylamine}}{(CH_3)_3N} + 4HCl \xrightarrow[\textit{pressure}]{\Delta} \underset{\text{chloride}}{3CH_3Cl} + NH_4Cl$$

Thus, trimethylamine is used as a source of industrial methyl chloride.

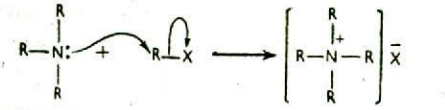
TETRAALKYLAMMONIUM SALTS

They are regarded as derived from ammonium salts in which all the four hydrogen atoms of the ammonium ion have been substituted by alkyl groups. They are commonly referred to as **Quaternary Ammonium Salts.**

$$\underset{\text{ammonium chloride}}{\overset{H}{\underset{H}{\overset{|}{\underset{|}{H-\overset{+}{N}-H}}}}\ \overset{-}{Cl}} \xrightarrow[+4R]{-4H} \underset{\text{tetralkylammonium chloride, or quaternary ammonium chloride}}{\overset{R}{\underset{R}{\overset{|}{\underset{|}{R-\overset{+}{N}-R}}}}\ \overset{-}{Cl}}$$

Quaternary (4°) ammonium salts are completely ionic substances. Tetraalkylammonium ion (R_4N^+) is a stable cation, like Na^+ or K^+, and exists only in combination with amines (X^-). Thus quaternary ammonium salts behave like inorganic salts. The reactions of quaternary salts have no relation, whatever, to those of amines.

Tetraalkylammonium Halides, $R_4\overset{+}{N}\overset{-}{X}$. They are prepared by treating an ethanolic solution of ammonia with excess of alkyl halide (RX) in a sealed tube at 100°. Alternatively, tetraalkylammonium salts can be obtained by direct reaction of a tertiary amine with an alkyl halide.



e.g., $(CH_3)_3N: + CH_3-I \longrightarrow (CH_3)_4\overset{+}{N}\,\overset{-}{I}$
trimethylamine methyl iodide tetramethylammonium iodide

Quaternary ammonium halides are white, crystalline solids, soluble in water in which solution they are completely dissociated. Thus,

$$CH_3-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-CH_3\,\overset{-}{I} \longrightarrow CH_3-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-CH_3 + \overset{-}{I}$$

tetramethylammonium cation

When a quaternary ammonium halide is heated in vacuum, it gives the tertiary amine and alkyl halide.

Quaternary ammonium salts in which one of the four alkyl groups contains a long carbon chain, are used as detergents and germicides.

Tetraalkylammonium Hydroxides, $R_4\overset{+}{N}\overset{-}{O}H$. These are prepared by treatment of quaternary ammonium halides with moist silver oxide (AgOH) in water.

$$R-\overset{R}{\underset{R}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-R\,\overset{-}{X} + AgOH \longrightarrow R-\overset{R}{\underset{R}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-R\,\overset{-}{O}H + AgX\downarrow$$

4° ammonium halide — tetraalkylammonium hydroxide (4° ammonium hydroxide)

For example,

(*a*) $CH_3-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-CH_3\,\overset{-}{I} + AgOH \longrightarrow CH_3-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-CH_3\overset{-}{O}H + AgI$

tetramethylammonium iodide — tetramethylammonium hydroxide

(*b*) $CH_3CH_2CH_2CH_2-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-CH_3\,\overset{-}{I} + AgOH \longrightarrow CH_3CH_2CH_2CH_2-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-CH_3\overset{-}{O}H + AgI$

n-butyl-trimethylammonium iodide — *n*-butyl-trimethylammonium hydroxide

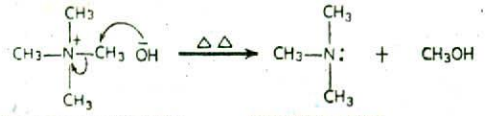
Quaternary ammonium hydroxides are white deliquescent crystalline solids. They are extremely soluble in water. They are completely ionised in solution.

$$R-\overset{R}{\underset{R}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-R\,\overset{-}{O}H \longrightarrow R-\overset{R}{\underset{R}{\overset{|}{\underset{|}{\overset{+}{N}}}}}-R + \overset{-}{O}H$$

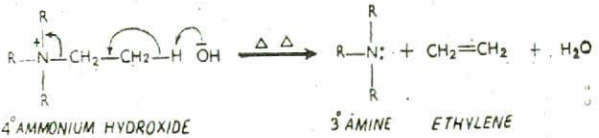
4° ammonium hydroxide — 4° ammonium cation

They are as strong bases as NaOH or KOH. Their aqueous solutions precipitate hydroxides of heavy metals from the solutions of their salts. They absorb carbon dioxide.

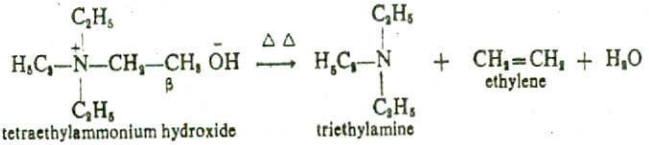
Pyrolysis of Quaternary Ammonium Hydroxides. Tetramethylammonium hydroxide on thermal decomposition or pyrolysis yields trimethylamine and methyl alcohol.



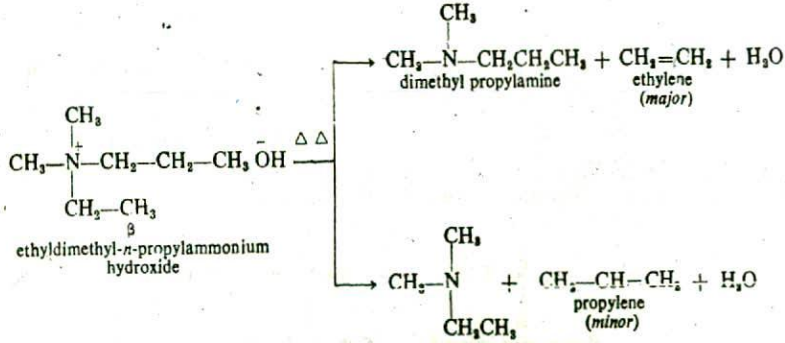
All other tetraalkylammonium hydroxides, in which one of the substituent groups on the nitrogen atom bears at least one β hydrogen, on pyrolysis form a tertiary amine and an alkene by E2 mechanism.



This reaction which has been known since 1851, is called **Hofmann Elimination**. Thus tetraethylamine on pyrolysis gives triethylamine and ethylene.



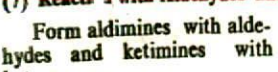
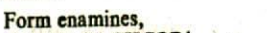
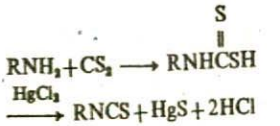
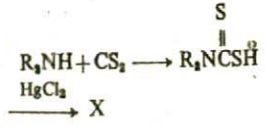
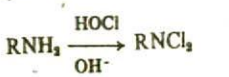
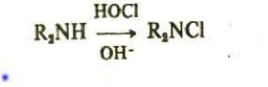
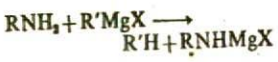
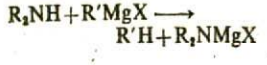
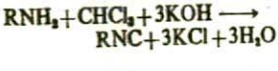
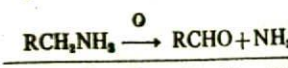
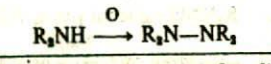
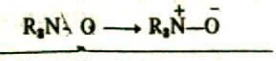
When there are four different alkyl groups attached to the nitrogen atom of the ammonium ion, the pyrolysis of the tetraalkylammonium hydroxide may theoretically lead to the formation of more than one type of alkene. In such cases, the elimination takes place in a fashion that the major product is the alkene containing the least alkylated double bond *i.e.*; the least substituted alkene (*Hofmann Rule*). For example,



COMPARISON OF PROPERTIES OF 1°, 2° AND 3° AMINES

The primary, secondary and tertiary amines can be distinguished from each other by a study of the following properties.

Primary (RNH_2)	*Secondary* (R_2NH)	*Tertiary* (R_3N)
(1) Basic Character :		
More basic than ammonia	More basic than 1° amines	Less basic than 2° amines
(2) Formation of Salts with acids :		
Form alkylammonium salts, $RNH_2 + \overset{+}{H}\overset{-}{Cl} \longrightarrow R\overset{+}{N}H_3\overset{-}{Cl}$	Form dialkylammonium salts, $R_2NH + \overset{+}{H}\overset{-}{Cl} \longrightarrow R_2\overset{+}{N}H_2\overset{-}{Cl}$	Form trialkylammonium salts, $R_3N + \overset{+}{H}\overset{-}{Cl} \longrightarrow R_3\overset{+}{N}H\overset{-}{Cl}$
(3) Reaction with Alkyl halides (Alkylation) :		
React with three molecules of RX to form 4° salt : $RNH_2 \xrightarrow{RX} R_2NH \xrightarrow{RX} R_3N \xrightarrow{RX} R_4\overset{+}{N}\overset{-}{X}$	React with two molecules of RX to form 4° salt. $R_2NH \xrightarrow{RX} R_3N \xrightarrow{RX} R_4\overset{+}{N}\overset{-}{X}$	React with one molecule of RX to form 4° salt. $R_3N + RX \longrightarrow R_3\overset{+}{N}\overset{-}{X}$
(4) Reaction with Acid chlorides (RCOCl) Acylation :		
Form *N*-substituted amides, $RNH_2 + R'COCl \longrightarrow RNHCOR' + HCl$	Form *N,N*-disubstituted amides, $R_2NH + R'COCl \longrightarrow R_2NCOR' + HCl$	*No Reaction*
(5) Reaction with Benzene sulphonyl chloride ($C_6H_5SO_2Cl$) :		
Form *N*-alkylbenzene sulphonamides soluble in NaOH solution. $RNH_2 + C_6H_5SO_2Cl \longrightarrow RNHSO_2C_6H_5$	Form *N,N*-dialkylbenzene sulphonamides, insoluble in NaOH solution. $R_2NH + C_6H_5SO_2Cl \longrightarrow R_2NSO_2C_6H_5$	*No Reaction*
(6) Reaction with Nitrous acid (HONO) :		
Form mixtures of alcohols, alkenes, alkyl halides etc., with evolution of N_2. For example, $RNH_2 + HONO \longrightarrow ROH + N_2\uparrow$	Form oily nitrosoamines which give *Libermann Reaction*. $R_2NH + HONO \longrightarrow R_2NNO + H_2O$ $R_2NNO + \text{phenol} + \text{conc } H_2SO_4 \xrightarrow{NaOH} \textit{green soln.} \longrightarrow \textit{deep blue}$	Form salts $R_3N + HNO_2 \longrightarrow R_3\overset{+}{N}H\overset{-}{NO_2}$

Primary (RNH_2)	*Secondary* (R_2NH)	*Tertiary* (R_3N)
(7) Reaction with Aldehydes and Ketones :		
Form aldimines with aldehydes and ketimines with ketones. 	Form enamines, 	No reaction
(8) Reaction with CS_2 :		
Form dithiocarbamic acid which gives alkylthiocyanate with $HgCl_2$, 	Form dithiocarbamic acid, not decomposed by $HgCl_2$ 	No reaction
(9) Halogenation with Hypochlorous acid in presence of Alkali :		
Form *N, N*-dichloroamine, 	Form *N*-chloroamine, 	No reaction
(10) Reaction with Grignard Reagents :		
Form alkanes, 	Form alkanes, 	No reaction
(11) Carbylamine Reaction : When warmed with $CHCl_3$ and ethanolic KOH, 1° amines produce carbylamine having obnoxious odour, 	No Reaction	No reaction
(12) Oxidation :		
With $KMnO_4$ form aldehydes and ammonia, 	With $KMnO_4$ form tetraalkylhydrazine, 	With H_2O_2 form *N*-oxide, 

Reaction (2), (5), (6), (8) and (10) are used for distinguishing between primary, secondary and tertiary amines.

QUESTIONS

1. What are primary, secondary and tertiary amines? Write their general structural formulas and indicate the functional groups characteristic of each class.

2. Give the structure of each of the following and indicate whether it is a primary, secondary or tertiary amine: (*a*) methylamine; (*b*) diethylamine; (*c*) triisopropylamine; (*d*) 2-aminopentane; (*e*) di-*tert*-butylamine.

3. What types of isomerism do you come across in aliphatic amines? Give one example of each type.

4. Build up the orbital structure of a primary, a secondary and a tertiary amine. Support your arguments with diagrams of orbital models of each type.

5. Discuss the geometry of amines. While the value of bond angle (H—N—H) of ammonia is 107°, that of trimethylamine(C—N—C) is 108°. How do you explain the difference between the two?

6. Describe the methods of preparation of 1°, 2° and 3° amines.

7. How can you separate a mixture of 1°, 2°, 3° amines and 4° salt obtained by the action of ethyl bromide on ammonia?

8. Arrange each of the following groups in order of increasing boiling points.
   (*a*) $CH_3CH_2NH_2$, $CH_3CH_2CH_3$, CH_3CH_2OH.
   (*b*) $CH_3CH_2NHCH_3$, $(CH_3)_3N$, $CH_3CH_2CH_2NH_2$.
   (*c*) $CH_3CH_2NH_2$, $(CH_3)_2NH$, $CH_3CH_2CH_3$.

9. Arrange the following groups of compounds in order of increasing basicity.
   (*a*) Dimethylamine, methylamine, and ammonia.
   (*b*) Sodium hydroxide, ammonia, and methylamine.
   (*c*) Water, ethyl alcohol, and ammonia.
   (*d*) Methylamine, dimethylamine, and trimethylamine.

10. Write the reaction of *n*-propylamine with each of the following reagents:
    (*a*) Acetyl chloride; (*b*) Benzenesulphonyl chloride; (*c*) Nitrous acid; (*d*) excess Methyl bromide; (*e*) Sulphuric acid.

11. For each of the following descriptions suggest the structure of an amine that satisfies the data:
    (*a*) an amine dissolved in nitrous acid.
    (*b*) an amine reacted with benzenesulphonyl chloride to give a solid benzenesulphonamide which was insoluble in NaOH.
    (*c*) an amine reacted with nitrous acid, but the product was unstable at 0°C evolving nitrogen gas and giving a mixture of products.

12. Describe the reaction of acyl chloride on 1°, 2° and 3° amines. Give examples. Discuss the mechanism of acylation of amines and show why only one of the two hydrogens of primary amine is replaced by acyl group.

13. What is sulphonylation of amines? Describe in detail Hinsberg test for finding whether a given amine is 1°, 2° or 3°.

14. State:—(*a*) Liebermann Nitrosoamine Reaction used as a test for 2° amines; (*b*) Carbylamine test for 1° amines; and (*c*) Mustard oil test for 1° amines.

15. What are tetraalkylammonium salts? How are 4° ammonium chlorides prepared? What happens when tetramethylammonium iodide is heated?

16. How are quaternary ammonium hydroxides prepared? Give two examples of Hofmann elimination indicating how in these cases Hofmann Rule is followed.

17. Write structures and give names for all the isomeric amines with the formula $C_4H_{11}N$. Arrange these in three groups—primary, secondary and tertiary. State one characteristic test for each type of amine.

18. Give an example each of the following reactions:
    (*i*) Gabriel's method of synthesis of a primary aliphatic amine.
    (*ii*) Hofmann rearrangement of a primary amide.
    (*iii*) Carbylamine reaction. *(Kerala BSc III, 1980)*

19. How are primary, secondary, and tertiary amines separated from a mixture of the three? How are the three types of amines distinguished? *(Saugar BSc, 1993; Kerala BSc, 1994)*

20. Give any one method of synthesis of a pure aliphatic (*a*) primary amine, and (*b*) secondary amine.
(Panjab BSc, 1993)

21. How are aliphatic amines classified ? Describe suitable reactions by which they can be distinguished from each other *(Osmania BSc Hons, 1992)*

22. Explain why methylamine is a stronger base than ammonia. *(Meerut BSc. 1994)*

23. Arrange the following compounds in order of increasing base strength. Give a reason for the order you select.

(*a*) NH_3 , (*b*) CH_3NH_2 ; (*c*) $(CH_3)_2NH$; (*d*) $(CH_3)_3N$

Hint. Weakest base (*a*) < (*d*) < (*b*) < (*c*) Strongest base.

24. Arrange the following compounds in order of increasing boiling point. Give a reason for the order you select.

(a) $CH_3(CH_2)_4CH_3$

(b) $CH_3(CH_2)_4NH_2$

(c) $CH_3CH_2CH_2N(CH_3)_2$

(d) $NH_2(CH_2)_4\ NH_2$

Hint. Lowest bp (*a*) < (*c*) < (*b*) < (*d*) Highest bp.

25. Explain why dimethylamine has a higher boiling point than trimethylamine, even though the latter has an appreciably higher molecular weight. *(Marathwada BSc. 1994)*

Answer. Hydrogen bonding is possible in dimethylamine, but not in trimethylamine. Energy is required to break these bonds to vaporise dimethylamine, thus raising its boiling point.

26. How will you distinguish oetween :

(*a*) 1-Aminobutane and diethylamine

(*b*) Diethylamine and triethylamine *(Jadavpur BSc, 1994)*

Hint. (*a*) Threat each amine separately with cold, freshly prepared nitrous acid. 1-Aminobutane (a primary amine) liberates nitrogen (seen as bubbles) whereas diethylamine (a secondary amine) yields a yellow oily layer (nitrosamine); (*b*) Diethylamine (a secondary aliphatic amine) forms a yellow oily layer when treated with cold freshly prepared nitrous acid (formation of *N*-nitroso compound). Treatment of triethylamine (a tertiary amine) gives no visible reaction with nitrous acid. The tertiary amine simply dissolves in the acidic solution to form an ammonium salt.

27. An amine (*a*) has the formula C_3H_7N. When (A) was treated with nitrous acid at 0-5°C, a reaction took place and an oily yellow layer separated from the reaction mixture. Write a structure for (A) and give an equation for the reaction.

Answer. (A) is CH_3CH_2-NH-CH_3 (Ethylmethylamine)

Chapter **29**

Cyan Compounds

The cyan compounds are characterised by the presence of a cyan group (CN). They are considered to be derivatives of hydrogen cyanide (HCN). Since the cyanide ion ($:C^{-}\equiv N:$) has an unshared electron pair on both the carbon and nitrogen atoms, the proton (H^{+}) can attach itself to either of these atoms. Thus hydrogen cyanide exists as a tautomeric equilibrium mixture of the cyanide form (I) and the isocyanide form (II). As shown by spectroscopic examination the cyanide form dominates.

$$\underset{\text{cyanide form (I)}}{H-C\equiv N:} \rightleftharpoons H^{+} + \underset{\text{cyanide ion}}{:C^{-}\equiv N:} \rightleftharpoons \underset{\text{isocyanide form (II)}}{:C^{-}\equiv N^{+}:H} \quad \text{or} \quad :C^{-}\equiv N^{+}-H$$

The organic cyan compounds derived from the cyanide form are called **Alkyl Cyanides** or **Nitriles**, while those derived from isocyanide form are called **Alkyl Isocyanides** or **Isonitriles**.

$$\underset{\text{(I)}}{H-C\equiv N} \longrightarrow \underset{\text{alkyl cyanides}}{R-C\equiv N} \quad \text{or} \quad RCN$$

$$\underset{\text{(II)}}{H-N^{+}\equiv C^{-}} \longrightarrow \underset{\text{alkyl isocyanides}}{R-N^{+}\equiv C^{-}} \quad \text{or} \quad RNC$$

The methods of formation and reactions of the two series of cyan compounds leave no doubt that in alkyl cyanides the alkyl group (R) is attached to nitrogen and in alkyl isocyanides it is attached to carbon.

The cyan compounds have proved to be important synthetic reagents.

ALKYL CYANIDES OR NITRILES

They are alkyl derivatives of hydrogen cyanide (or hydrocyanic acid) in which the substituent R is linked to the carbon of the cyan group $-CN$. They are frequently referred to as **Nitriles** (containing nitrogen). Alkyl Cyanides or Nitriles have the general formula $R-C\equiv N$ where $-C\equiv N$ is the functional group.

STRUCTURE

There is a close similarity between the structure of a $-CN$ group of alkyl cyanides and that of acetylene. The carbon and the nitrogen atoms of the cyan group are both in *sp* state of hybridization. The valence orbitals of the carbon atom in *sp* state of hybridization are shown in Fig. 29·1(*a*). The two *sp* hybrid orbitals are linear while the remaining pure *p* orbitals lie prependicular to each other and also to the hybrid orbitals. All these four orbitals have one electron each.

The electronic configuration of N-atom ($1s^2$; $2s^2$, $2p_x^1$, $2p_y^1$, $2p_z^1$) indicates that there are five electrons in four orbitals in the valence shell. The *2s* orbital and one of the three *p* orbitals (say $2p_z$) hybridize to give two *sp* hybrid orbitals. Two *p* orbitals ($2p_y$ and $2p_z$) are left as such. One of the hybrid orbitals will have only one electron while the other accomodates the lone pair originally belonging to *2s* orbital. The two *p* orbitals lie perpendicular to each other and also to the *sp* hybrid as shown in Fig. 29·1 (*b*) as in case of carbon.

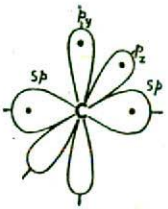


Fig. 29·1. (*a*)
Valence orbitals of Carbon in *sp* state of hybridization

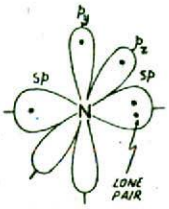


Fig. 29·1.(*b*)
Valence orbitals of Nitrogen in *sp* state of hybridization

In the formation of —CN group, one half-filled *sp* orbital on carbon atom overlaps with half-filled *sp* orbital on nitrogen atom, forming a σ bond. The second *sp* orbital of carbon overlaps with the sp^3 orbital of an alkyl R forming another σ bond in line with the first one. Now there are two *p* orbitals ($2p_y$ and $2p_z$) on carbon and nitrogen atoms both. These effect sidewise overlaps to form two π bonds (π_y and π_z) as shown in Fig. 29·2. It may be noted that the second *sp* orbital on N atom contains a lone pair of electrons.

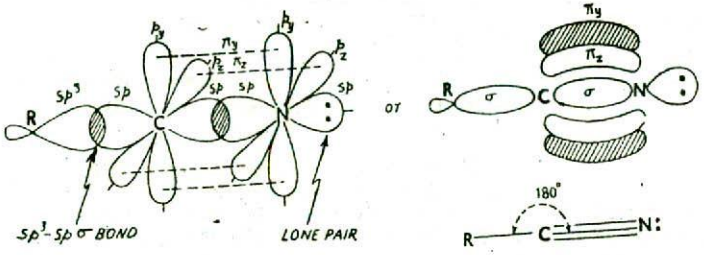


Fig. 29·2. Orbital structure of Nitriles.

NOMENCLATURE

The compounds having the formula R—C≡N are named in three ways.

Cyanide System. In this system, they are named as if they were salts of hydrogen cyanide. Just as salts of hydrogen chloride are the *chlorides*, those of hydrogen cyanide would be named as *cyanides*. Thus the cyanide name of an individual member is derived by putting down the name of the alkyl group and adding the word 'cyanide'. For example, CH_3CN is named as methyl cyanide and C_2H_5CN as ethyl cyanide. Their class name is therefore, *Alkyl Cyanides*.

(2) **Common System.** Their common names are derived from the *common names* of the acids to which they are hydrolysed. The ending *-ic acid* of the corresponding acid is dropped and the suffix *-onitrile* is added. For example, CH_3CN upon hydrolysis yields acetic acid,

$$CH_3—C\equiv N + H_2O \xrightarrow{H^+/OH^-} \underset{\text{acetic acid}}{CH_3—COOH} + NH_3$$

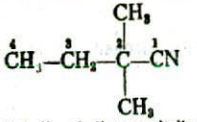
and is, therefore, named as acetonitrile.

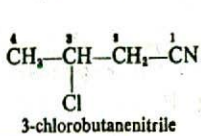
ACETIC ACID − IC ACID + ONITRILE ⟶ ACETONITRILE

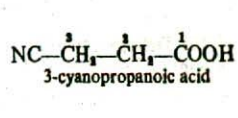
Table Names of some Alkyl Cyanides or Nitriles

Structure	'Cyan Name	Common Name	IUPAC Name
$CH_3—CN$	methyl cyanide	acetonitrile	ethanenitrile
$CH_3CH_2—CN$	ethyl cyanide	propiononitrile	propanenitrile
$CH_3CH_2CH_2—CN$	propyl cyanide	butyronitrile	butanenitrile
$CH_3—CH(CH_3)—CN$	isopropyl cyanide	isobutyronitrile	2-methyl propanenitrile

(3) **IUPAC System.** In this system, the longest carbon chain containing the cyan group (CN) as the terminal gro. p determines the parent name. The IUPAC name of an individual nitrile is derived by adding the name of the parent hydrocarbon on the suffix -nitrile. The name is written as single continuous one word. Thus CH_3CN is named as ethanenitrile, the parent hydrocarbon being ethane. While naming substituted nitriles, the carbon atom triply linked to the nitrogen is assigned number 1. In polyfunctional compounds CN group may be treated as a substituent when it is denoted by the prefix *-cyano.*


2, 2-dimethylbutanenitrile


3-chlorobutanenitrile


3-cyanopropanoic acid

METHODS OF PREPARATION

Alkyl cyanides or nitriles can be obtained by many methods of which the more important ones are listed below.

(1) **Action of Metal Cyanides on Alkyl halides.** Nitriles can be prepared conveniently by heating an alkyl halide with sodium or potassium cyanide in aqueous-ethanolic solution.

$$\underset{\text{alkyl halide}}{R—X} + \overset{+}{Na}\overset{-}{CN} \longrightarrow \underset{\text{nitrile}}{R—CN} + \overset{+}{Na}\overset{-}{X}$$

e.g., $\underset{\text{ethyl bromide}}{CH_3CH_2—Br} + \overset{+}{Na}\overset{-}{CN} \longrightarrow \underset{\text{propanenitrile}}{CH_3CH_2—CN} + \overset{+}{Na}\overset{-}{Br}$

Small amounts of alkyl isocyanide are also formed which can be removed by partial hydrolysis, because it is hydrolysed more rapidly than the alkyl cyanide.

When nitriles are prepared from alkyl halides by this method, an extra carbon atom is introduced. This is the key step for ascending the series of carboxylic acids (or 1° alcohols)

$$RCOOH \xrightarrow[H^+]{CH_3OH} RCOOCH_3 \xrightarrow{LiAlH_4} RCH_2OH \xrightarrow{PBr_3} RCH_2Br \xrightarrow{KCN} RCH_2CN \xrightarrow[H^+]{H_2O} RCH_2COOH$$

(2) **Dehydration of Amides or Ammonium salts of Carboxylic acids.** Simple amides on drastic dehydration by heating with phosphorus pentoxide yield nitriles.

$$\underset{\text{amide}}{R—\overset{O}{\overset{\|}{C}}—NH_2} \xrightarrow[\Delta]{P_2O_5} \underset{\text{nitrile}}{R—C\equiv N} + H_2O$$

e.g., $\underset{\text{propionamide}}{CH_3CH_2—CO—NH_2} \xrightarrow[\Delta]{P_2O_5} \underset{\text{propanenitrile}}{CH_3CH_2—CN} + H_2O$

Higher-molecular-weight amides may be dehydrated by heating alone.

Ammonium salts of carboxylic acids dehydrate first to form amide which on loss of a molecule of water yields nitrile. Thus when carboxylic acid vapours mixed with ammonia are passed over heated alumina at 500°, a nitrile results (*Industrial*).

$$\underset{\text{carboxylic acid}}{R-\overset{O}{\overset{\|}{C}}-OH} + NH_3 \longrightarrow \underset{\text{amm salt}}{R-\overset{O}{\overset{\|}{C}}-O^{-}NH_4^{+}} \xrightarrow[-H_2O]{Al_2O_3,\ 500^\circ} \underset{\text{amide}}{R-\overset{O}{\overset{\|}{C}}-NH_2} \longrightarrow \underset{\text{nitrile}}{R-C\equiv N}$$

(3) **Dehydration of Aldoximes.** Aldoximes upon dehydration with acetic anhydride or thionyl chloride yield nitriles.

$$\underset{\text{aldoxime}}{R-\overset{H}{\overset{|}{C}}=N-OH} \xrightarrow[-H_2O]{(CH_3CO)_2O} \underset{\text{nitrile}}{R-C\equiv N}$$

e.g.,
$$\underset{\text{acetaldoxime}}{CH_3-\overset{H}{\overset{|}{C}}=N-OH} \xrightarrow[-H_2O]{(CH_3CO)_2O} \underset{\substack{\text{ethanenitrile,}\\ \text{acetonitrile}}}{CH_3-C\equiv N}$$

(4) **Dehydrogenation of Higher Amines.** Higher amines get dehydrogenated by passing their vapours over a Cu or Ni catalyst at high temperature.

$$\underset{\text{amine}}{R-\overset{H}{\overset{|}{C}}-\overset{H}{\overset{|}{N}}} \xrightarrow[300^\circ]{Cu} \underset{\text{nitrile}}{R-C\equiv N} + 2H_2$$

(5) **Ammoxidation of Alkanes or Aldehydes.** An alkane having a terminal methyl group is oxidised at elevated temperature (500—600°) over a catalyst in presence of ammonia to form nitrile.

$$\underset{\text{alkane}}{R-CH_3} + NH_3 + 3/2\ O_2 \xrightarrow{550^\circ} \underset{\text{nitrile}}{R-C\equiv N} + 3H_2O$$

e.g.,
$$\underset{\text{propane}}{CH_3CH_2CH_3} + NH_3 + 3/2\ O_2 \xrightarrow{550^\circ} \underset{\text{propanenitrile}}{CH_3CH_2-C\equiv N} + 3H_2O$$

An aldehyde gives a similar reaction in presence of sodium methoxide ($NaOCH_3$) and Cu^{2+} ion at 30°.

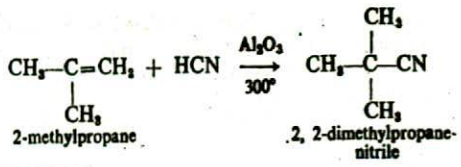
$$CH_3-CHO + NH_3 + O_2 \xrightarrow[Cu^{2+},\ 30^\circ]{NaOCH_3} \underset{\text{ethanenitrile}}{CH_3-C\equiv N} + 2H_2O$$

(6) **Action of Grignard Reagents with Cyanogen Chloride.** Grignard reagents react with cyanogen chloride (Cl—C≡N) to form nitriles.

$$\underset{\substack{\text{Grignard}\\ \text{reagent}}}{RMgX} + Cl-C\equiv N \xrightarrow{\text{ether}} \underset{\text{nitrile}}{R-C\equiv N} + \overset{2+}{M}\overset{-}{g}X\overset{-}{Cl}$$

e.g.,
$$\underset{\substack{\text{ethylmagnesium}\\ \text{bromide}}}{C_2H_5MgBr} + Cl-C\equiv N \xrightarrow{\text{ether}} \underset{\text{propanenitrile}}{C_2H_5-C\equiv N} + \overset{2+}{M}\overset{-}{g}\overset{-}{Br}\overset{-}{Cl}$$

(7) **Addition of HCN to Alkanes.** Hydrogen cyanide adds to terminal alkenes in the gaseous phase at 350° in presence of alumina to give nitriles.



PHYSICAL PROPERTIES

(1) Lower molecular weight (up to C_{14}) aliphatic nitriles are colourless liquids at room temperature. The higher members are crystalline solids.

(2) They have fairly pleasant smells, resembling that of bitter almonds.

(3) Nitriles are dipolar compounds. Their dipole moments being pretty high (CH_3CN = 4·0D), they are highly associated molecules. Their boiling points are, therefore, abnormally high.

(4) The lower members are soluble in water with which they form hydrogen bonds. The solubility decreases as the hydrocarbon group gets larger. Thus acetonitrile is miscible with water and propiononitrile is fairly soluble, while higher members are oily and slightly soluble. All cyanides are soluble in organic solvents.

(5) They are moderately poisonous in contrast to hydrogen cyanide which is a deadly poison.

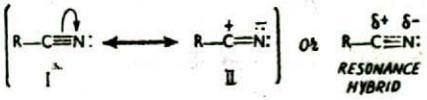
(6) Nitriles absorb in their infrared spectra in the region 2000 to 2300 cm^{-1}, owing to the stretching vibrations of the carbon-nitrogen triple bond (C≡N).

Table. Physical properties of some Nitriles

Name	*Formula*	*mp°C*	*bp°C*	*Density g/ml, 20°*
Acetonitrile	$CH_3—CN$	−45	82	0·78
Propiononitrile	$CH_3—CH_2—CN$	−92	97	0·78
n-Butyronitrile	$CH_3—CH_2CH_2—CN$	−112	118	0·80
Isobutyronitrile	$CH_3—CH(CH_3)—CN$	−72	104	0·78

CHEMICAL PROPERTIES

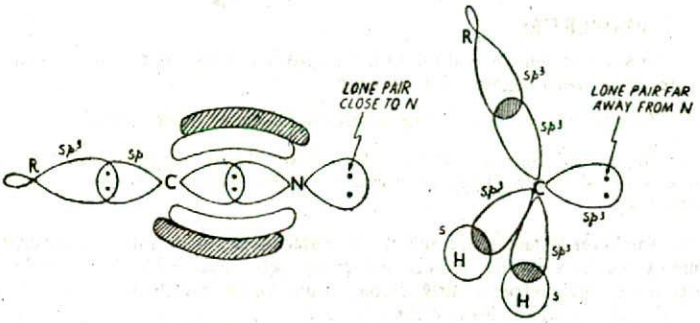
The cyan group (C≡N) in nitriles is strongly polarised as indicated by the high dipole moment of 4·0D. It is polar in the same way as a carbonyl group (C=O). Thus nitriles can be represented as a resonance hybrid of two canonical forms, in which there is a high contribution from the dipolar form.



Because of the dipole, a nitrile is subject to electrophilic attack on nitrogen and to nucleophilic attack on carbon. The cyan group being electron attracting activates the α hydrogen which can be easily removed as a proton by strong bases. In fact the cyan group could be compared to the carbonyl group in its chemical behaviour. Thus nitriles give the addition reactions just like aldehydes and ketones.

(1) **Weak Basic Character.** Despite the presence of an unshared pair of electrons at the nitrogen atom, the nitriles are not basic enough to form salts with aqueous acids. They are, therefore, less basic than amines and ammonia. However, they form addition compounds with strong acids in the absence of water.

The weaker basic character of nitriles has been associated with a greater *s* character in the orbital containing the unshared electaron pair. Unlike amines where the lone pair of electrons is in sp^3 orbital, the lone pair of N atom in nitriles belongs to an *sp* orbital. This orbital (*sp*) evidently has greater *s* character than sp^3 orbital. Therefore, the lone pair of nitrogen in nitriles is less readily available and they are much weaker bases than amines.



NITRILE

Lone pair held *closer* to the N atom in *sp* orbital is *less* readily available; hence nitriles are LESS BASIC.

PRIMARY AMINE

Lone pair lying relatively *away* from the N atom in sp^3 orbital is *more* readily available; hence amines are MORE BASIC.

(2) **Hydrolysis.** On boiling with aqueous mineral acid or aqueous alkali, nitriles are hydrolysed to a carboxylic acid and ammonia. This reaction takes place through the formation of an amide which is then hydrolysed to a carboxylic acid.

$$\underset{\text{nitrile}}{R-C\equiv N} \xrightarrow[+H_2O]{\overset{+}{H}\text{ or }O\bar{H}} \underset{\text{amide}}{R-\overset{O}{\overset{\|}{C}}-NH_2} \xrightarrow[+H_2O]{\overset{+}{H}\text{ or }O\bar{H}} \underset{\text{carboxylic acid}}{R-\overset{O}{\overset{\|}{C}}-OH} + NH_3$$

e.g.,

$$\underset{\text{acetonitrile}}{CH_3-C\equiv N} \xrightarrow[+H_2O]{\overset{+}{H}\text{ or }O\bar{H}} \underset{\text{acetamide}}{CH_3-\overset{O}{\overset{\|}{C}}-NH_2} \xrightarrow[+H_2O]{\overset{+}{H}\text{ or }O\bar{H}} \underset{\text{acetic acid}}{CH_3-\overset{O}{\overset{\|}{C}}-OH} + NH_3$$

When a mineral acid (say HCl) is used for hydrolysis, the product is a carboxylic acid and ammonia. On the other hand, if an alkali (say NaOH) is used, the hydrolysis results in the formation of sodium salt of the carboxylic acid.

$$R-C\equiv N + 2H_2O + HCl \longrightarrow RCOOH + \overset{+}{N}H_4\bar{Cl}$$

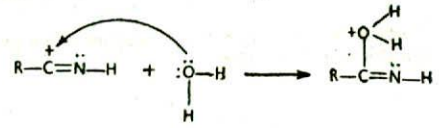
$$R-C\equiv N + H_2O + NaOH \longrightarrow RCO\bar{O}\,\overset{+}{N}a + NH_3$$

MECHANISM OF ACID CATALYSED HYDROLYSIS :

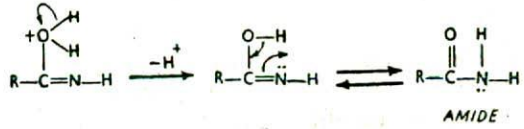
(*a*) Protonation of nitrile :

$$\underset{\text{ALKYL CYANIDE}}{R-C\equiv N:} + H^+ \longrightarrow \underset{\text{I}}{R-C\equiv\overset{+}{N}-H} \longleftrightarrow \underset{\text{II}}{R-\overset{+}{C}=N-H}$$

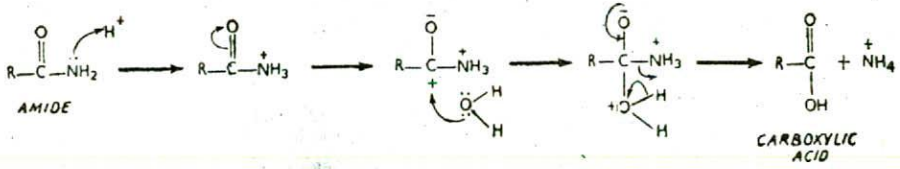
(*b*) **Nucleophilic addition of water to II :**



(*c*) Proton loss followed by tautomeric rearrangement :



The amide thus produced undergoes the same sequence of steps leading to the formation of carboxylic acid.

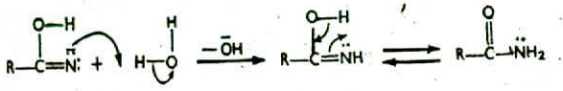


MECHANISM OF BASE CATALYSED HYDROLYSIS :

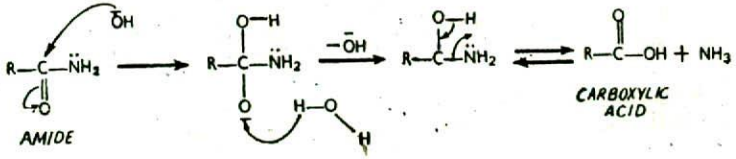
(*a*) Nucleophilic attack at the carbon atom by $\bar{O}H$ ions.



(*b*) Nucleophilic N atom takes up a proton from water regenerating $\bar{O}H$ ion. The product rearranges to produce stable amide.



The amide thus formed gets further hydrolysed to give carboxylic acid and ammonia.



(2) **Alcoholysis.** Nitriles on boiling with excess of alcohol in the presence of concentrated sulphuric acid or hydrogen chloride, form esters.

$$\underset{\text{nitrile}}{R-C\equiv N} + \underset{\text{alcohol}}{R'-OH} + H_2O \xrightarrow{H^+} \underset{\text{ester}}{R-\overset{O}{\overset{\|}{C}}-OR'} + NH_4^+$$

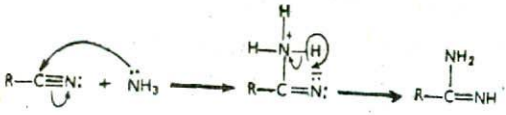
e.g.,
$$\underset{\text{propanenitrile}}{CH_3CH_2-C\equiv N} + \underset{\text{methanol}}{CH_3OH} \xrightarrow{H^+} \underset{\text{methyl propionate}}{CH_3CH_2-\overset{O}{\overset{\|}{C}}-OCH_3} + NH_4^+$$

(3) **Addition of Ammonia and Hydroxylamine.** Nitriles when reacted with ammonia or hydroxylamine in the presence of $NaNH_2$ as catalyst, form amidines and amidoximes respectively.

$$\underset{\text{nitrile}}{R-C\equiv N:} + \ddot{N}H_3 \xrightarrow{NaNH_2} \underset{\text{amidine}}{R-\overset{NH}{\overset{\|}{C}}-NH_2}$$

$$R-C\equiv N: + \underset{\text{hydroxylamine}}{\ddot{N}H_2OH} \xrightarrow{NaNH_2} \underset{\text{amidoxime}}{R-\overset{NH_2}{\overset{|}{C}}=N-OH}$$

MECHANISM. Both these reagents add by nucleophilic addition mechanism similar to those in case of carboxyl compounds. For illustration,



(4) **Addition of Grignard Reagents.** Nitriles react with Grignard reagents to form ketimines which on hydrolysis yield ketones.

$$\underset{\text{nitrile}}{R-C\equiv N} + \overset{\delta-}{R'}\overset{\delta+}{MgX} \longrightarrow \underset{\text{ketimine}}{R-\overset{R}{\overset{|}{C}}=NMgX} \xrightarrow[H^+]{H_2O} \underset{\text{ketone}}{R-\overset{R'}{\overset{|}{C}}=O} + \overset{2+}{Mg}\,\bar{X}\,\bar{O}H$$

e.g.,
$$\underset{\text{acetonitrile}}{CH_3-C\equiv N} + \underset{\substack{\text{methylmagnesium}\\ \text{bromide}}}{CH_3MgBr} \longrightarrow CH_3-\overset{CH_3}{\overset{|}{C}}=NMgBr \xrightarrow[H^+]{H_2O} \underset{\text{acetone}}{CH_3-\overset{CH_3}{\overset{|}{C}}=O} + \overset{2+}{Mg}\,\bar{B}r\bar{O}H$$

(5) **Reduction.** (*a*) *Partial Reduction.* When nitriles are reduced with lithium triethoxyaluminium hydride, $LiAlH(OCH_2CH_3)_3$, in ether, aldimine is first produced. This on subsequent hydrolysis yields an aldehyde.

$$\underset{\text{nitrile}}{R-C\equiv N} + LiAlH(OCH_2CH_3)_3 \xrightarrow{\text{ether}} \underset{\text{aldimine}}{R-CH=NH} \xrightarrow[H^+]{H_2O} \underset{\text{aldehyde}}{RCHO}$$

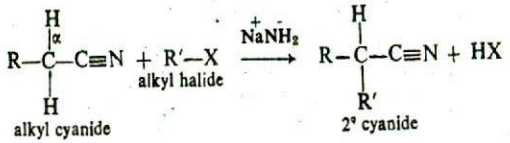
(b) Complete Reduction to primary amines. On treatment with lithiumaluminium hydride, $LiAlH_4$, nitriles undergo complete reduction to yield primary amines.

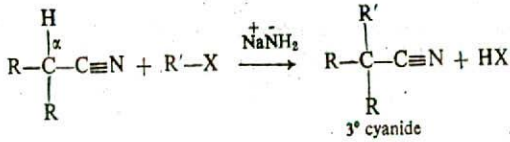
$$\underset{\text{nitrile}}{R-C\equiv N} + 4H \xrightarrow[\text{ether}]{LiAlH_4} \underset{\text{primary amine}}{R-CH_2-NH_2}$$

This reduction may also be carried with sodium and ethanol (*Mendius Reaction*), or wit hydrogen and metal catalyst (Raney nickel).

$$\underset{\text{acetonitrile}}{CH_3-C\equiv N} + 2H_2 \xrightarrow{\text{Raney Ni}} \underset{\text{ethylamine}}{CH_3-CH_2-NH_2}$$

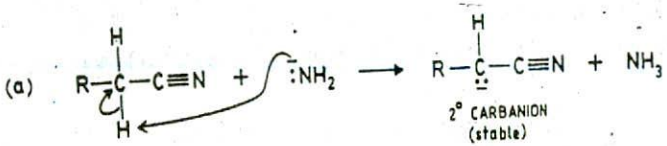
(6) **Alkylation.** Nitriles having α-hydrogen atoms are alkylated readily when heate with an alkyl halide in presence of finely divided sodium amide ($Na^+NH^-_2$).

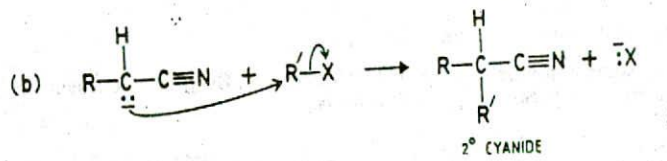




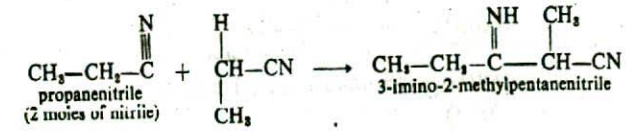
This reaction provides a procedure for preparing tertiary amines.

MECHANISM. The base $:\bar{N}H_2$ furnished by sodium amide initiates the reactio producing carbanion which is then alkylated by alkyl halide as follows.





(7) **Thorpe Nitrile Condensation.** Nitriles undergo condensation in the presence o sodium in ether, when only the α hydrogen atoms are involved. Two molecules of the nitril undergo Claisen-type condensation as follows.



This reaction is known as *Thorpe Nitrile Condensation.*

ALKYL ISOCYANIDES OR ISONITRILES

As the name implies, the isocyanides or isonitriles are structural isomer of the cyanides or nitriles. They are regarded as alkyl derivatives of th isocyanide form of hydrogen cyanide ($H-\bar{N}^+\equiv C:^-$). They have the general formul

$R-\overset{+}{N}\equiv\overset{-}{C}:$ where $-\overset{+}{N}\equiv\overset{-}{C}:$ is the functional group. In isonitriles the alkyl group is directly attached to nitrogen atom in contrast to nitriles where it is attached to carbon. Thus the longest carbon chain in isonitriles has one carbon atom less than in the isomeric nitriles.

Structurally isonitriles are best represented as a resonance hybrid of two canonical forms.



I II

The dipolar form I makes a higher contribution.

NOMENCLATURE

They are commonly named as *Alkyl isocyanides*. To the name of the alkyl group attached to the group NC is added the suffix 'isocyanide' as a separate word. The IUPAC system names them as *Alkylcarbylamines*. Here the suffix 'carbylamine' goes after the name of the alkyl group as one word. For illustration,

Formula	*Common name*	*IUPAC Name*
CH_3—NC	methyl isocyanide	methylcarbylamine
CH_3CH_2—NC	ethyl isocyanide	ethylcarbylamine
$CH_3CH_2CH_2$—NC	propyl isocyanide	propylcarbylamine

METHODS OF PREPARATION

(1) By heating an alkyl iodide with silver cyanide (Ag—C≡N:) in aqueous ethanolic solution.

$$\underset{\text{alkyl iodide}}{R-I} + Ag-C\equiv N: \xrightarrow{\Delta} \underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + AgI$$

A small amount of the isomeric cyanide is also produced.

(2) By heating a primary amine and chloroform ($CHCl_3$) with ethanolic potassium hydroxide solution. (*Hofmann Carbylamine Reaction*).

$$\underset{1^\circ \text{ amine}}{R-NH_2} + \underset{\text{chloroform}}{CHCl_3} + 3KOH \xrightarrow{\Delta} \underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + 3KCl + 3H_2O$$

(2) By heating isocyanates (RNCO) with alkyl phosphites.

$$\underset{\text{alkyl isocyanate}}{R-N=C=O} + \underset{\text{triethyl phosphite}}{(C_2H_5O)_3P} \xrightarrow{150-190^\circ} \underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + (C_2H_5O)_3PO$$

(4) By heating *N*-alkylformamides with phosphoryl chloride in pyridine solution.

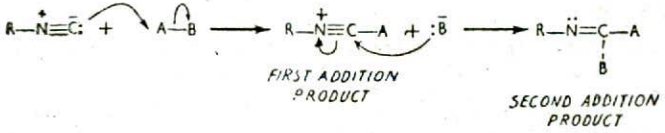
$$\underset{\textit{N}\text{-alkyl formamide}}{R-\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-H} \xrightarrow[\text{pyridine}]{POCl_3} \underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + H_2O$$

PROPERTIES

(*Physical*). Isonitriles are highly unpleasant smelling liquids. They are almost insoluble in water, the nitrogen atom not having a lone pair of electrons for hydrogen bonding. They have lower boiling points than the respective isomeric nitriles (CH_3CN *bp* 81° ; CH_3NC *bp* 68°).

This is attributed to their lower dipole moments (3D) compared to that of nitriles (4D). The $\overset{+}{N}\equiv\overset{-}{C}$ stretching absorption is in the infrared region 2185—2120 cm^{-1} (S).

(Chemical). It is clear from the structure of isocyanides that they have highly polar molecules having an unshared pair of electrons on the triply bonded carbon. This is why they are a very reactive class of compounds. Their reactions usually involve nucleophilic attack on the reagent (A—B) followed by the nucleophilic attack by the fragment $B:^-$ on the carbon atom of the isocyanide. Thus both the fragments of the attacking reagent are added to the isocyanide carbon.

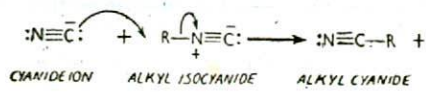


Some of the common reactions of alkyl isocyanides are listed below.

(1) **Isomerisation.** Isocyanides on heating with NaCN or KCN rearrange to more stable cyanides.

$$\underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}} \xrightarrow[100^\circ]{KCN} \underset{\text{alkyl cyanide}}{R-C\equiv N}$$

MECHANISM. Here the cyanide ion brings about a nucleophilic displacement reaction.



(2) **Addition Reactions.** Isocyanides react with hydrogens, sulphur, mercuric oxide, Grignard reagents, amines, alcohols etc., to form addition compounds. For example,

$$\underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + Cl_2 \longrightarrow \underset{\text{alkyliminocarbonyl chloride}}{R-N=C\begin{matrix}Cl\\Cl\end{matrix}}$$

$$R-\overset{+}{N}\equiv\overset{-}{C}: + S \longrightarrow \underset{\text{alkyl isothiocyanate}}{R-N=C=S}$$

$$R-\overset{+}{N}\equiv\overset{-}{C}: + HgO \longrightarrow \underset{\text{alkyl isocyanate}}{R-N=C=O}$$

(3) **Hydrolysis.** They are hydrolysed by dilute acids to form a primary amine and formic acid, but are not hydrolysed by alkalis.

$$\underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + 2H_2O \xrightarrow{\text{acid}} \underset{1^\circ\text{ amine}}{R-NH_2} + \underset{\text{formic acid}}{HCOOH}$$

$$R-\overset{+}{N}\equiv\overset{-}{C}: + H_2O \xrightarrow{\text{alkali}} \textit{No reaction}$$

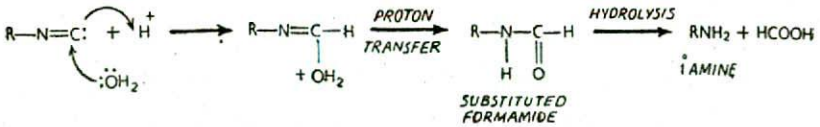
In contrast, nitriles (RCN) undergo both acid and base hydrolysis to form the corresponding carboxylic acids (RCOOH). This reaction brings out clearly that in isocyanides the alkyl group R is attached to nitrogen, while in nitriles it is attached to the terminal carbon. Thus,

$$\underset{\text{methyl isocyanide}}{CH_3-\overset{+}{N}\equiv\overset{-}{C}:} + 2H_2O \xrightarrow{H^+} \underset{\text{methylamine}}{CH_3-NH_2} + HCOOH \quad ...(i)$$

$$\underset{\text{acetonitrile}}{CH_3-C\equiv N} + 2H_2O \xrightarrow{H^+} \underset{\text{acetic acid}}{CH_3-\overset{O}{\overset{\|}{C}}-OH} + NH_3 \quad ...(ii)$$

In reaction (*i*) the original H_3C-N bond remains intact, and in reaction (*ii*) the original H_3C-C bond remains intact.

MECHANISM. Isocyanide undergoes acid hydrolysis by the following mechanism.



(4) **Reduction.** Isocyanides are reduced to secondary amines either by sodium and ethanol, or by catalytic hydrogenation (Pt, H_2).

$$\underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + 2H_2 \xrightarrow{Na,\ C_2H_5OH} \underset{2^\circ\text{ amine}}{R-NH-CH_3}$$

e.g., $$\underset{\text{propanenitrile}}{CH_3CH_2-\overset{+}{N}\equiv\overset{-}{C}:} + 2H_2 \longrightarrow \underset{\text{ethylmethylamine}}{CH_3CH_2-NH-CH_3}$$

It may be recapitulated that nitriles on reduction with sodium and ethanol form primary amines. Thus,

$$CH_3-\overset{+}{N}\equiv\overset{-}{C}: + 2H_2 \xrightarrow{Na,\ C_2H_5OH} \underset{\text{dimethylamine}}{CH_3-NH-CH_3}$$

$$CH_3-C\equiv N + 2H_2 \xrightarrow{Na,\ C_2H_5OH} \underset{\text{ethylamine}}{CH_3-CH_2-NH_2}$$

This reaction also proves the structural difference between isocyanides and cyanides.

VINYL CYANIDE, *Acrylonitrile*, $CH_2=CH-CN$

It is commercially the most important nitrile. In 1964 USA alone produced 594 million pounds.

Preparation. (1) Acrylonitrile is chiefly made by the catalytic addition of hydrogen cyanide to acetylene.

$$\underset{\text{acetylene}}{H-C\equiv C-H} + H-C\equiv N \xrightarrow[90^\circ]{Cu_2Cl_2,\ NH_4Cl} \underset{\text{acrylonitrile}}{\overset{H}{\underset{|}{H-C=}}\overset{C\equiv N}{\underset{|}{C-H}}} \text{ or } CH_2=CH-CN$$

(2) It is also obtained from ethylene and propylene derived from petroleum sources.

$$\underset{\text{ethylene}}{CH_2=CH_2} \xrightarrow[\text{cat.}]{O_2} \underset{\text{ethylene oxide}}{\overset{O}{\overset{/\ \backslash}{CH_2-CH_2}}} \xrightarrow{HCN} \overset{OH}{\underset{|}{CH_2}}-CH_2-CN \xrightarrow{-H_2O} \underset{\text{acrylonitrile}}{CH_2=CH-CN}$$

$$\underset{\text{propene}}{2CH_3{=}CH{-}CH_3} + 2NH_3 + 3O_2 \xrightarrow[450^\circ]{\text{cat.}} \underset{\text{acrylonitrile}}{2CH_2{=}CH{-}CN} + 6H_2O$$

Properties. Acrylonitrile is a colourless liquid, bp 77·3°. It polymerises readily in the presence of catalyst (organic peroxides and other oxidising agents) to form polyacrylonitrile.

$$x\ \underset{\text{acrylonitrile}}{CH_2{=}CH{-}CN} \xrightarrow{\text{cat.}} \underset{\text{polyacrylonitrile}}{\left[\begin{array}{l}-CH_2-CH-\\ \qquad\quad |\\ \qquad\quad CN\end{array}\right]_x}$$

Polyacrylonitrile is used for making synthetic fibres such as *Orlon*, *Acrilan*, *Creslan* and *Zefran*.

Owing to the electron-withdrawing effect of the nitrile group

$$CH_2{=}CH{-}C{\equiv}N \longleftrightarrow \overset{+}{C}H_2{-}CH{=}C{=}\bar{N}:$$

the double bond in acrylonitrile exhibits high reactivity towards nucleophilic reagents. Thus in the presence of basic catalysts, the double bond in acrylonitrile undergoes addition of a number of reagents such as water, alcohols, hydrogen sulphide, amines and also with active methylene compounds (R—CH_2—CO—R'). In these reactions the active hydrogen of the reagent (H—A) is replaced by cyanoethyl group (—CH_2CH_2CN).

$$\underset{\text{acrylonitrile}}{CH_2{=}CH{-}CN} + H{-}A \xrightarrow{\text{base}} \underset{\text{cynoethyl derivative}}{A{-}CH_2{-}CH_2{-}CN}$$

This procedure by which an active hydrogen of a compound is substituted by cynoethyl group is referred to as **Cynoethylation**. Thus,

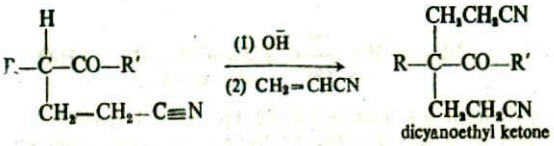
$$\underset{\text{acrylonitrile}}{CH_2{=}CH{-}CN} \left|\begin{array}{ll} + H_2O & \xrightarrow{\text{base}} HO{-}CH_2CH_2CN \\ + ROH & \xrightarrow{\text{base}} RO{-}CH_2CH_2CN \\ + H_2S & \xrightarrow{\text{base}} HS{-}CH_2CH_2CN \\ + RNH_2 & \xrightarrow{\text{base}} RNH{-}CH_2CH_2CN \\ + RCH_2COR' & \xrightarrow{\text{base}} R'CH(CO{-}R){-}CH_2CH_2CN \end{array}\right.$$

MECHANISM. The cynoethylation in case of a ketone containing active methylene group may be interpreted to take place as follows.

$$R{-}\underset{\cdot\cdot}{\underset{H}{C}}{-}CO{-}R' + \bar{O}H \longrightarrow R{-}\underset{\cdot\cdot}{C}{-}CO{-}R' + H_2O$$

$$R{-}\underset{\cdot\cdot}{\underset{H}{C}}{-}CO{-}R' + CH_2{=}CH{-}C{\equiv}N \xrightarrow{H_2O} R{-}\underset{CH_2{-}CH{=}C{=}NH}{\underset{|}{CH}}{-}CO{-}R \longrightarrow R{-}\underset{CH_2{-}CH_2{-}C{\equiv}N}{\underset{|}{CH}}{-}CO{-}R'$$

Since the product still has an active hydrogen atom the above steps are repeated.



ALKYL CYANATES AND ISOCYANATES

These are the alkyl derivatives of cyanic acid (HO—C≡N), an oxidation product of hydrogen cyanide (H—C≡N). Since hydrogen cyanide exists into two tautomeric forms, so does its oxidation product.

$$\underset{\text{cyanic acid}}{H-O-C\equiv N} \rightleftharpoons \underset{\text{isocyanic acid}}{H-N=C=O}$$

Thus cyanic acid can give two types of alkyl derivatives corresponding to each tautomeric form,

$$\underset{\text{cyanic acid}}{H-O-C\equiv N} \longrightarrow \underset{\text{alkyl cyanate}}{R-O-C\equiv N}$$

$$\underset{\text{isocyanic acid}}{H-N=C=O} \longrightarrow \underset{\text{alkyl isocyanate}}{R-N=C=O}$$

Alkyl cyanates may be obtained by treating sodium alkoxide (RONa) with cyanogen chloride.

$$\underset{\text{sod alkoxide}}{R-O-Na} + \underset{\substack{\text{cyanogen}\\\text{chloride}}}{Cl-C\equiv N} \longrightarrow \underset{\text{alkyl cyanate}}{R-O-C\equiv N} + NaCl$$

But the alkyl cyanates so produced are unstable and at once polymerise to form a trimer $(R-OCN)_3$.

Isocyanates, on the other hand, are stable compounds and are useful synthetic reagents.

ALKYL ISOCYANATES, R—N=C=O

They are named as if they were esters of isocyanic acid (H—N=C=O). Thus $CH_3-N=C=O$ is methyl isocyanate and $C_2H_5-N=C=O$ is ethyl isocyanate.

Methods of Preparation. (1) By action of carbonyl chloride ($COCl_2$) on amines. The alkylcarbonyl chloride first produced on pyrolysis gives isocyanate.

$$\underset{\text{1° amine}}{2\,R-NH_2} + \underset{\text{carbonyl chloride}}{Cl-C(=O)-Cl} \longrightarrow \underset{\substack{\text{alkylcarbanyl}\\\text{chloride}}}{R-N(H)-C(=O)-Cl} + R\overset{+}{N}H_3\,\overset{-}{Cl}$$

$$R-N(H)-C(=O)-Cl \xrightarrow{\Delta\Delta} \underset{\text{alkyl isocyanate}}{R-N=C=O} + HCl$$

(2) By heating a dialkyl sulphate (R_2SO_4) and potassium cyanate ($\overset{+}{K}\overset{-}{N}CO$) in presence of sodium carbonate.

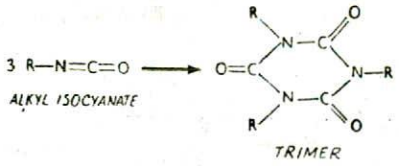
$$R_2SO_4 + \overset{+}{K}\overset{-}{N}CO \xrightarrow{Na_2CO_3} \underset{\text{alkyl isocyanate}}{R-N=C=O} + R\overset{-}{O}SO_2\overset{+}{K}$$

(3) By oxidation of isocyanides with ozone.

$$\underset{\text{alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + O_3 \longrightarrow \underset{\text{alkyl isocynate}}{R-N=C=O} + O_2$$

Properties. (*Physical*). Alkyl isocyanates are volatile liquids having a powerful and extremely unpleasant smell. They are typically toxic substances. Their boiling points lie well above those of alkanes of comparable molecular weight, indicating an appreciable dipole moment. They are almost insoluble in water.

(*Chemical*). Alkyl isocyanates polymerise at once in the presence of traces of impurities.

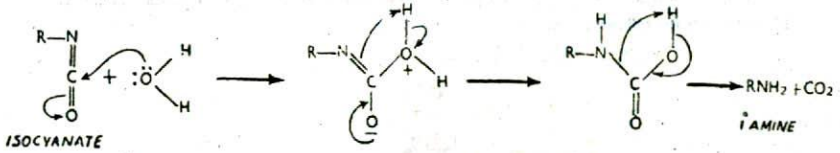


In general, the chemical reactions of isocyanates are similar to those of ketones. They readily undergo addition reactions at the carbon atom by a nucleophile which is followed by protonation at the nitrogen.

(1) *Hydrolysis.* Alkyl isocyanates react with water to form carbamic acid which at once eliminates carbon dioxide to yield primary amines.

$$\underset{\text{alkyl isocyanate}}{R{-}N{=}C{=}O} + H_2O \longrightarrow \underset{\text{carbamic acid}}{R{-}NH{-}COOH} + R{-}NH_2 + CO_2$$

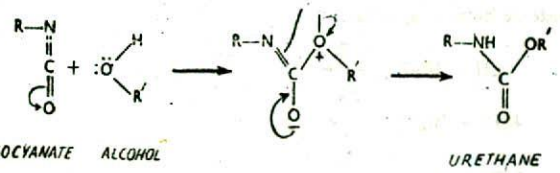
MECHANISM :



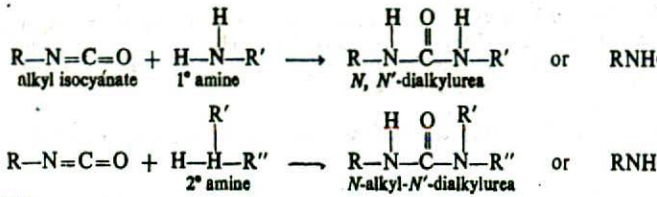
(2) *Addition of Alcohols.* They react readily with alcohols and phenols to form addition products called *Urethanes.*

$$\underset{\text{alkyl isocyanate}}{R{-}N{=}C{=}O} + \underset{\text{alcohol}}{R'{-}O{-}H} \longrightarrow \underset{\textit{O}\text{-alkyl-}\textit{N}\text{-alkylurethane}}{R{-}NH{-}\overset{\overset{O}{\|}}{C}{-}OR'}$$

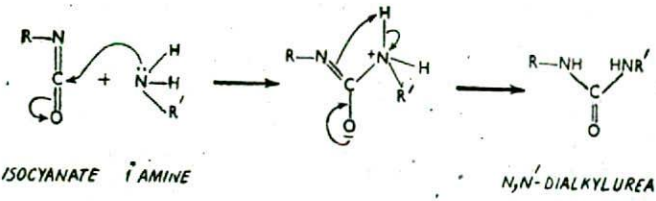
MECHANISM :



(3) *Action of Amines.* Primary and secondary amines add to alkyl isocyanates to form *substituted ureas.*



MECHANISM :



QUESTIONS

1. What are Nitriles and Isonitriles ? Write their general structural formulae and indicate the functional groups of the two classes of compounds.

2. Write the orbital structure of Alkyl cyanides and show its similarily with the orbital structure of acetylene.

3. Give the structural formulae of the following : acetonitrile, butanenitrile, 2, 2-dimethylbutanenitrile and 3-bromobutanenitrile.

4. Describe the methods of preparation of Alkyl cyanides.

5. 'The chemical behaviour of cyanides resembles with that of aldehydes and ketones.' Comment.

6. Complete the following equations :

$$CH_3CN + 2H_2O + HCl \longrightarrow$$

$$CH_3CN + NH_3 \xrightarrow{NaNH_2}$$

$$C_2H_5CN + 4H \xrightarrow{LiAlH_4}$$

$$2\,C_6H_5CN \xrightarrow[ether]{Na}$$

$$CH_3CH_2CN + CH_3Cl \xrightarrow[NaNH_2]{\Delta}$$

7. What happens when a nitrile is boiled with an aqueous strong acid or aqueous alkali ? Give the mechanism of acid hydrolysis of nitriles.

8. What is the structural relationship between nitriles and isonitriles ? What methods of preparation and reactions of the two classes of compounds bring out the difference in their structures ?

9. Discuss the general methods of preparation and properties of alkyl isocyanides.

10. Complete the following equations :

(a) $RCN + 2H_2O \xrightarrow{H^+}$

$RNC + 2H_2O \xrightarrow{H^+}$

(b) $RCN + 4H \xrightarrow{Na,\ ethanol}$

$RNC + 4H \xrightarrow{Na,\ ethanol}$

What conclusions do you make from the above reactions regarding the structure of nitriles and isonitriles ?

11. How is acrylonitrile prepared ? State its important reactions and uses.

12. Write the type formulae of alkyl cyanates and isocyanates. Mention briefly their role in organic synthetic reactions.

13. How can you prepare : (*a*) an aldehyde from a cyanide ; (*b*) a cyanide from an aldoxime ; (*c*) a nitrile from an olefine ?

14. Give an account of the product or products obtained when alkyl halides react with (*i*) sodium cyanide ; (*ii*) silver cyanide. What structures would you assign to the products ?

15. What happens when acetonitrile is treated with dil acid ? (*Osmania BSc, 1993*)

16. How will you synthesise methyl cyanide from acetamide ? (*Saugar BSc, 1993*)

17. How will you distinguish between methyl cyanide and methyl isocyanide ? (*Delhi BSc, 1994*)

18. How will you distinguish between ethyl cyanide and ethyl isocyanide ? (*Annamalai BSc, 1994*)

Derivatives of Carbonic Acid

Carbonic acid, $HO-\overset{\overset{O}{\|}}{C}-OH$, has never been isolated in the free state. This is not unexpected, since compounds containing two hydroxyl groups attached to the same carbon atom are usually unstable. It is believed that the aqueous solutions of carbon dioxide contain carbonic acid in equilibrium with carbon dioxide and water.

$$O{=}C{=}O + H_2O \rightleftharpoons \underset{\text{carbonic acid (unstable)}}{HO-\overset{\overset{O}{\|}}{C}-OH}$$

Although carbonic acid itself is unstable, many of its derivatives have considerable stability and are of industrial and biological importance. Carbonic acid generally behaves as a dibasic acid. This is because it contains two hydroxyl groups bonded to a carbonyl group, and each hydroxyl group can behave like the hydroxyl group of a carboxylic acid.

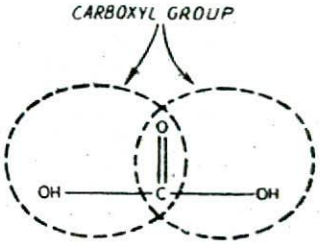


Fig. 30.1. Carbonic acid contains a $-\overset{\overset{O}{\|}}{C}-$ group which is shared by two —OH groups. Each —OH group can behave like the —OH group of a carboxylic acid.

Carbonic acid forms both monofunctional and difunctional derivatives. The monofunctional derivatives are very unstable and are known only as their salts. A few of the important derivatives are shown in Table 1. Notice that the names of these compounds are derived from the word *carbonic* by the same rules we have used for acid derivatives.

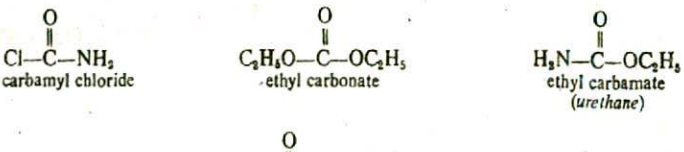
Table 30·1. Derivatives of Carbonic Acid, $HO-\overset{\overset{O}{\|}}{C}-OH$

Monofunctional Derivatives — All of them are ***Unstable***

$Cl-\overset{\overset{O}{\|}}{C}-OH$	$HO-\overset{\overset{O}{\|}}{C}-NH_2$	$HO-\overset{\overset{O}{\|}}{C}-OC_2H_5$
chlorocarbonic acid	carbamic acid	ethyl hydrogen carbonate

Difunctional Derivatives — All of them are ***Stable***

$Cl-\overset{\overset{O}{\|}}{C}-Cl$	$H_2N-\overset{\overset{O}{\|}}{C}-NH_2$	$Cl-\overset{\overset{O}{\|}}{C}-OC_2H_5$
phosgene (*carbonyl chloride*)	urea (*carbamide*)	ethyl chloroformate



PHOSGENE, *Carbonyl Chloride*, $Cl-\overset{\overset{O}{\|}}{C}-Cl$

Phosgene is the diacid chloride of carbonic acid. It is a highly toxic gas. When inhaled in high concentrations, it is so toxic that the lungs abruptly stop functioning and death occurs in a few minutes. In low concentrations, there are no immediate symptoms, but death occurs within 24 hours. The toxic action of phosgene is due its hydrolysis in the lungs with the liberation of HCl gas. Phosgene was extensively used in World War I as a chemical warfare agent.

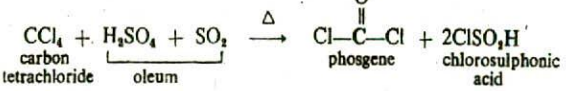
The name *phosgene* is derived from the fact that it was first produced by the action of sunlight on a mixture of carbon monoxide and chlorine (Gr. *phos*, light + *gennas*, to produce).

Preparation. Phosgene may be obtained :

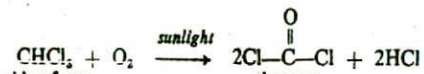
(1) By passing a mixture of carbon monoxide and chlorine over activated charcoal at 200—250°. (*Commercial Method*).



(2) By the action of fuming sulphuric acid (*oleum*) on carbon tetrachloride at 78°.



(3) By the oxidation of chloroform with potassium dichromate in the presence of sulphuric acid, or by oxygen of the air in the presence of sunlight.

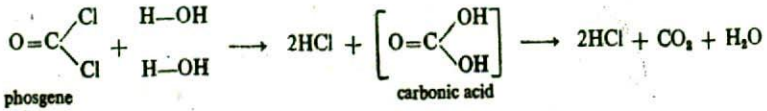


Phosgene is also produced when carbon tetrachloride is thrown upon a hot flame, such as that of burning gasoline and, for this reason, the use of carbon tetrachloride for extinguishing indoor fires is very dangerous.

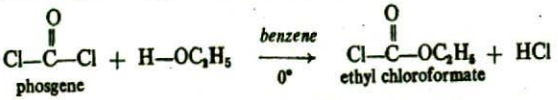
Properties. (*Physical*). Phosgene is a colourless gas with suffocating odour, bp 8°. When diluted with air, it has sickish, musty odour like that sometimes noticed in a hay field. Phosgene dissolves readily in toluene (or benzene), and such a solution is usually employed for keeping and transporting it.

(*Chemical*). Phosgene resembles acid chlorides in general chemical behaviour. Some of its important reactions are given below.

(i) **Hydrolysis.** Phosgene is decomposed by water to give hydrogen chloride and carbon dioxide.

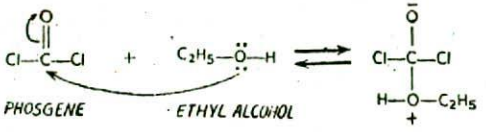


(2) **Reaction with Alcohols.** Phosgene reacts with one mole of an alcohol in an inert solvent (*e.g.*, benzene) at 0° to yield the corresponding alkyl chloroformate.



MECHANISM. The mechanism of this reaction follows the general scheme of *Nucleophilic Substitution* and involves the following *three* steps.

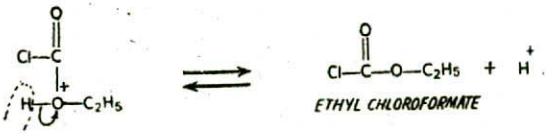
Step I. The nucleophile attacks the carbonyl carbon of the phosgene molecule.



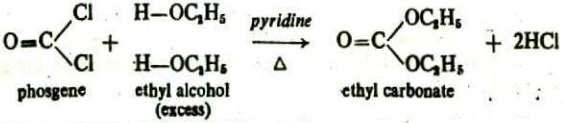
Step II. One of the chloride ions is eliminated.



Step III. A hydrogen ion is lost to give ethyl chloroformate.

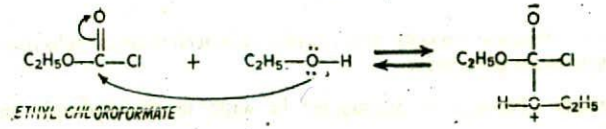


When phosgene is heated with an excess of alcohol in the presence of pyridine, the product is an alkyl carbonate.

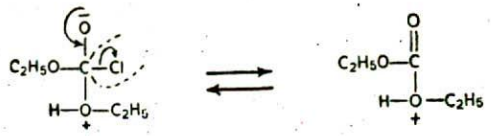


MECHANISM. The mechanism of this reaction involves the following *three* steps in addition to the three steps described above.

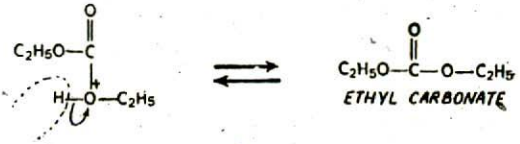
Step I. The nucleophile attacks the carbonyl carbon of ethyl chloroformate molecule.



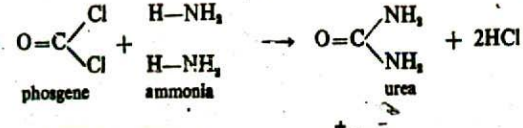
Step II. Chloride ion is eliminated.



Step III. A hydrogen ion is lost to yield ethyl carbonate.

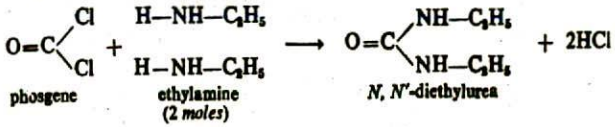


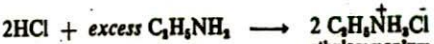
(3) **Reaction with Ammonia.** Phosgene reacts with ammonia to yield urea.





(4) **Reaction with Amines.** Phosgene reacts with an excess of primary amine to form the corresponding substituted urea.

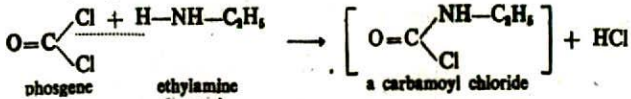




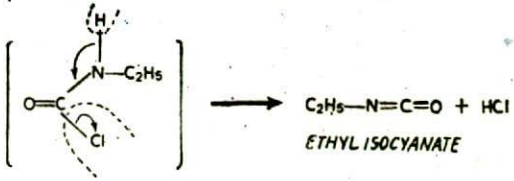
The prefix *N, N'-* in the name *N, N'*-dimethylurea indicates that the ethyl groups are attached to the nitrogen atoms.

When an excess of phosgene is used, the reaction proceeds in two stages. *First*, an unstable carbamoyl chloride (R—NH—COCl) is produced. *Second*, this unstable intermediate loses a molecule of hydrogen chloride to form an isocyanate.

(*i*)

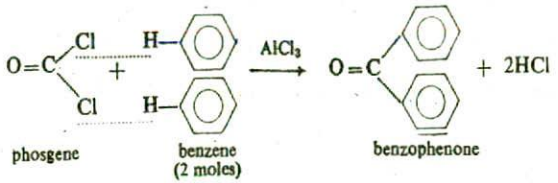


(*ii*)

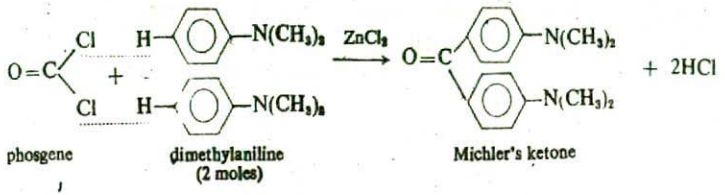


Secondary amines also react with phosgene to give substituted ureas. *Tertiary amines do not react.*

(5) **Reaction with Benzene.** Phosgene reacts with benzene in the presence of aluminium chloride to form benzophenone.

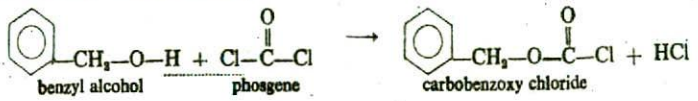


(6) **Reaction with Dimethylaniline.** Phosgene reacts with dimethylaniline in the presence of zinc chloride to form Michler's ketone. Notice that this reaction is an extension of reaction (5).



Michler's ketone is an important derivative of benzophenone which is widely used in dye industry.

(7) **Reaction with Benzyl Alcohol.** Phosgene reacts with benzyl alcohol to form carbobenzoxy chloride (benzyl chlorocarbonate).



Carbobenzoxy chloride is an important reagent which is widely used in *Peptide Synthesis.*

Uses. Inspite of its toxicity, phosgene is an important industrial chemical. It is used in the manufacture of : (1) toluenediisocyanate (TDI) for foam-rubber industry : (2) Michler's ketone for dye industry ; and (3) carbobenzoxy chloride for peptide synthesis.

CHLOROCARBONIC ACID, *Chloroformic acid*, Cl—C(=O)—OH

Chlorocarbonic acid is the monoacid chloride of carbonic acid. It does not exist in the free state, but its esters are well-known. Two of these esters are described below.

Ethyl Chloroformate, Cl—C(=O)—OC_2H_5. It is obtained by treating phosgene with one mole of ethyl alcohol in benzene at 0° (p. 706). Ethyl chloroformate is a colourless liquid with suffocating odour, bp 94°. It behaves both as an ester and as an acid halide. Ethyl chloroformate reacts with compounds containing *active* hydrogen atoms, for example, alcohols, ammonia, and amines.

$$\underset{\text{ethyl alcohol}}{C_2H_5O{-}H} + \underset{\text{ethyl chloroformate}}{Cl{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} \longrightarrow \underset{\text{ethyl carbonate}}{C_2H_5O{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} + HCl$$

$$\underset{\text{ammonia}}{H_2N{-}H} + \underset{\text{ethyl chloroformate}}{Cl{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} \longrightarrow \underset{\substack{\text{ethyl carbamate}\\(\textit{urethane})}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} + HCl$$

$$\underset{\text{methylamine}}{CH_3{-}\overset{\overset{H}{|}}{N}{-}H} + \underset{\text{ethyl chloroformate}}{Cl{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} \longrightarrow \underset{(\textit{N}\text{-methylurethane})}{CH_3{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} + HCl$$

As shown above, ethyl chloroformate may be used in Organic Synthesis for the introduction of carbethoxy group ($-CO-OC_2H_5$) on nitrogen.

Ethyl chloroformate also reacts with Grignard reagents (1 mole) to produce esters of monocarboxylic acids. For example, with methyl magnesium bromide it forms ethyl acetate.

$$\underset{\substack{\text{methylmagnesium}\\\text{bromide}}}{CH_3MgBr} + \underset{\text{ethyl chloroformate}}{Cl{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} \longrightarrow \underset{\text{ethyl acetate}}{CH_3{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} + Mg(Br)Cl$$

To prevent the reaction between ethyl acetate and methylmagnesium bromide, the latter is added gradually.

Ethyl Carbonate, $C_2H_5O{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5$. It may be obtained by heating phosgene with an excess of ethyl alcohol in the presence of pyridine (p. 707). Ethyl carbonate may also be obtained by heating silver carbonate with ethyl iodide.

$$\underset{\substack{\text{silver}\\\text{carbonate}}}{Ag_2CO_3} + \underset{\substack{\text{ethyl}\\\text{iodide}}}{2C_2H_5I} \longrightarrow \underset{\text{ethyl carbonate}}{C_2H_5O{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} + 2AgI$$

Ethyl carbonate is a pleasant-smelling liquid, bp 126°. It is soluble in water. Ethyl carbonate undergoes *Claisen Condensation* with ketones containing two α-hydrogen atoms to form β-keto esters. For example, with acetone it forms ethyl acetoacetate.

$$\underset{\text{acetone}}{CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}H} + \underset{\text{ethyl carbonate}}{C_2H_5O{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5} \xrightarrow{C_2H_5\overset{-}{O}\overset{+}{Na}} \underset{\substack{\text{ethyl acetoacetate}\\\text{(acetoacetic ester)}}}{CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5}$$

CARBAMIC ACID, *Aminoformic Acid*, $HO{-}\overset{\overset{O}{\|}}{C}{-}NH_2$

Carbamic acid is the monoamide of carbonic acid. It does not exist in the free state, but its salts and esters are important compounds. Some of these are described below.

Ammonium Carbamate. $H_2N-\overset{O}{\overset{\|}{C}}-O\overset{+}{N}H_4$. It may be obtained by treating dry carbon monoxide with ammonia.

$$O=C=O + 2NH_3 \longrightarrow \underset{\text{ammonium carbamate}}{H_2N-\overset{O}{\overset{\|}{C}}-O\overset{-}{\overset{+}{N}}H_4}$$

Ammonium carbamate is a colourless crystalline solid, which is very soluble in water. When its aqueous solution is warmed to 60°, it is hydrolysed to ammonium carbonate.

$$\underset{\text{ammonium carbamate}}{H_2N-\overset{O}{\overset{\|}{C}}-O\overset{-}{\overset{+}{N}}H_4} + H_2O \xrightarrow{\Delta} \underset{\text{ammonium carbonate}}{H_4\overset{+}{N}O-\overset{O}{\overset{\|}{C}}-O\overset{-}{\overset{+}{N}}H_4}$$

When ammonium carbamate is heated at 130—150° under pressure, urea is formed.

Carbamyl Chloride, $Cl-\overset{O}{\overset{\|}{C}}-NH_2$. It may be obtained by passing *dry* hydrogen chloride over potassium cyanate.

$$\underset{\text{pot cyanate}}{KOCN} + HCl \longrightarrow \underset{\text{carbamyl chloride}}{Cl-\overset{O}{\overset{\|}{C}}-NH_2}$$

Carbamyl chloride boils at 62° with decomposition into hydrogen chloride and cyanic acid. It behaves as an acid halide and reacts with water, alcohols, ammonia and amines.

Ethyl Carbamate. *Urethane*, $H_2N-\overset{O}{\overset{\|}{C}}-OC_2H_5$. Esters of carbamic acid as a class are often called *urethanes*. The ethyl ester is known as urethane or ethyl carbamate. It may be obtained :

(1) By the action of ammonia on ethyl chloroformate (p. 709).

(2) By heating carbamyl chloride with alcohol.

$$\underset{\text{carbamyl chloride}}{H_2N-\overset{O}{\overset{\|}{C}}-Cl} + \underset{\text{ethyl alcohol}}{H-OC_2H_5} \xrightarrow{\Delta} \underset{\text{ethyl carbamate}}{H_2N-\overset{O}{\overset{\|}{C}}-OC_2H_5} + HCl$$

(3) By heating urea with ethyl alcohol. The reaction proceeds in two stages. *First*, urea is converted into ammonia and isocyanic acid which is tautomeric with cyanic acid. *Second*, isocyanic acid reacts with ethyl alcohol to form ethyl carbamate.

(*i*) $$\underset{\text{urea}}{H_2N-\overset{O}{\overset{\|}{C}}-NH_2} \longrightarrow [\underset{\text{isocyanic acid}}{H-N=C=O} \rightleftharpoons \underset{\text{cyanic acid}}{HO-C\equiv N}] + NH_3$$

(*ii*) $\underset{\text{isocyanic acid}}{H-N=C=O} + C_2H_5OH \longrightarrow \underset{\substack{\text{ethyl carbamate}\\(\textit{urethane})}}{H_2N-\overset{\overset{O}{\|}}{C}-OC_2H_5}$

Ethyl carbamate (urethane) is a crystalline solid, mp 50°. It is soluble in water, alcohols, and ethers. Ethyl carbamate reacts with ammonia to give urea.

$$\underset{\text{ethyl carbamate}}{H_2N-\overset{\overset{O}{\|}}{C}-OC_2H_5} + NH_3 \xrightarrow{\Delta} \underset{\text{urea}}{H_2N-\overset{\overset{O}{\|}}{C}-NH_2} + \underset{\text{ethyl alcohol}}{C_2H_5OH}$$

When heated with aqueous sodium hydroxide, ethyl carbamate is decomposed into ethyl alcohol, ammonia, and sodium carbonate.

$$\underset{\text{ethyl carbamate}}{H_2N-\overset{\overset{O}{\|}}{C}-OC_2H_5} + 2NaOH \xrightarrow{\Delta} \underset{\text{ethyl alcohol}}{C_2H_5OH} + NH_3 + Na_2CO_3$$

Ethyl carbamate has a mild hypnotic action which is intensified if the ethyl group is replaced by a larger group having a branched chain. It is used in the treatment of cancer and lukemia.

UREA, *Carbamide*, $H_2N-\overset{\overset{O}{\|}}{C}-NH_2$

Urea is the diamide of carbonic acid. It is of historical interest because the synthesis of this compound by Friedrich Wholer in 1928 was the keystone in the development of Modern Organic Chemistry.

Urea is an important industrial chemical. It is used as a slow acting nitrogenous fertilizer and in the manufacture of several well-known drugs, *e.g.*, burbiturates. Urea is also an end product in the metabolism of proteins in our body. It is produced in the liver indirectly from ammonia and carbon dioxide and excreted in the urine A normal adult excretes about 30 grams of urea per day The name *urea* directs attention to the occurrence of this compound in urine.

Isolation from Urine. Urea can be isolated from urine by first concentrating it by evaporation. The concentrated urine is then mixed with a hot solution of oxalic acid. Sparingly soluble urea oxalate, $2CO(NH_2)_2H_2C_2O_4$, separates as crystals which are filtered off. These are then boiled with an aqueous suspension of calcium carbonate, which throws down insoluble calcium oxalate, and liberates urea in the solution. The calcium oxalate is removed by filtration and the solution of urea is evaporated to dryness on a water-bath. The residue is finally recrystallised from alcohol to give pure crystalline urea.

Preparation. Urea may be obtained :

(1) By heating an aqueous solution of ammonium cyanate. (*Wohler Synthesis*

$$\underset{\substack{\text{ammonium}\\\text{cyanate}}}{NH_4OCN} \underset{\leftarrow}{\overset{\Delta}{\rightleftharpoons}} \underset{\text{urea}}{H_2N-\overset{\overset{O}{\|}}{C}-NH_2}$$

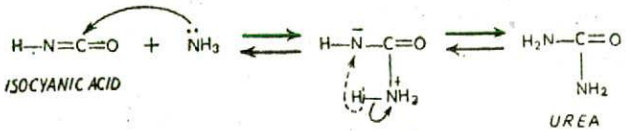
The reaction is somewhat reversible, for it has been noticed that when silver ion is added to hot aqueous urea solution, silver cyanate is precipitated.

MECHANISM. The mechanism of the above reaction involves *two* steps.

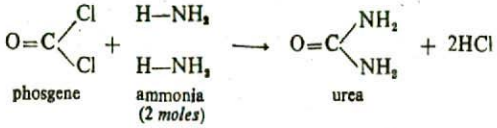
Step I. Decomposition of ammonium cyanate gives ammonia and isocyanic acid which is tautomeric with cyanic acid.

$$\underset{\text{ammonium cyanate}}{NH_4OCN} \rightleftharpoons NH_3 + [\underset{\text{isocyanic acid}}{H-N=C=O} \rightleftharpoons \underset{\text{cyanic acid}}{HO-C\equiv N}]$$

Step II. Action of ammonia on isocyanic acid yields urea.



(2) By the action of ammonia on phosgene (carbonyl chloride).



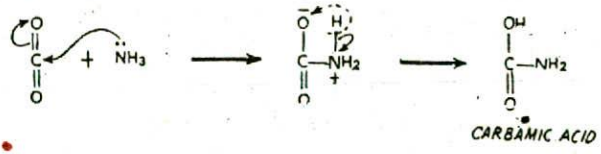
$$2HCl + \textit{excess}\ NH_3 \longrightarrow \underset{\text{ammonium chloride}}{NH_4Cl}$$

(3) By heating ammonia and carbon dioxide together under pressure at 130—150°. (*Commercial Method*)

$$CO_2 + 2NH_3 \xrightarrow[\textit{pressure}]{\Delta} \underset{\text{urea}}{H_2N-\overset{\overset{O}{\|}}{C}-NH_2}$$

MECHANISM. The reaction is not as simple as shown above. It involves the following *three* steps.

Step I. Ammonia reacts with carbon dioxide to give an unstable carbamic acid.



Step II. Carbamic acid reacts with ammonia to form ammonium carbamate.

$$\underset{\text{carbamic acid}}{\left[H_2N-\overset{\overset{O}{\|}}{C}-OH\right]} + NH_3 \longrightarrow \underset{\text{ammonium carbamate}}{H_2N-\overset{\overset{O}{\|}}{C}-O^-NH_4^+}$$

Step III. A molecule of water is eliminated from ammonium carbamate to yield urea.

$$H_2N-\underset{\underset{O}{\|}}{C}-\overset{-}{O}\overset{+}{N}H_4 \xrightarrow{\Delta} H_2N-\underset{\underset{O}{\|}}{C}-NH_2 + H_2O$$

urea

(4) By the action of ammonia on urethanes and alkyl carbamates.

$$O=C\begin{matrix}OC_2H_5\\NH_2\end{matrix} + H-NH_2 \longrightarrow O=C\begin{matrix}NH_2\\NH_2\end{matrix} + C_2H_5OH$$

ethyl carbamate (urethane) — urea

$$O=C\begin{matrix}OC_2H_5\\OC_2H_5\end{matrix} + \begin{matrix}H-NH_2\\H-NH_2\end{matrix} \longrightarrow O=C\begin{matrix}NH_2\\NH_2\end{matrix} + 2C_2H_5OH$$

ethyl carbonate — ammonia — urea

(5) By the partial hydrolysis of cyanamide with dilute sulphuric acid at 70°.

$$H_2N-C\equiv N + H_2O \xrightarrow[\Delta]{H^+} H_2N-\underset{\underset{O}{\|}}{C}-NH_2$$

cyanamide — urea

(6) By the action of dilute sulphuric acid on calcium cyanamide,

$$CaN-C\equiv N + H_2SO_4 + H_2O \xrightarrow{warm} H_2N-\underset{\underset{O}{\|}}{C}-NH_2 + CaSO_4$$

calcium cyanamide — urea

Structure of Urea. In urea the two nitrogen atoms, the oxygen atom, and the carbon atom are all sp^2 hybridized. These sp^2 hybrid orbitals overlap with each other and with s orbitals of the four hydrogen atoms forming C—O, C—N, and N—H σ bonds as shown in Fig. 30·2. These σ bonds lie in one plane and are approximately 120° apart.

In addition to the sp^2 orbitals, each atom in urea also possesses an unhybridized p orbital which is perpendicular to the plane of σ bonds. The p orbital on each nitrogen atom contains a pair of electrons, the p orbital on carbon contains one electron, and the p orbital on oxygen also contains one electron. These p orbitals laterally overlap forming a delocalized π molecular orbital above and below the plane of the σ bonds (Fig. 30·3)

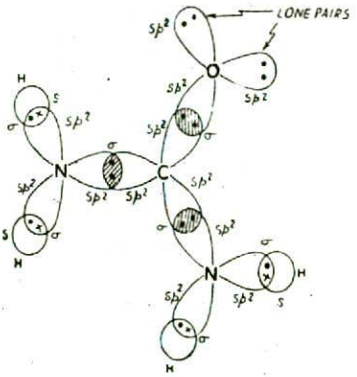


Fig. 30·2. Formation of σ bonds in urea molecule.

According the Valence Bond Theory, urea is considered to be a *resonance hybrid* of the following canoncial forms.

$$H_2N-\underset{\underset{O}{\|}}{C}-NH_2 \longleftrightarrow H_2\overset{+}{N}=\overset{-}{\underset{|}{C}}-NH_2 \longleftrightarrow H_2N-\overset{-}{\underset{|}{C}}=\overset{+}{N}H_2$$

X-ray diffraction studies have shown that both C—N bonds in urea are the same length (1·33 Å). This is shorter than the C—N *single* bond in amines (1·48°) but longer than the normal C—N *double* bond (1·28 Å). These values suggest that the C—N bonds in urea are identical and possess significant double bond character. That is, they confirm the hybrid nature of the urea molecules.

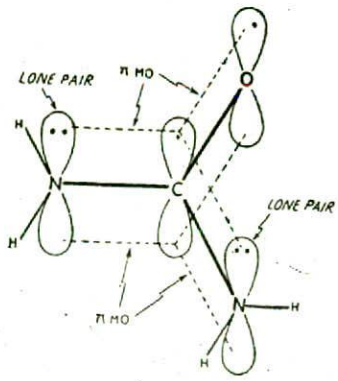
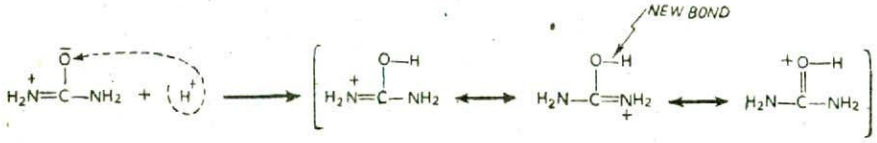


Fig. 30·3. Formation of delocalized π molecular orbital in urea molecule.

Basicity of Urea. Urea is a weak base. The reason for this is that the lone pair of electrons on nitrogens are involved in the formation of the delocalized π molecular orbital. They are, therefore, not available for the formation of a *new* N—H bond with proton. However, a proton can and does attack the negatively charged oxygen atom and form an O—H bond. This has been confirmed by NMR studies of salts of urea.

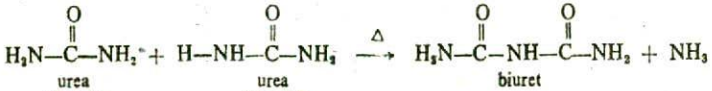
The positive ion formed when oxygen takes up a proton is also stabilised by resonance.



Properties. (*Physical*) Urea is a non-toxic colourless crystalline solid, mp 132°. It is soluble in water and alcohol, but insoluble in non-hydroxylic solvents such as ether, chloroform, or benzene.

(*Chemical*). Urea resembles amides in general chemical behaviour. Some of its important reactions are described below.

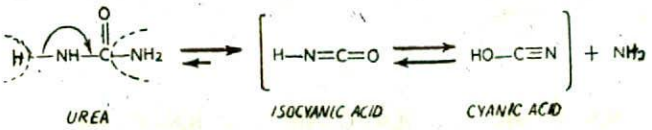
(1) **Action of Heat.** When urea is heated to a temperature above its melting point (132°), ammonia is evolved and crystalline **biuret** is formed.



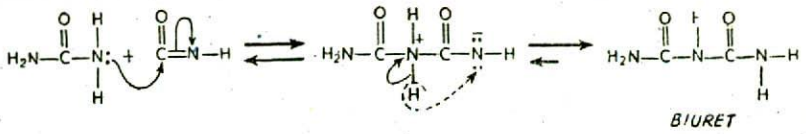
If an alkaline solution of biuret is treated with a drop of copper (II) sulphate solution, a violet colour appears. This serves as a test (**Biuret Test**) for the urea, and also for proteins, peptides, and other compounds containing the —CO—NH— linkage.

MECHANISM. The mechanism of the above reaction involves *two* steps.

Step 1. Conversion of urea into ammonia and isocyanic acid which is tautomeric with cyanic acid.

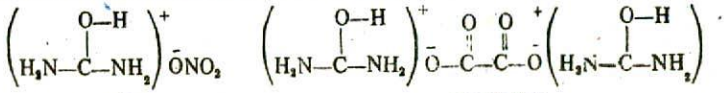


Step II. **Reaction of isocyanic acid with another molecule of urea gives biuret.**

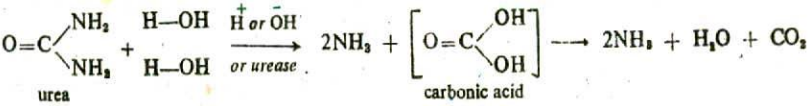


If urea is heated more strongly the above reaction is reversed. Isocyanic acid is obtained which rapidly polymerises to cyanuric acid, $(HNCO)_3$.

(2) **Salt Formation.** As already mentioned, urea is a weak *monoacidic* base. It forms stable, water-insoluble salts with nitric acid and oxalic acid. With nitric acid it forms urea nitrate, and with oxalic acid it forms urea oxalate.



(3) **Hydrolysis.** Urea is hydrolysed on heating with dilute acids or dilute alkalis to give carbon dioxide and ammonia. The hydrolysis can also be brought about by the enzyme *urease.* This enzyme is found in soil bacteria, water-melon seeds, and in soya beans.

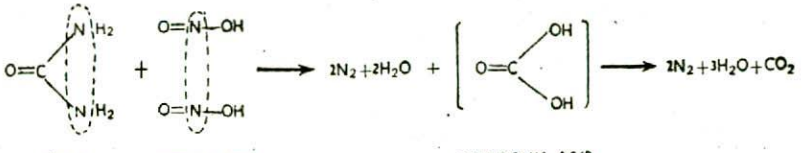


With *urease* the yield of ammonia and carbon dioxide is quantitative and this reaction is used for the accurate estimation of urea in solutions (p 719).

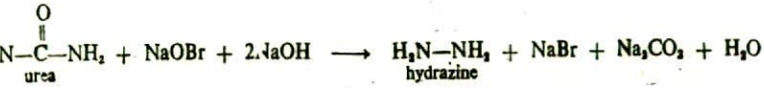
(4) **Reaction with Thionyl Chloride.** Urea undergoes dehydration with thionyl chloride ($SOCl_2$) to yield cyanamide.



(5) **Reaction with Nitrous Acid.** Urea reacts with nitrous acid (or $NaNO_2+HCl$) to give nitrogen, carbon dioxide, and water.



(6) **Reaction with Alkaline Solutions of Hypohalites.** Urea reacts with an alkaline solution of sodium hypobromite (or Br_2+NaOH) to yield hydrazine, which is immediately oxidised by sodium hypobromite to nitrogen.



$$\underset{\text{hydrazine}}{HN_2{-}NH_2} + 2NaOBr \longrightarrow 2NaBr + N_2 + H_2O$$

The *over-all* reaction is :

$$\underset{\text{urea}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2} + 3NaOBr + 2NaOH \longrightarrow 2NaBr + Na_2CO_3 + N_2 + 2H_2O$$

The reaction is used for the clinical estimation of urea in various body fluids (*e.g.* urine) This is done by measuring the volume of nitrogen evolved when a test sample is mixed with an alkaline solution of sodium hypobromite (p. 719).

(7) **Reaction with Fuming Sulphuric Acid.** Urea reacts with fuming sulphuric acid (oleum) to yield sulphamic acid.

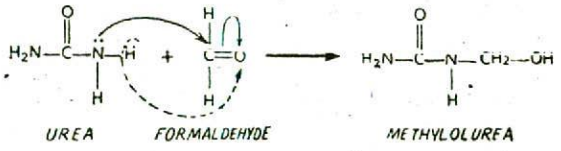
$$\underset{\text{urea}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2} + \underbrace{H_2SO_4 + SO_3}_{\textit{oleum}} \longrightarrow \underset{\text{sulphamic acid}}{2NH_2SO_3H} + CO_2$$

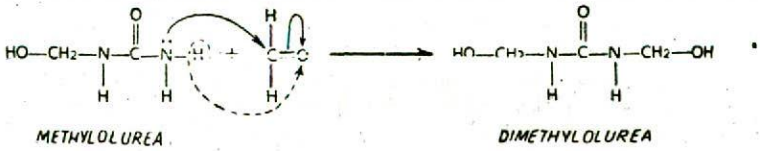
Sulphamic acid is a colourless crystalline solid, mp 205° with decomposition. It is a strong acid and can be used as a primary standard for the standardisation of solutions of bases. Two of the derivatives find many industrial applications. They are ammonium sulphamate and sodium cyclohexylsulphamate.

Ammonium Sulphamate, $NH_2SO_3NH_4$, is used as a flameproofing agent for paper and textiles ; it does not cause stiffening of materials and is not removed from fabrics by dry cleaning. It is also an effective weed killer and has been used for the eradication of *poison ivy* and *wild cherry*.

Sodium cyclohexylsulphamate, $C_6H_{11}NHSO_3Na$, is about 50 times as sweet as table sugar (sucrose) and has no food value. Since it is not affected by heat, it can be used in cooking without undergoing change. It is sold under the name *Sucaryl* and *Cyclamate*.

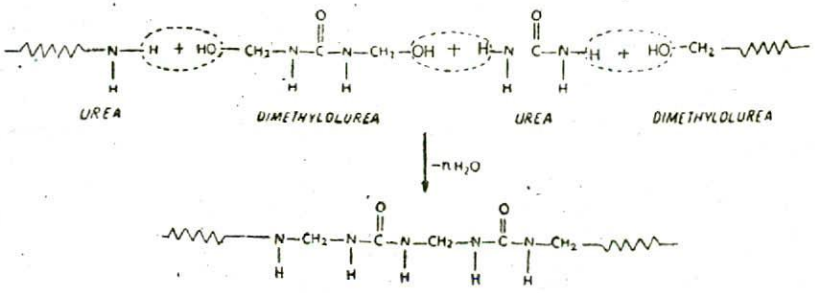
(8) **Reaction with Formaldehyde (Urea-Formaldehyde Resins).** Urea adds to formaldehyde in the presence of a base or an acid to form methylolurea and dimethylolurea.



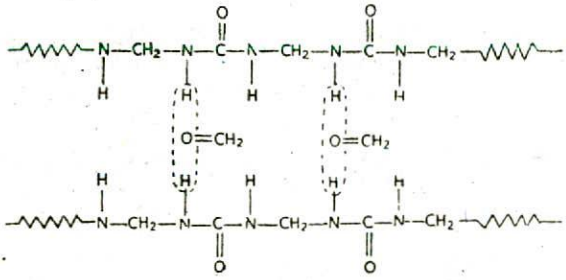


Under carefully controlled reaction conditions, both methylolurea and dimethylolurea can be isolated. If the reaction is carried further, *three* things can happen.

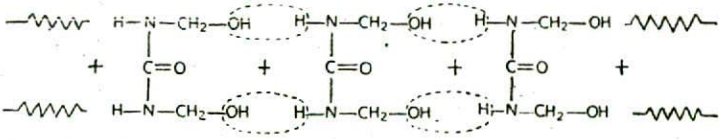
(*a*) The dimethylolurea molecules can condense with more urea molecules to form linear polymers.



(*b*) The linear polymers can condense with more formaldehyde molecules to form cross-linked polymers.

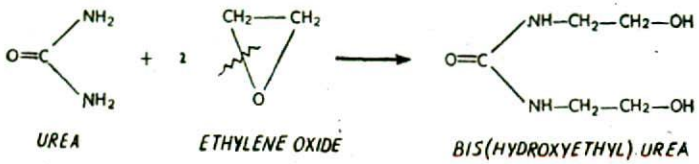


(*c*) The dimethylolurea molecules can condense with each other to form linear polymers.



This gives rise to a complex mixture of *linear* and *cross-linked* condensation polymers known as **Urea-Formaldehyde Resins**. Depending upon the reaction conditions, resins of different types are obtained. These resins find many industrial applications. They are used for gluing and impregnating timber, as ingredients of varnishes and lacquers, and in the manufacture of electrical fittings, radio cabinets, dishes, telephones, table tops, toys, etc

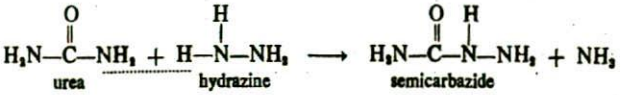
(9) **Reduction with Ethylene Oxide**. Urea reacts with ethylene oxide to form bis(hydroxyethyl)urea.



UREA ETHYLENE OXIDE BIS(HYDROXYETHYL) UREA

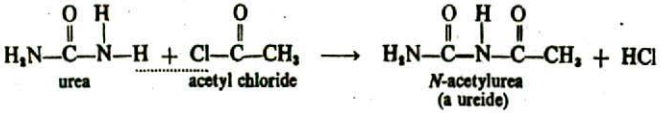
Bis(hydroxyethyl)urea is an important intermediate in the manufacture of non-ionic detergents.

(10) **Reaction with Hydrazine.** Urea reacts with hydrazine in the presence of aqueous amyl alcohol as solvent at 100° to yield semicarbazide.

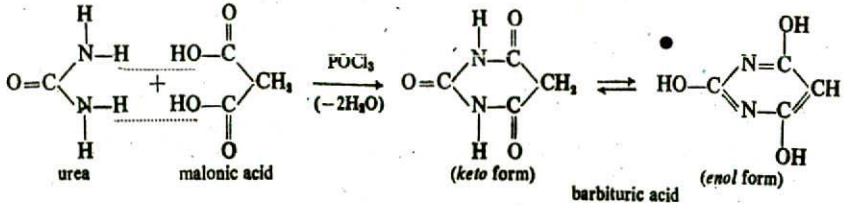


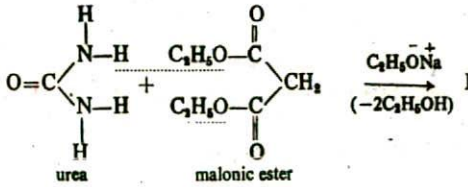
Semicarbazide is an important reagent used for the identification of aldehydes and ketones.

(11) **Reaction with Acid Chlorides.** Urea reacts with acid halides to form acyl derivatives or *ureides*. For example, acetyl chloride reacts with urea to give *N*-acetylurea.



(12) **Reaction with Malonic Acid and Malonic Ester.** Urea reacts with malonic acid in the presence of phosphorous oxychloride ($POCl_3$) to yield a tautomeric mixture of barbituric acid (malonylurea). Barbituric acid can also be obtained by heating urea with malonic ester in the presence of sodium ethoxide.





Barbituric acid is a slightly stronger acid than acetic acid and is the parent substance of of the barbiturate drugs. The latter are made from substituted malonic esters and are used as hypnotics (drugs to induce sleep). These drugs are habit forming substances and their use is regulated by Doctor's prescription.

(13) **Formation of Inclusion Complexes.** It has been noticed that certain compounds, when crystallised from liquid media have the ability to trap other molecules in the crystal lattice. The trapped molecules occupy spaces or holes in the crystal lattice. The crystalline compounds which result are often referred to as the *Inclusion Complexes.*

Urea forms such inclusion complexes with a number straight-chain aliphatic compounds, but not with branched-chain or cyclic compounds. The aliphatic compounds that form inclusion complexes are hydrocarbons, alkyl halides, alcohols, ketones, acids, and esters. The procedure for making such compounds consists of mixing a saturated methanol solution of urea with saturated methanol solutions of other compounds. A crystalline precipitate results from which the components can be separated by extracting urea with water or the trapped compound with a suitable organic solvent. The process can be used for removing unbranched-chain compounds from branched-chain compounds.

Uses. Urea is used : (1) in agriculture as a fertilizer ; (2) as a protein supplement in cattle feed ; (3) in the manufacture of urea-formaldehyde resins ; (4) as a stabilizer for nitrocellulose explosives ; (5) in the manufacture of barbiturates — a group of drugs which induce sleep ; (6) to improve octane number of gasoline by removing normal hydrocarbons through formation of inclusion complexes ; and (7) in the manufacture of non-ionic detergents.

Estimation of Urea. The estimation of urea in urine or other body fluids can be done by the following two methods.

(1) **Hypobromite Method.** In this method urea is decomposed by alkaline sodium hypobromite solution (*See* reaction 6 of urea) and the volume of nitrogen evolved is measured.

The estimation is carried in an apparatus known as Ureometer (Fig. 30·4). The large central tube is filled with freshly prepared hypobromite solution (10g NaOH/25 ml H_2O+25 ml Br_2), while the sample of urine is placed in the narrow side tube. Now 1 ml of urine is introduced into the large tube by opening the tap. Evolution of nitrogen occurs. When the decomposition is complete, the volume of gas collected is noted. The wide tube is so graduated as to directly give the weight of urea per ml of urine.

The hypobromite method is used only where an approximate estimation of urea is needed.

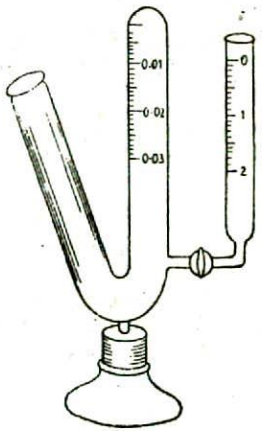


Fig. 30·4. Doremus—Hinds Ureometer.

(2) **Urease Method.** In this method urea is hydrolysed by the enzyme *urease* (*See* reaction 3 of urea) and the ammonia evolved determined volumetrically.

The apparatus for the estimation consists of three test tubes as shown in Fig. 30·5. The test tube (A) contains water which removes any ammonia from air drawn through the apparatus. A mixture of 25 ml of urine, 5 g of powdered soya bean, and a small quantity of liquid paraffin (to prevent frothing) is placed in the test tube (B) which is warmed by immersion in hot water. After allowing the mixture to stand for 15 minutes, a current of air is aspirated from (A) to (C). The ammonia evolved in test tube (B) is swept into the test tube (C) where it is absorbed by the standard acid. This is continued for an hour. Then 5 g of potassium carbonate are added to the test tube (B) in order to decompose any ammonium carbonate formed in it. The ammonia produced is again conveyed to test tube (C) by a current of air and absorbed in the acid. Finally, the apparatus is disconnected and the acid back titrated against standard aikali in order to know the amount of ammonia evolved during the reaction. Once we know the amount of ammonia evolved, we can calculate the amount of urea present in 25 ml of urine with the help of the following equation :

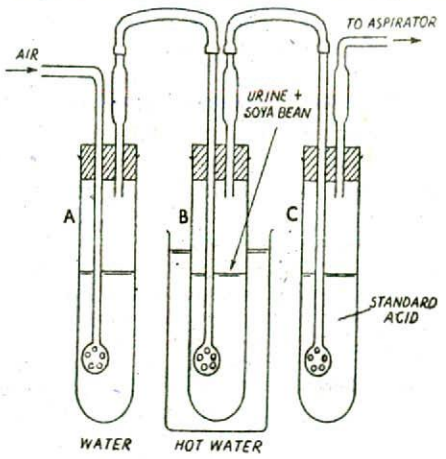


Fig. 30·5. Estimation of Urea by Urease Method.

$$\underset{\text{urea}}{H_2N-\overset{\overset{O}{\|}}{C}-NH_2} + H_2O \longrightarrow CO_2 + 2NH_3$$

The Urease method of estimation of urea is convenient and more accurate as compared to the Hypobromite method.

COMPOUNDS RELATED TO UREA

Nitrourea, $H_2N-\overset{\overset{O}{\|}}{C}-NH-NO_2$. It may be obtained by treating urea nitrate with *cold* concentrated sulphuric acid.

$$\underset{\text{urea nitrate}}{\left(H_2N-\overset{O-H}{\overset{|}{C}}-NH_2\right)^{+}\bar{O}NO_2} \xrightarrow[0^\circ]{H_2SO_4} \underset{\text{nitrourea}}{H_2N-\overset{\overset{O}{\|}}{C}-NH-NO_2} + H_2O$$

Nitrourea is crystalline solid, mp 152°. It is soluble in cold water, but *unstable* in hot water. Nitrourea is reduced by zinc and acetic acid or better electrolytically to yield semicarbazide.

$$\underset{\text{nitrourea}}{H_2N-\overset{\overset{O}{\|}}{C}-NH-NO_2} + 6[H] \longrightarrow \underset{\text{semicarbazide}}{H_2N-\overset{\overset{O}{\|}}{C}-NH-NH_2} + 2H_2O$$

Semicarbazide, $H_2N-\overset{\overset{O}{\|}}{C}-NH-NH_2$. It may be obtained from nitrourea (*see above*)

or by heating urea with hydrazine in the presence of aqueous amyl alcohol at 100°. It can also be obtained by treating hydrazine sulphate with potassium cyanate.

$$\underset{\text{hydrazine sulphate}}{(H_2N{-}NH_2)H_2SO_4} + 2KOCN \longrightarrow \underset{\text{semicarbazide}}{2H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH{-}NH_2} + K_2SO_4$$

Semicarbazide is a crystalline solid, mp 96°. It is basic, and forms crysttaline salts with strong acids. Its hydrochloride is frequently used for the identification of aldehydes and ketones, with which it forms sparingly soluble semicarbazones. Semicarbazide is hydrolysed on heating with dilute acids ar alkalis to give hydrazine, ammonia, and carbon dioxide.

Guanidine, $H_2N{-}\overset{\overset{N{-}H}{\|}}{C}{-}NH_2$. It is the imide corresponding to urea. Guanidine occurs in beet juice, and is one of the degradation products of the purines. Several derivatives of guanidine are of biological importance, *e.g.*, creatine, creatinine, and arginine. Guanidine is colourless solid (mp about 50°) which is very hygroscopic and difficult to isolate in pure form. It is usually isolated as its hydrochloride or nitrate. Guanidine hydrochloride is obtained by heating cyanamide (*or* dicyandiamide) with ammonium chloride solution at 100° under pressure.

$$\underset{\text{cyanamide}}{H_2N{-}C{\equiv}N} + \overset{+}{N}H_4\overset{-}{Cl} \xrightarrow[\textit{pressure}]{\Delta} \underset{\substack{\text{guanidine}\\\text{hydrochloride}}}{H_2N{-}\overset{\overset{\overset{+}{N}H_2\overset{-}{Cl}}{\|}}{C}{-}NH_2}$$

Guanidine nitrate is prepared by treating dicyandiamide with ammonium nitrate.

$$\underset{\text{dicyandiamide}}{H_2N{-}\overset{\overset{N{-}H}{\|}}{C}{-}NH{-}C{\equiv}N} + 2NH_4NO_3 \longrightarrow \underset{\text{guanidine}}{2H_2N{-}\overset{\overset{\overset{+}{N}H_2\overset{-}{O}NO_2}{\|}}{C}{-}NH_2}$$

Guanidine is a very strong base. It forms stable salts even with weak acids. The basic strength of guanidine is due to the stability of the positive guanidinium ion, which is stabilised by resonance. Guanidine is hydrolysed on warming with dilute alkalis to give urea and ammonia. When fused with potassium hydroxide it yields cyanamide.

Nitroguanidine, $H_2N{-}\overset{\overset{N{-}NO_2}{\|}}{C}{-}NH_2$. It is formed by the action of *cold* concentrated sulphuric acid on guanidine nitrate.

$$\underset{\substack{\text{guanidine}\\\text{nitrate}}}{H_2N{-}\overset{\overset{\overset{+}{N}H_2\overset{-}{O}NO_2}{\|}}{C}{-}NH_2} \xrightarrow[0°]{H_2SO_4} \underset{\substack{\text{nitroguanidine}}}{H_2N{-}\overset{\overset{N{-}NO_2}{\|}}{C}{-}NH_2} + H_2O$$

Nitroguanidine is used as a component of some explosives. It is about as powerful as *TNT* and explodes without producing a flash.

THIOUREA, *Thiocarbamide*, $H_2N{-}\overset{\overset{S}{\|}}{C}{-}NH_2$

Thiourea is the sulphur analogue of urea and is the diamide of the unknown thiocarbonic acid, $HO{-}\overset{\overset{S}{\|}}{C}{-}OH$. It is more toxic to plant life than urea and hence is not a

suitable fertilizer material. However, it is interesting to note that treatment of potato tubers with thiourea causes them to sprout without wintering.

Preparation. Thiourea may be obtained :

(1) By heating ammonium thiocyanate at 175°. This reaction is analogous to the conversion of ammonium cyanate into urea.

$$\underset{\text{ammonium thiocyanate}}{NH_4SCN} \rightleftharpoons \underset{\text{thiourea}}{H_2N-\overset{\overset{S}{\|}}{C}-NH_2}$$

(2) By treating cyanamide with hydrogen sulphide in the presence of ammonia under pressure.

$$\underset{\text{cyanamide}}{H_2N-C\equiv N} + H_2S \xrightarrow[\text{pressure}]{NH_3} H_2N-\overset{\overset{S}{\|}}{C}-NH_2$$

(3) By heating calcium cyanamide with hydrogen sulphide at 160—180°. (*Commercial Method*).

$$\underset{\text{calcium cyanamide}}{CaN-C\equiv N} + 2\,H_2S \xrightarrow{\Delta} \underset{\text{thiourea}}{H_2N-\overset{\overset{S}{\|}}{C}-NH_2} + CaS$$

Structure. The structure of thiourea is similar to that of urea. It is considered to be a resonance hybrid of the following canonical forms.

$$H_2N-\overset{\overset{S}{\|}}{C}-NH_2 \longleftrightarrow H_2\overset{+}{N}=\overset{\overset{\bar{S}}{|}}{C}-NH_2 \longleftrightarrow H_2N-\overset{\overset{\bar{S}}{|}}{C}=\overset{+}{N}H_2$$

Thiourea exists in two tautomeric forms.

$$H_2N-\overset{\overset{S}{\|}}{C}-NH_2 \rightleftharpoons \underset{\textit{iso} \text{ form}}{H_2N-\overset{\overset{S-H}{|}}{C}=NH}$$

Properties. (*Physical*). Thiourea is a colourless crystalline solid. It is soluble in water and *hot* ethanol, but insoluble in ether and *cold* ethanol. Thiourea has no true melting point because it isomerises to ammonium thiocyanate when heated. When heated rapidly, it appears to melt at *about* 180°.

(*Chemical*). Thiourea behaves as a *monoacidic* base and like urea, forms well defined salts. It forms *Inclusion Complexes* with branched-chain and cyclic aliphatic compounds, and with the straight-chain compounds containing more than fourteen carbon atoms.

Some of the more important reactions of thiourea are given below:

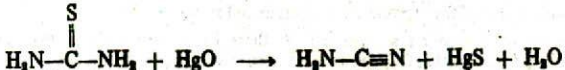
(1) **Hydrolysis.** Thiourea is decomposed on boiling with dilute alkalis to give ammonia, carbon dioxide and hydrogen sulphide.

$$\underset{\text{thiourea}}{H_2N-\overset{\overset{S}{\|}}{C}-NH_2} + 2H_2O \xrightarrow[\Delta]{\bar{O}H} 2NH_3 + CO_2 + H_2S$$

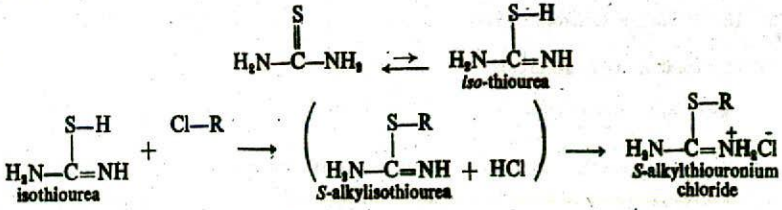
(2) **Oxidation.** Thiourea is oxidised on treatment with an alkaline solution of potassium permanganate or an alkaline solution of hydrogen peroxide to yield urea.



(3) **Reaction with Metal Oxides.** Thiourea reacts with oxides of mercury, silver, or lead to form cyanamide.

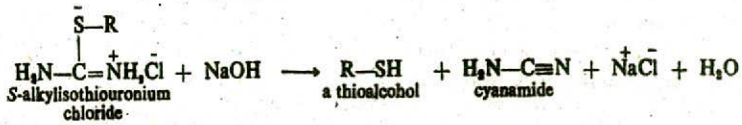


(4) **Reaction with Alkyl Halides.** Thiourea reacts with alkyl halides to form *S*-alkyl isothiouronium halides (*the prefix S-indicates that the alkyl group is attached to the sulphur atom*).



Notice that it is the *iso*-form of thiourea which takes part in the reaction.

The *S*-alkylisothiouronium halides are stable, crystalline salts. They are used to characterise sulphonic acids, with which they form insoluble salts. They are also used to prepare thioalcohols by alkaline hydrolysis.



Like urea, thiourea also reacts with formaldehyde to form resins.

Uses. Thiourea is used : (1) to protect furs and clothing from insects ; (2) in the synthesis of drugs ; (3) in photography as a gold or sepia tonner ; (4) in the preparation of thiols ; (5) as a reagent for the estimation of lead and cadmium ; and (6) in the manufacture of *nonglare* mirrors.

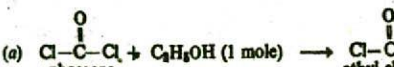
QUESTIONS

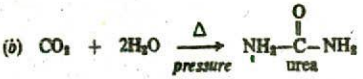
1. How is phosgene (carbonyl chloride) prepared on a large scale ? How does it react with (*a*) ethyl alcohol ; (*b*) ammonia ; (*c*) ethylamine ; and (*d*) benzene in the presence of $AlCl_3$.

2. Give an account of the occurrence, methods of formation, and uses of urea. How does it react with : (*a*) nitrous acid ; (*b*) nitric acid ; (*c*) formaldehyde ; (*d*) acetyl chloride ; and (*e*) on heating alone.

3. Draw Molecular Orbital Picture of urea, labelling each of the orbitals involved, and showing all bond angles.

4. Give a reasonable *mechanism* for the following reactions :





(c) $$\underset{\text{urea}}{2\,NH_2-\overset{\overset{O}{\|}}{C}-NH_2} \xrightarrow{\Delta} \underset{\text{biuret}}{NH_2-\overset{\overset{O}{\|}}{C}-NH-\overset{\overset{O}{\|}}{C}-NH_2} + NH_3$$

5. Write equations for the preparation of : (*a*) benzophenone from phosgene ; (*b*) ethyl carbamate urethane) from ethyl chloroformate ; (*c*) biuret from urea ; (*d*) semicarbazide from hydrazine sulphate ; (*e*) barbituric acid from urea ; (*f*) guanidine hydrochloride from cyanamide ; and (*g*) urea from thiourea. *Note : These are all one step conversions.*

6. Give an account of the preparation, properties and structure of urea.

7. How is urea obtained on a large scale ? State its important uses. How does it react with : (*i*) sodium hydroxide ; (*ii*) nitric acid ; (*iii*) nitrous acid ; and (*iv* alkaline hypobromite.

8. How is urea prepared on a large scale ? State its important uses. How does it react with : (*a*) alkaline hypobromite ; and (*b*) malonic ester ?

9. How is urea manufactured ? Give its characteristic reactions and discuss its structure.

10. How is urea manufactured ? What is the action of : (*i*) nitrous acid, and (*ii*) alkaline hypobromite on urea ?

11. Give the structural formulae of urethane and urea. What happens when urea is heated ?

12. Indicate any one method of preparation of urea. How does urea react with nitrous acid ? What is Biuret reaction ? *(Tripura BSc, 1993)*

13. How is urea prepared ? Give three of its important reactions. Discuss its strucure. *(Aligarh BSc, 1992)*

14. Give preparation, properties, and uses of urea ? How is it estimated ? *(Saugar BSc 1993)*

15. What happens when urea is heated ? *(Delhi BSc, 1993)*

16. What happens when urea is treated with acetyl chloride ? *(Kakatiya BSc, 1993)*

17. How will you distinguish between urea and acetamide ? *(Madras BSc, 1994)*

18. Which of the following compounds is isomeric with urea :

(*a*) Ammonium cyanide ; (*b*) Ammonium thiocyanate ; (*c*) Glycine ; (*d*) Ammonium cyanate

Answer. (*d*)

19. Write a note on : Biuret test of urea. *(Kerala BSc, 1993)*

20. Write a note on : Estimation of urea. *(Gauhati BSc Hons, 1994)*